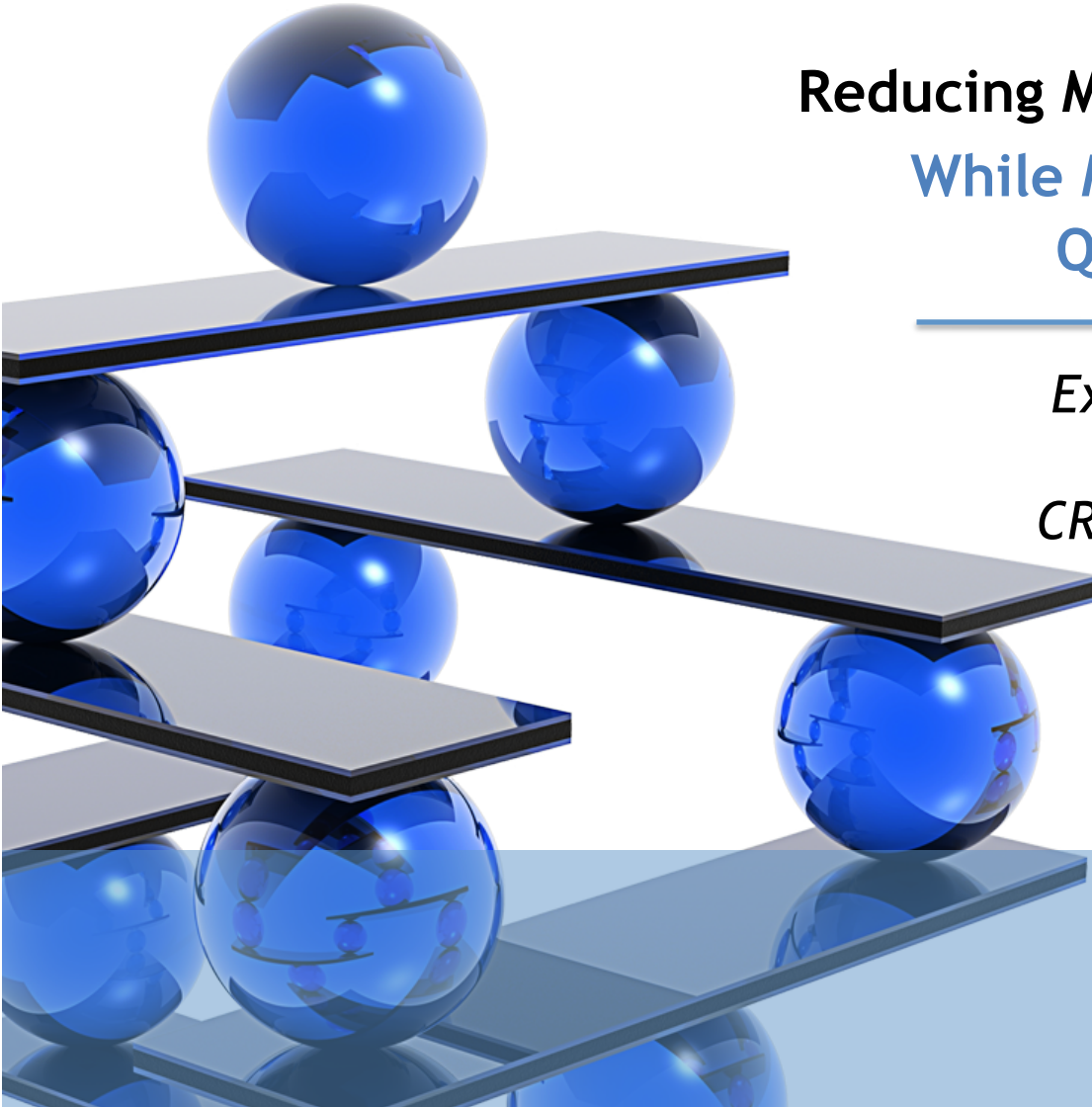


A Sponsor Outsourcing Dilemma:

Reducing Micromanagement of CROs
While Maintaining Effective
Quality Oversight

Executive Summary:
2011 Avoca
CRO Oversight Survey



Introduction

Introduction

- ▶ Each year, The Avoca Group surveys industry executives and managers to understand trends in the outsourcing of clinical research by pharmaceutical companies and other sponsors.
- ▶ At the end of 2010, many sources of information suggested that clinical research outsourcing was on the rise, and that outsourced work was being increasingly consolidated within a smaller number of more strategic partnerships.
- ▶ These trends, coupled with an increase in the number of high-profile warning letters and increased conduct of clinical trials in less-experienced developing regions, were increasing industry focus on the quality delivered by CROs in the conduct of clinical trials.
- ▶ Therefore, for the topic of Avoca's first Industry Survey of 2011, we chose to ask sponsor and service provider companies to share their views and specific practices regarding oversight of quality in outsourced clinical trials.

Introduction

Introduction

- ▶ This “Avoca CRO Oversight Survey” explored respondents’ views and experiences regarding:
 - ◆ Satisfaction with quality
 - ◆ Delivery of quality versus sponsor expectations
 - ◆ Needs, issues and best practices in the delivery of quality
 - ◆ Perceived quality of deliverables of clinical service providers by geographic region
 - ◆ The extent to which companies are being proactive about ensuring high quality
 - ◆ Management of third party vendors and the impact on quality
 - ◆ Quality considerations in selection of CROs and selection of sites

Methods

Methods: 2011 Avoca Industry Survey

- ▶ Web-based survey, with links directing respondents to the appropriate instruments:
 - ◆ Sponsor perspective
 - ◆ Provider perspective

- ▶ “Quality” was defined as *“The ability to effectively and efficiently answer the intended question about the benefits and risks of a medical product or procedure while assuring patient safety and protection of human subjects.”*

- ▶ Respondents who completed the survey were offered an executive summary of the survey results.

- ▶ Data was scrubbed of entries that were inappropriate, duplicate, etc.
 - ◆ Small consultancies and sites were excluded from this analysis.

Respondents

Respondents: 2011 Avoca Industry Survey

- ▶ 247 surveys

- ◆ 104 sponsor surveys

- 73% pharma, 17% biotech
 - 52% “Top 20”
 - 44% Operations, 40% Outsourcing
 - 17% executives, 58% middle management

- ◆ 143 provider surveys

- 78% CROs
 - 64% “Top 20”
 - 38% Operations, 31% BD, 22% Management
 - 48% executives, 39% middle management

List of Sponsor Companies

List of Sponsor Companies

| | | | |
|-------------------------|---------------------------------|----------------------------|---------------------------|
| Abbott | Cardiokine | GSK | Otsuka |
| Achaogen | Cardiome | Hoffmann La Roche | Pfizer |
| Actavis | Celgene | Incyte | Prosidion |
| Adnexus | Celtic Therapeutics Development | J&J PRD | Purdue Pharma |
| Allergan | Cordis | Janssen | Regeneron |
| Allon Therapeutics | Covidien | JCRCO | Sanofi Pasteur MSD |
| Amgen | CR Bard | Johnson & Johnson | Shire Pharmaceuticals |
| ArthroCare | CTI | LEO Pharma A/S | Sticares InterACT |
| Astellas Pharma | Cubist Pharmaceuticals | Louisville Bioscience | STS Biomedical Consulting |
| AstraZeneca | Eisai | Lundbeck | Swedish Orphan Biovitrum |
| Bard Electrophysiology | Endo | Lupin Limited | Takeda |
| Bayer Healthcare | Ferring Pharmaceuticals | Merck | Theratechnologies |
| Biogen Idec | Five Prime Therapeutics | Millennium Pharmaceuticals | UCB |
| Biotest AG | Forest Research Institute | Novo Nordisk | Vicus Therapeutics |
| Boehringer Ingelheim | Genzyme | Nycomed | |
| Bristol-Myers Squibb | GRT | OPDC | |
| Cadence Pharmaceuticals | Grünenthal | Orion Pharma | |

List of Provider Companies

List of Provider Companies

| | | | |
|-----------------------------------|-----------------------------------|---|---------------------------------|
| Accovion | Coram Clinical Trials | LatAm Clinical Trials | Quest Diagnostics |
| Acurian | CoreLab Partners | MEDTOX | Quintiles |
| Allphase Clinical Research | Covance | MedTrials | Radiant Research |
| Almac | CRF Health | MGH Clinical Trials Network and Institute | REGISTRAT MAPI |
| Asiatic Clinical Research | Crown CRO Oy | Myoderm | ResearchDx |
| Averion International | CTI | Nuvisan Pharma Services | RPS |
| AXIS Clinicals | Cyncron | Ockham | S&P Pharmaterra Management |
| BioClinica | Datatrial | Omnicare Clinical Research | SIRO Clinpharm |
| BioStorage Technologies | EastHORN Clinical Services in CEE | Paragon Biomedical | SRA Global Clinical Development |
| Cancer Research And Biostatistics | ERT | PAREXEL International | Stefanini TeachTeam |
| Chiltern | Global Clinical Trials | PharmaNet Development Group | Sticares InterACT |
| Clearstone Central Laboratories | Harrison Clinical Research | Pharm-Olam International | Stiris Research |
| Clinical Resource Network | ICON | PHT Corp. | Synteract |
| Clinical Solutions | Imaging Endpoints | Popsi Cube | TFS International |
| Clininvent | IMPACT Core | PPD | The Clinical Resource Network |
| Clinlogix | INC Research | PRA International | Trio Clinical research |
| Community Research | Kendle International | ProTrials Research | University of Hull |
| COMSYS | LabConnect | PSI | |

Results: Part 1

Part 1:

Is there an issue with quality in outsourced clinical trials?

If so, what specific areas are problematic?
In what areas is quality strong?



Results: Part 1

Sponsor Point of View



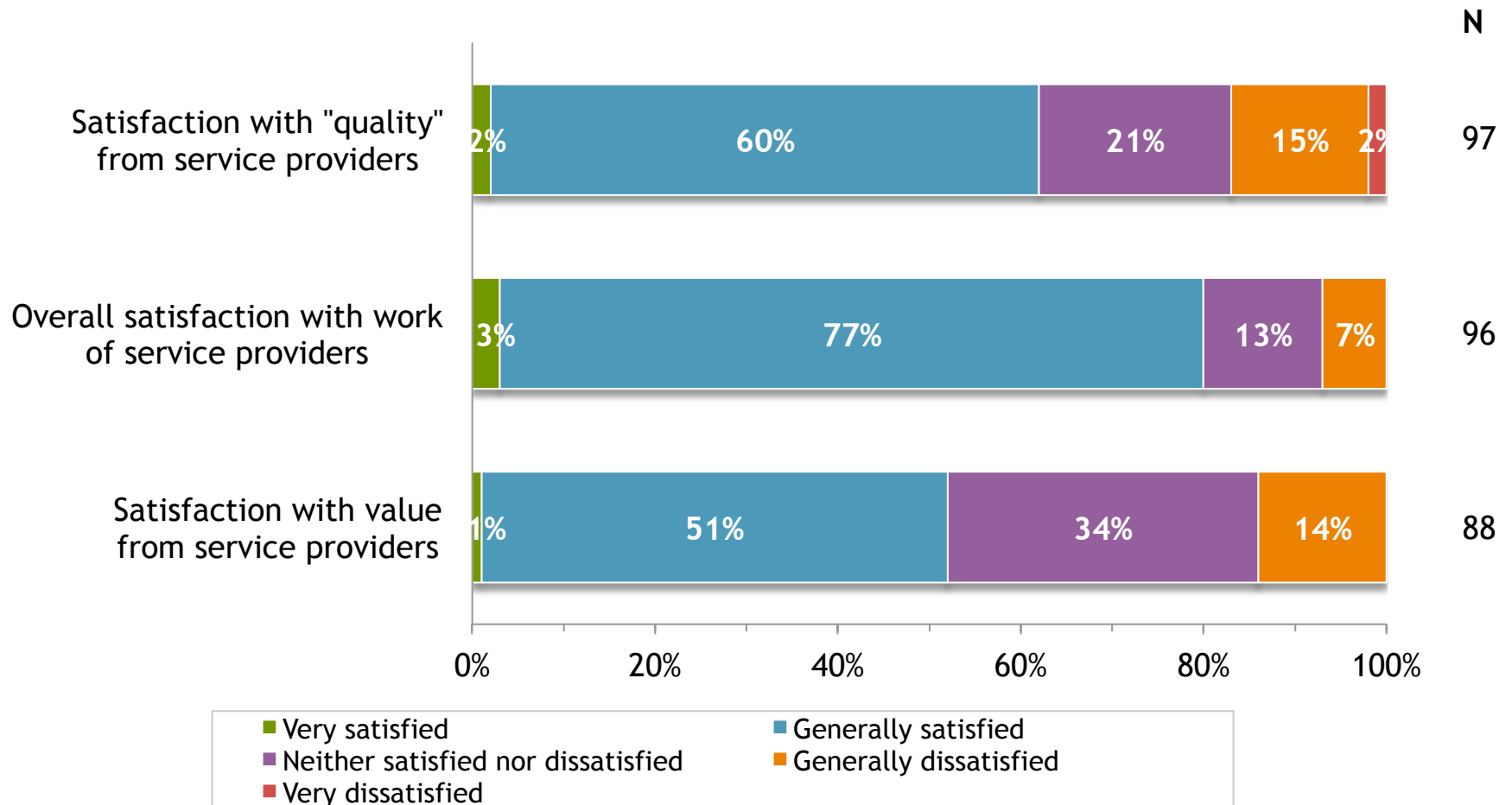
Sponsors: Is there an issue with quality in outsourced clinical trials?

Sponsors: Is there an issue with quality in outsourced clinical trials?

- ▶ Sponsors were asked to rate their overall levels of satisfaction with the quality they received from service providers. Slide 11 shows the results.
 - ◆ Only slightly over half of sponsors were satisfied with providers' delivery of quality overall. Seventeen percent were quite dissatisfied. Thus for a significant fraction of sponsors, failure of providers to deliver a satisfactory level of quality appears to be an issue.
 - ◆ For the sake of comparison, the other bars on the following slide provide the figures for satisfaction with the work of service providers overall and satisfaction with the value received for outsourcing spend.
- ▶ Underscoring the notion that quality is an issue for outsourced clinical trials in particular is the data on Slides 12 and 13.
 - ◆ Regarding Slide 12, sponsors were asked to compare the quality delivered by their CROs over the last 3 years to that delivered by in-house teams. Of those who could answer the question, more than half stated that the quality delivered by CROs was worse than that delivered by in-house staff.
 - ◆ Regarding Slide 13, sponsors were asked what they felt to be the root cause of the recent increase in FDA warning letters. Most of the most common responses had to do with outsourcing.

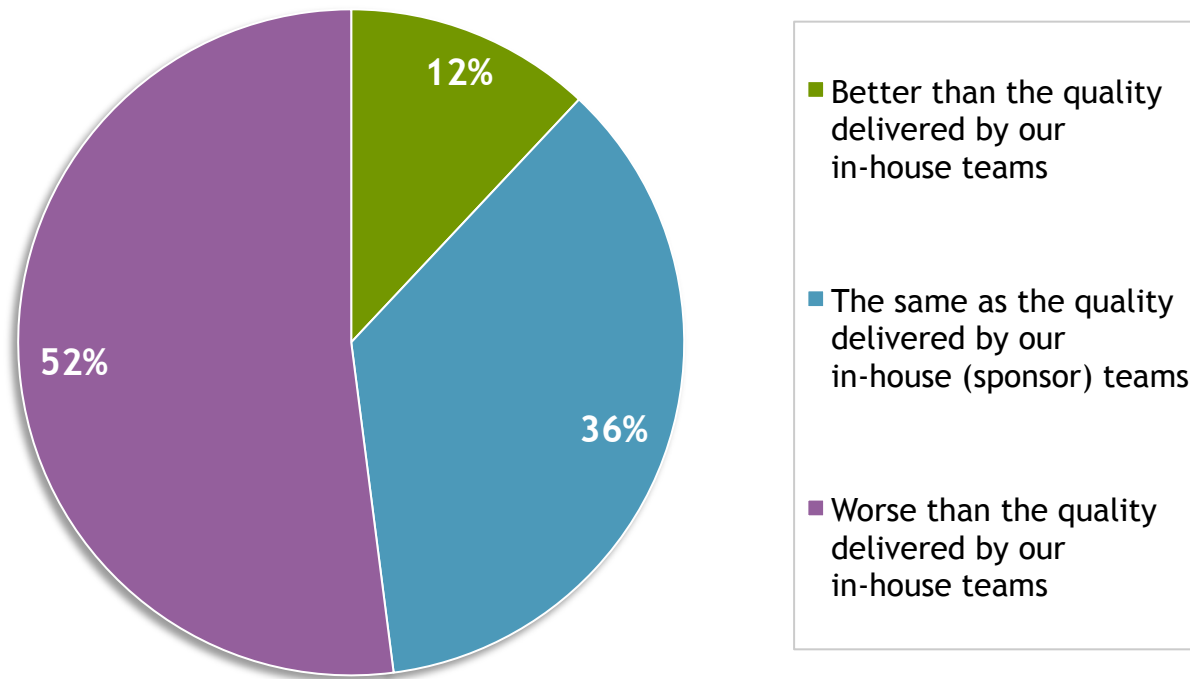
Sponsors: Overall Satisfaction

Sponsors: Overall Satisfaction with Service, Value, and Quality



Sponsors: Satisfaction with Quality

Over the last 3 years, the quality delivered by our CROs has been:



N=50

Sponsors: Root Cause of Quality Issues

Root Cause of Increase in FDA Warning Letters

- ▶ Sponsors were asked what they felt to be the root cause of the recent increase in FDA warning letters.
- ▶ Of the most common responses, listed below, most had to do with the outsourcing of clinical trials:
 - ◆ Increased levels of clinical research outsourcing
 - ◆ Inadequate performance/lack of accountability by CROs
 - ◆ Inadequate sponsor oversight of CROs
 - ◆ Political pressure on the FDA to intensify oversight function.
- ▶ Other themes among the responses included:
 - ◆ Selection of and/or sponsor failure to close inadequately-performing sites
 - ◆ Excessive delegation by Principal Investigators
 - ◆ Overly complicated protocols, coupled with insufficient training
 - ◆ Inadequate use of “Lessons Learned”
 - ◆ Globalization of clinical trials.

Sponsors: Satisfaction with Quality

Specific Areas of Quality Satisfaction and Dissatisfaction

- ▶ The survey asked sponsors to rate their levels of satisfaction for 15 different aspects of quality in outsourced clinical trials.
- ▶ Areas with relatively high dissatisfaction (dissatisfaction rates of 22% - 31%) included:
 - ◆ Oversight of third party vendors
 - ◆ Governance of quality
 - ◆ Communications surrounding quality
 - ◆ Availability of quality personnel for projects
 - ◆ Efficiency/timeliness in achieving clean data
 - ◆ Adherence to monitoring plan
- ▶ Areas with relatively high satisfaction (satisfaction rates of 51% - 66%) included:
 - ◆ Compliance with SOPs and other written procedures
 - ◆ Data quality and integrity
 - ◆ Audit plans and execution

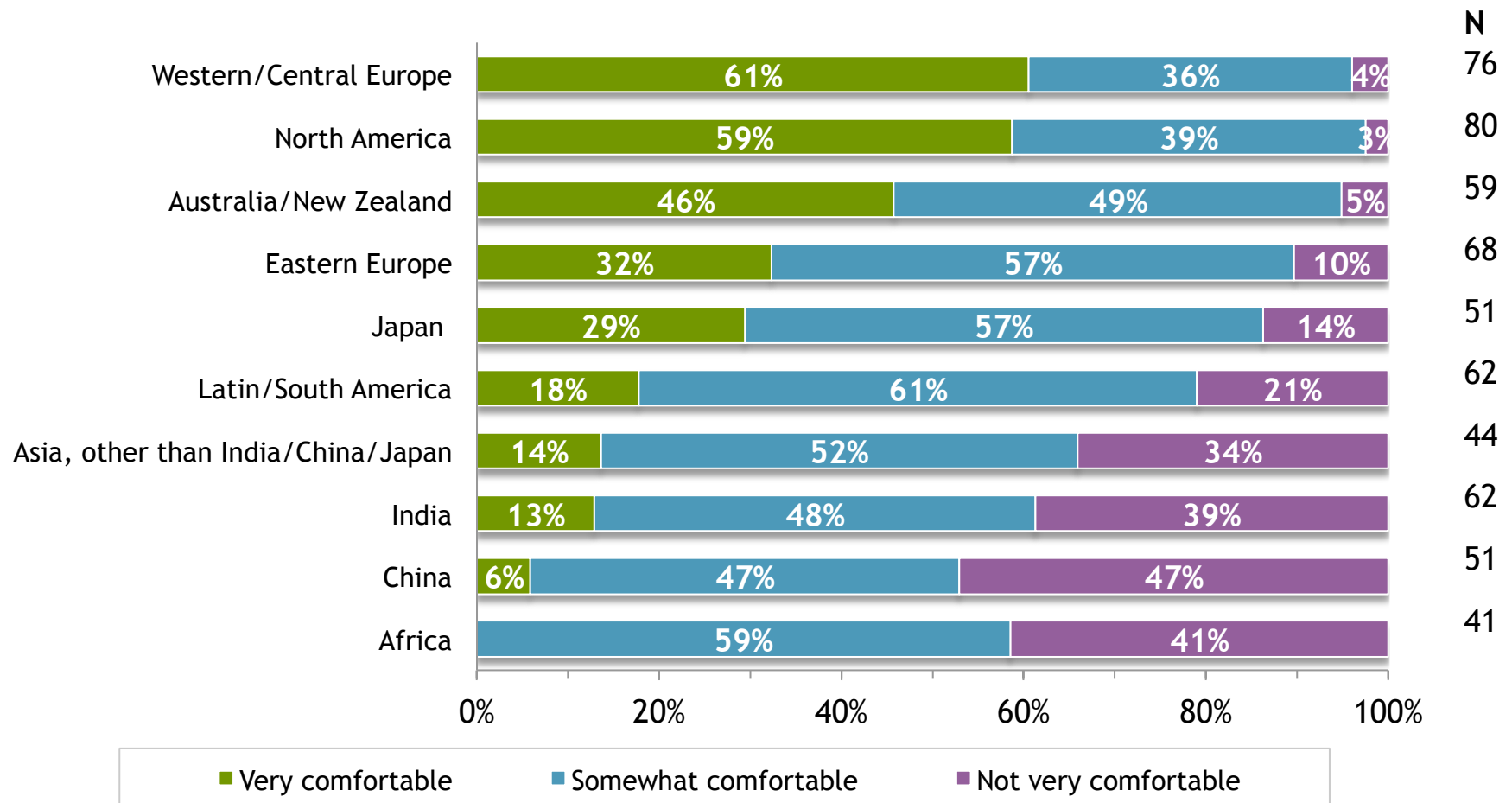
Sponsors: Satisfaction with Quality

Quality Satisfaction and Dissatisfaction by Region

- ▶ The survey also asked sponsors to rate their comfort levels with the quality of deliverables and services provided by clinical service providers in different regions.
- ▶ As can be seen in the green bars of Slide 16, Western and Central Europe and North America were the only regions for which most sponsor respondents were very comfortable. Comfort rates declined substantially for deliverables and services coming out of Asia, Latin America, and Africa.
- ▶ On the other side of the spectrum, in purple, high fractions of the respondents were quite uncomfortable with the quality of deliverables and services coming from providers in many of the “emerging” regions.

Sponsors: Quality by Region

Overall level of comfort with the quality of deliverables/services provided by clinical service providers in each region



Results: Part 1

Provider Point of View



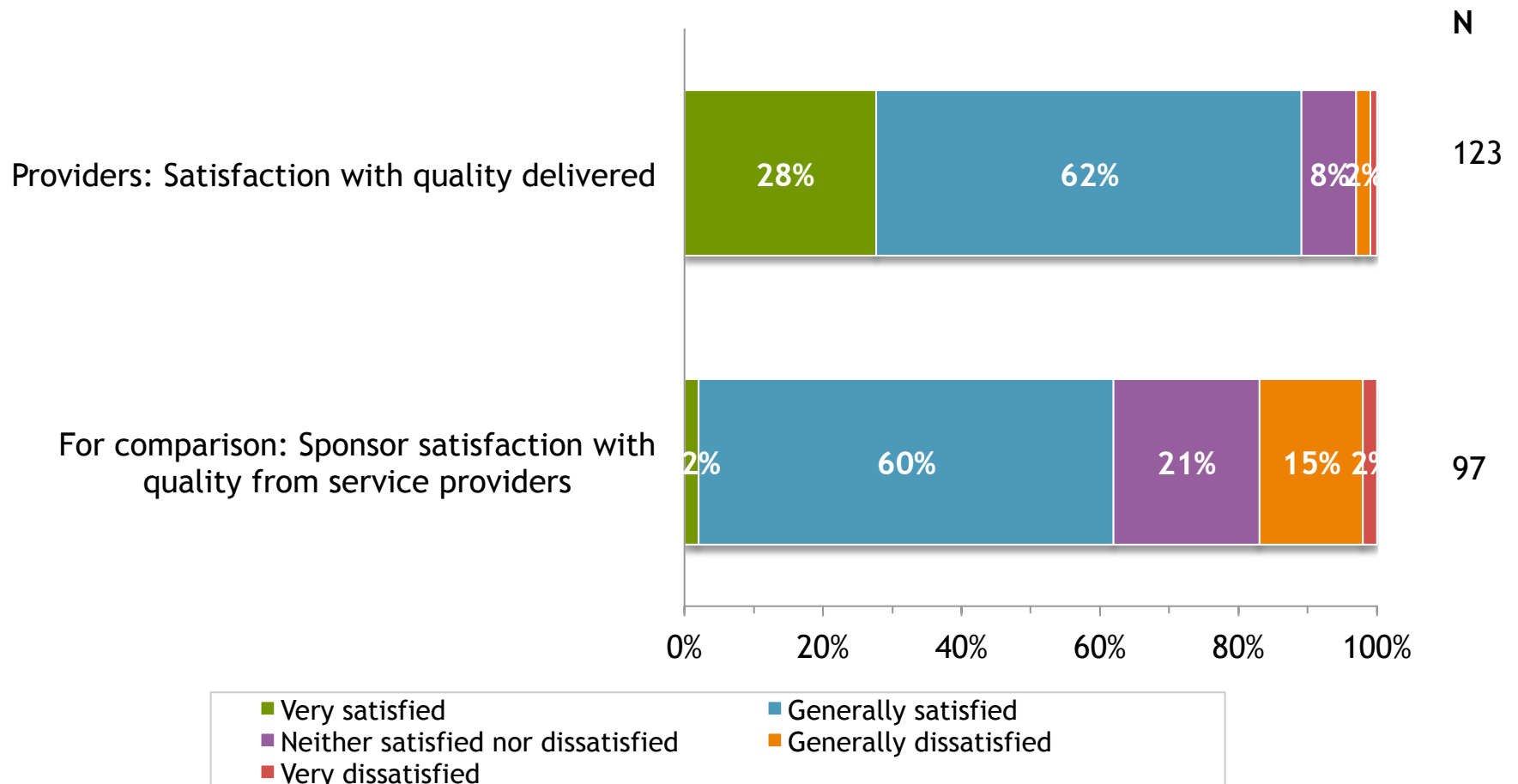
Providers: Is there an issue with quality in outsourced clinical trials?

Providers: Is there an issue with quality in outsourced clinical trials?

- ▶ Providers were asked to rate their satisfaction with the “quality” they delivered for sponsors. Slide 19 provides the detailed distribution of the results.
 - ◆ The results were strikingly positive: 28% of provider respondents were very satisfied with the quality they delivered, an additional 62% were generally satisfied, and only a tiny fraction was dissatisfied.
 - ◆ For comparison, the sponsor data from slide 11 is presented here again. This juxtaposition illustrates the large gap between how providers feel they deliver on quality and how sponsors feel about the quality they receive.
- ▶ This gap was also seen when specific areas of quality delivery were examined (data not shown).
- ▶ The pattern of comfort with quality by region among providers was similar to that seen among sponsors, except that providers were more confident about quality in the developed regions traditionally used for clinical trials (Western Europe, North America)(Slide 20).

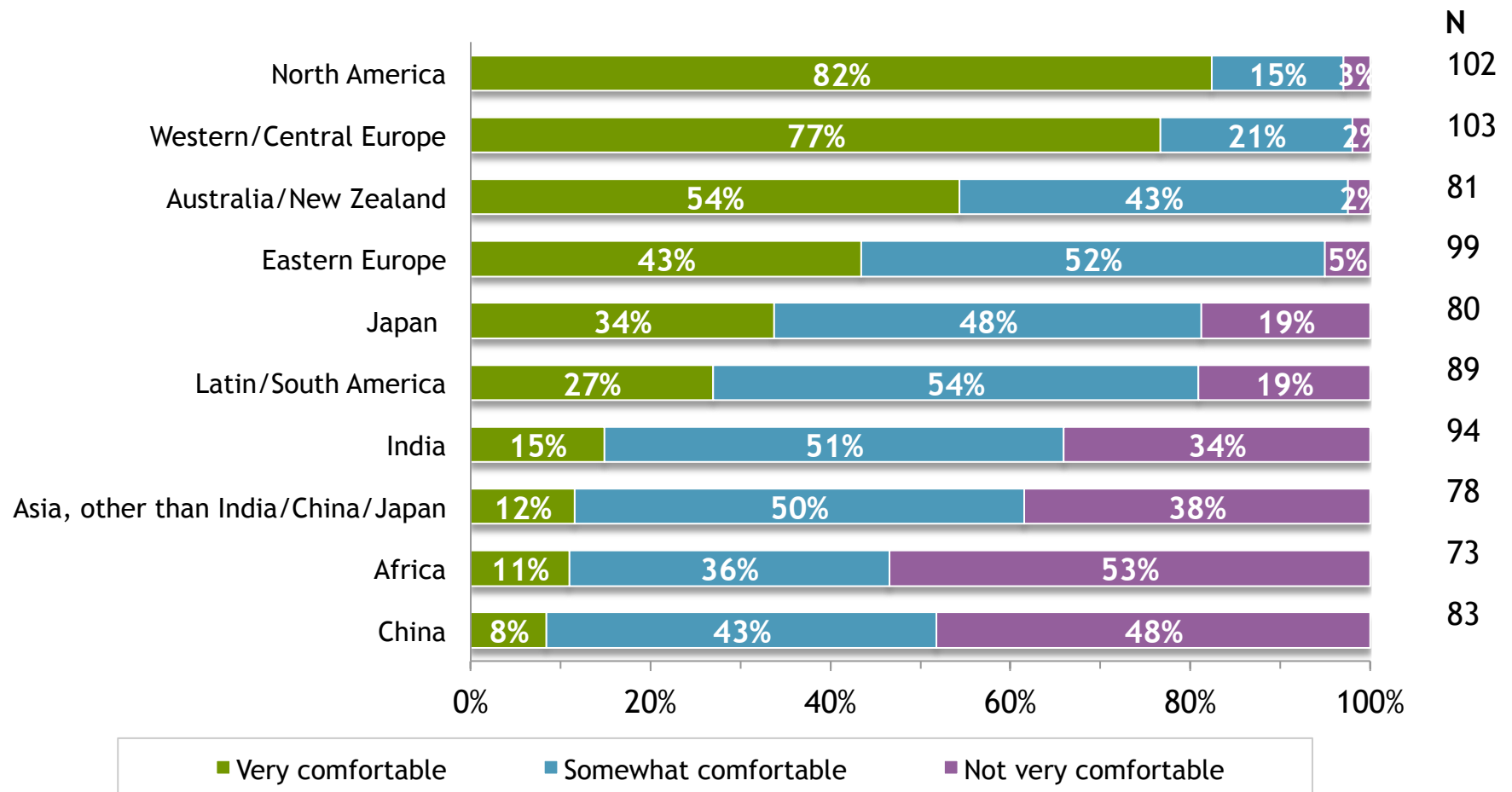
Provider Satisfaction

Overall, how satisfied have you been with the “quality” that your company has delivered for its sponsors in the last 3 years?



Providers: Quality by Region

Overall level of comfort with the quality of deliverables/services provided by clinical service providers (including your own company) in each regions.



Results: Part 2

Part 2:

Why are we having issues surrounding quality in outsourced clinical trials?

Why is there such a big gap in perception between sponsors and providers?



Causes of quality issues in outsourced clinical trials

Causes of Quality Issues in Outsourced Clinical Trials

- ▶ Sponsor and provider respondents were asked to describe what they felt to be the causes of quality issues in outsourced clinical trials.
- ▶ The statistics and quotations in the following slides illustrate some of the main themes in their responses, with a focus on those that help to explain the gap between sponsors and providers in perceptions of quality delivery. These themes include:
 - ◆ Inability of clinical service providers to consistently perform to their potential due to constraints placed by sponsors:
 - Costs
 - Processes/procedures
 - Timelines
 - Decision-making (including about site inclusion/closure)
 - Lack of expectation-setting
 - ◆ Cost pressures on the industry

Causes of Issues with Quality

“CROs, as service providers, are heavily incented to deliver and measure quality - and are prepared to do so. Too many sponsors are not prepared to do their part in assuring a relationship focused on quality. So CROs are forced to implement one model for sponsors ready to focus on quality, and another for the many focused on activities and unit-level cost.”

- Quotation from a Provider Respondent

Causes of Issues with Quality

Cost Pressures:

72% of provider respondents feel that there is a correlation between the demand for decreased prices by sponsors and an overall lowering of quality by CROs.

“The focus on price has driven out the reality of adequate monitoring and proper Quality Control processes to ensure quality at the site level.... Too many procurement officers are making decisions purely on cost without regards to quality product.”

“Price pressures, especially discounts..., have caused some CROs to cut corners and send work to low cost regions without adequately trained staff.”

Causes of Issues with Quality

Sponsors Decision-Making with Impacts on Quality (without provider input):

- ▶ Oversight
- ▶ Protocol design
- ▶ Investigators
- ▶ Timelines
- ▶ Regions
- ▶ Third-party vendors

“It is difficult to ensure quality for a functional provider for monitoring, when the protocol design/site selection are done by another CRO/ sponsor.”

“There is a percentage of work that we perform that is working with the Sponsor processes, etc...in these circumstances, quality, timeliness, training, governance and oversight are dictated by Sponsor requirements.”
“These documents are very poor when it comes to trial execution and quality oversight.”

Causes of Issues with Quality

Sponsor Failure to Proactively Make Decisions or Communicate with Providers about Quality Expectations

- ▶ Only 55% of sponsors are satisfied with their companies' identification of process/deliverables for which quality expectations of CROs need to be set.
- ▶ Only 58% feel that their companies effectively communicate quality expectations to CROs.

Results: Part 3

Part 3:

What can be done?



What can be done?

What can be done?

- ▶ In the survey, sponsor respondents were provided with descriptions of quality oversight practices and were asked to state whether or not their companies engaged in each practice, and, in some cases, to rate their companies' performance with respect to each.
- ▶ In the data analysis, we explored associations between specific quality-management practices and sponsor satisfaction with the work performed by CROs. We also explored associations between specific quality-management practices and a sponsor-perceived need to micromanage in order to ensure quality.
 - ◆ Our intention was to identify practices or sets of practices that were associated with higher probability of a successful outcome and/or lower need for micromanagement.

What can be done?

What can be done?

- ▶ The following slides illustrate a selection of the results of these analyses.
 - ◆ Slide 29 discusses the association between proactive quality management, increased satisfaction, and decreased need for micromanagement.
 - ◆ Slide 30 illustrates the association, among sponsors, between use of written Quality Agreements and overall satisfaction with the work performed by clinical service providers. As can be seen, 94% of sponsors who use written Quality Agreements are satisfied, as opposed to 59% of those who do not use written Quality Agreements.
 - ◆ Slide 31 illustrates the association, among sponsors, between use of adequate metrics in contracts with CROs, and overall satisfaction with the work performed. As can be seen, 94% of sponsors who use adequate metrics in this manner are satisfied, as opposed to 64% of those who do not have adequate metrics or do not use them in this manner.
 - ◆ Slide 32 discusses sponsors' satisfaction with formal, risk-based approaches to CRO oversight and site monitoring.

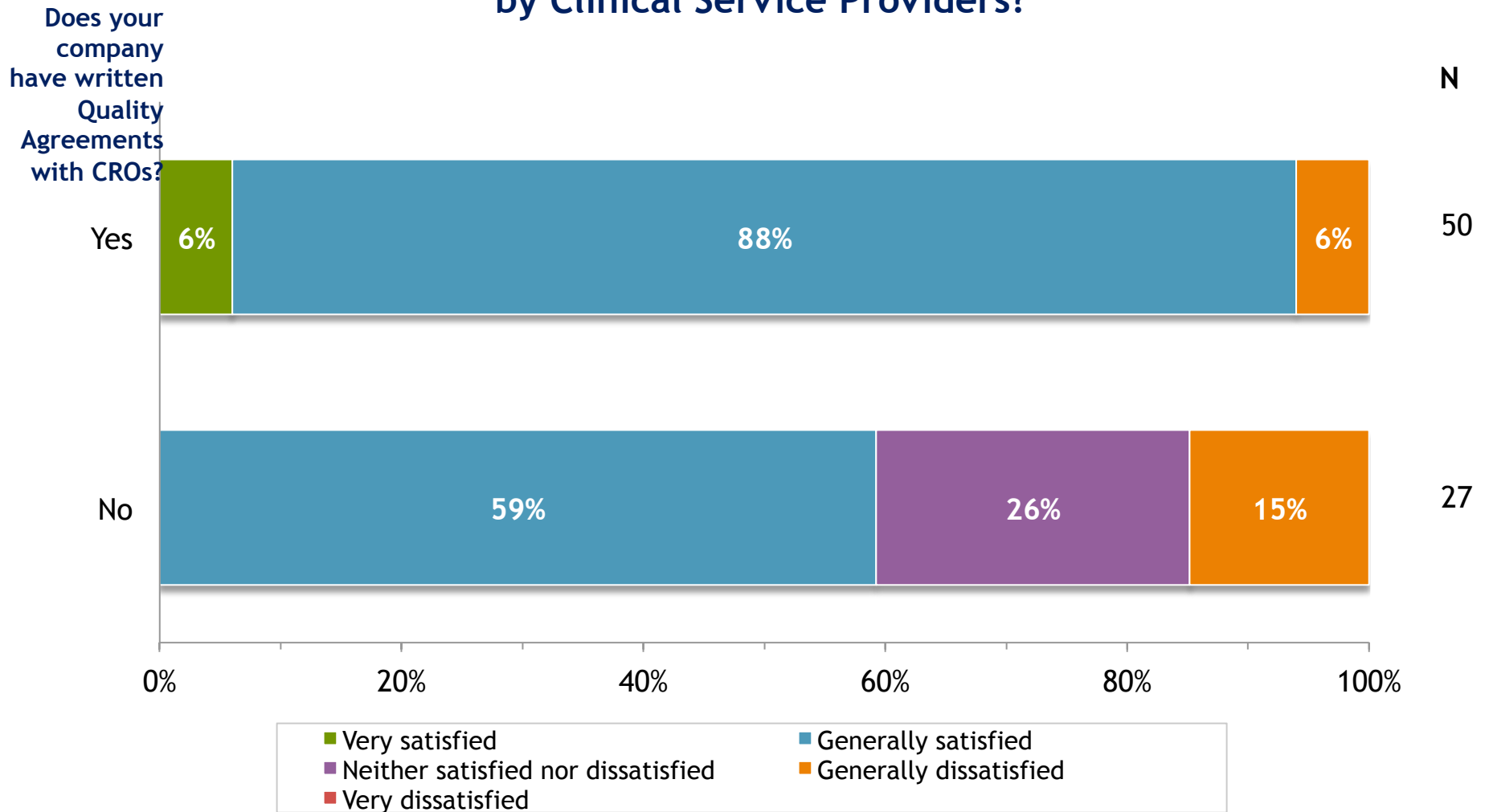
Sponsors: Management of Quality

Sponsor Respondent Self-Ratings Regarding Quality Management

- ▶ Among the sponsor group as a whole, ratings were relatively high for “reactive” management of quality in outsourced clinical trials
 - ◆ 80% were satisfied with their companies’ corrective actions in response to quality reviews.
- ▶ Ratings were relatively poor for “proactive” management of quality in outsourced clinical trials.
- ▶ Sponsors with strong “proactive management” responses were most likely to be satisfied with the service delivered by their providers.
- ▶ Sponsors with weak “proactive management” scores were the most likely to feel that micromanagement of providers was necessary to ensure adequate quality.

Example: Quality Agreements

Overall, how satisfied are you with the work that has been done for you by Clinical Service Providers?



Example: Quality Metrics

Overall, how satisfied are you with the work that has been done for you by Clinical Service Providers?

Metrics are adequate in scope and design, and incorporated into contracts with CROs?

N

Yes to all

6%

88%

6%

18

No to all

64%

18%

18%

11

0%

20%

40%

60%

80%

100%

Very satisfied

Neither satisfied nor dissatisfied

Very dissatisfied

Generally satisfied

Generally dissatisfied

Sponsors: Management of Quality

Other Approaches to Managing Quality While Containing Costs

- ▶ **39% of sponsors use a formal, risk-based approach to levels of CRO oversight**
 - ◆ 44% stated that their experiences were primarily positive; 53% mixed
- ▶ **57% of sponsors and 58% of CROs use a formal, risk-based approach to levels of site monitoring**
 - ◆ About 2/3 have had primarily positive experiences; about 1/3 mixed

Thank you

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