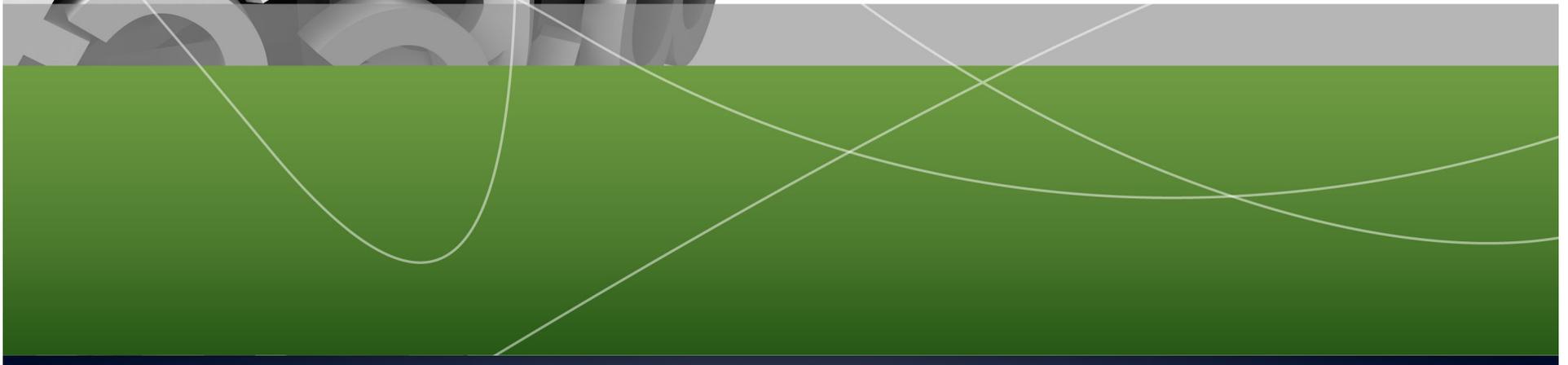




The 2013 Avoca Report

*Sponsor and Provider
Perceptions on Managing
Clinical Development Risk*

Executive Summary



2013 Avoca Research Overview

Introduction

- Each year The Avoca Group surveys industry executives and managers to understand trends in clinical development, with a particular focus on outsourcing dynamics and relationships between research sponsors and providers.
- Over the past several years we have participated in numerous conversations with biopharmaceutical companies and providers on the topic of risk reduction in the clinical development process.
- According to various sources and published metrics, the industry remains challenged by relatively low success rates for compounds in clinical development, and this has prompted many organizations to explore ways of reducing the risk associated with the clinical development process.
- With this in mind, Avoca chose to perform a comprehensive assessment of the methods used to evaluate and manage risk in outsourced clinical trials for our 2013 Industry Survey, with a focus on risk sharing models, risk assessment, risk management and risk-based monitoring.
- This report serves as an Executive Summary of key findings from the research.

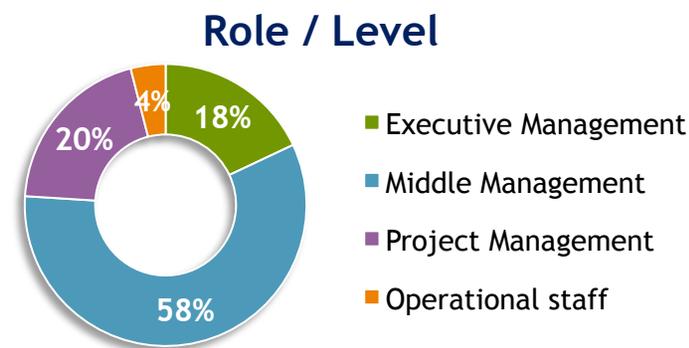
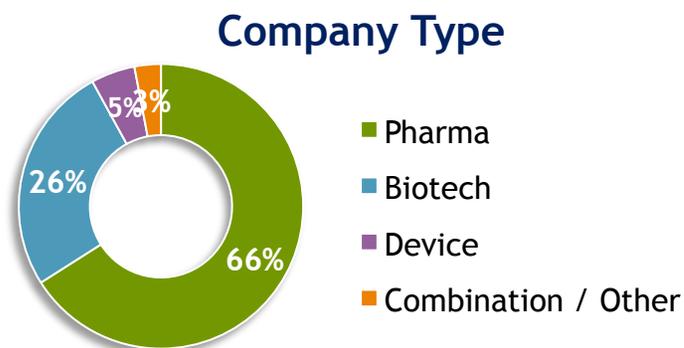
2013 Avoca Research Overview

Questions Explored

- **Risk-sharing models:** What types of models are used most often? Under what circumstances? What is the magnitude of incentives/penalties? Have the incentives/penalties been successful? Is success realized predominantly by improvements in time, cost, or quality? What have been the downsides?
- **Risk assessment:** Is it formally done? How is it done? To what extent are assessments qualitative vs. quantitative? Have they been successful? In what ways have they worked and in what ways have they not?
- **Risk-based management approaches:** To which tasks have such approaches been applied (e.g. monitoring, CRO management)? Have the approaches used formal quantitative modeling, or have they been qualitative? Have they been successful? Is success realized predominantly by improvements in time, cost, or quality? What have been the downsides? Are there any issues related to regulatory acceptance?

Respondent Demographics: Sponsors

113 respondents from 70 companies; ~1/2 in Top 20 (by revenue)

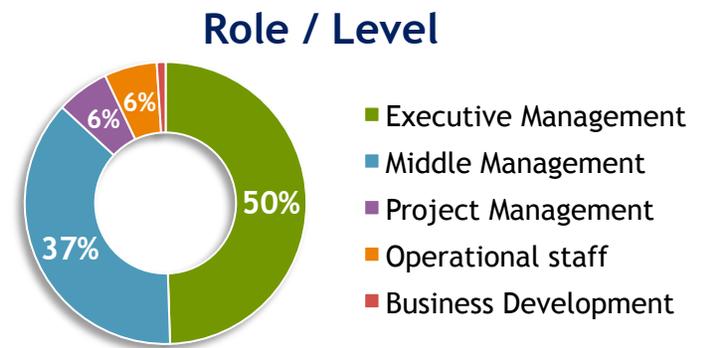
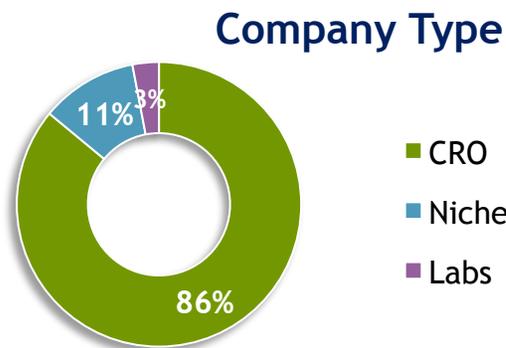


Companies Represented

| | | | |
|---------------------------------|--------------------------------|---|--|
| Abbott Diabetes Care | Creabilis | Johnson & Johnson | Roche |
| Abiomed | Cubist | JRD | Sangart |
| Actavis | Denmark | Lundbeck | Sanofi |
| Alexion | Eisai | Mallinckrodt / Covidien Pharmaceuticals | Santhera Pharmaceuticals Switzerland Ltd |
| Allergan | Elan Pharmaceuticals, Inc. | MannKind Corporation | Savient Pharmaceuticals |
| Amgen | Eli Lilly | MedImmune | Seattle Genetics |
| Amgen / Bergamo | Endo | Merck | Shire Pharmaceuticals |
| Apollidon | Firstkind Ltd | Merck KGaA | SSI |
| ASLAN Pharmaceutical | GE Healthcare | Merck Serono | Stiefel, a GSK Company |
| AstraZeneca | Genentech | Millennium | Sunovion Pharmaceuticals |
| Bavarian Nordic | Genzyme | Mundipharma Research Limited | Teva Pharma |
| Boehringer Ingelheim | Gilead Sciences Europe Ltd | NHS | ThromboGenics NV |
| Biogen Idec | GlaxoSmithKline | Ono Pharma USA, Inc | Unilever |
| BioMarin | Grunenthal | Orion Pharma | Warner Chilcott |
| BMS | Hospira | Otsuka | Wesley Coe |
| BTG | Inovio Pharmaceuticals | Panacea Biotech Ltd. | WomanCare Global |
| Celtic Therapeutics Development | Ipsen US | Pfizer | |
| Cerexa | Janssen Research & Development | Purdue Pharma | |

Respondent Demographics: Providers

124 respondents from 66 companies; ~60% in Top 20 (by revenue)



Companies Represented

| | | | |
|---------------------------------|--------------------------|-------------------------------------|----------------------------------|
| Acurian | CTB Solutions, Inc | Illingworth | QED Clinical Services Ltd |
| Aptiv Solutions | Cytel | INC Research | QPS Holdings, LLC |
| Axxiem | Datatrial | inSeption Group, LLC | Quintiles |
| BioStorage Technologies | DaVita Clinical Research | inVentiv Health Clinical | RDP Clinical Outsourcing |
| Cato Research Ltd. | DOCS Global Inc. | IRB Services | Research Pharmaceutical Services |
| CCRS Ltd | ERT | Makrocare Clinical Research Pvt Ltd | Researchnurses.co |
| Cerafor Limited | Eurofins | MGH | Social & Scientific Systems |
| Chiltern | EUROTRIALS | Mitsubishi Chemical Medience Corp | TFS International |
| ClinAudits LLC | Execupharm | PAREXEL International | Theorem Clinical Research |
| Clinical Start Up Solutions Ltd | Experis Clinical | PDP Couriers | UBC |
| Clinlogix | frictionless GmbH | PharmaCRO Inc. | Veeda CR |
| Clinstar LLC | gcc | PharmaNet/i3 | WCT Ltd |
| CluePoints | Greenphire | Pharm-Olam | Worldwide Clinical Trials |
| CompleWare Corporation | ICON Central Lab | Popsi Cube | WuXi AppTec |
| Covance | ICON Clinical Research | PRA International | Xceleron |
| CRF Health | ICON Medical Imaging | Premier Research | |
| Criterion, Inc. | Idis | PSI CRO AG | |

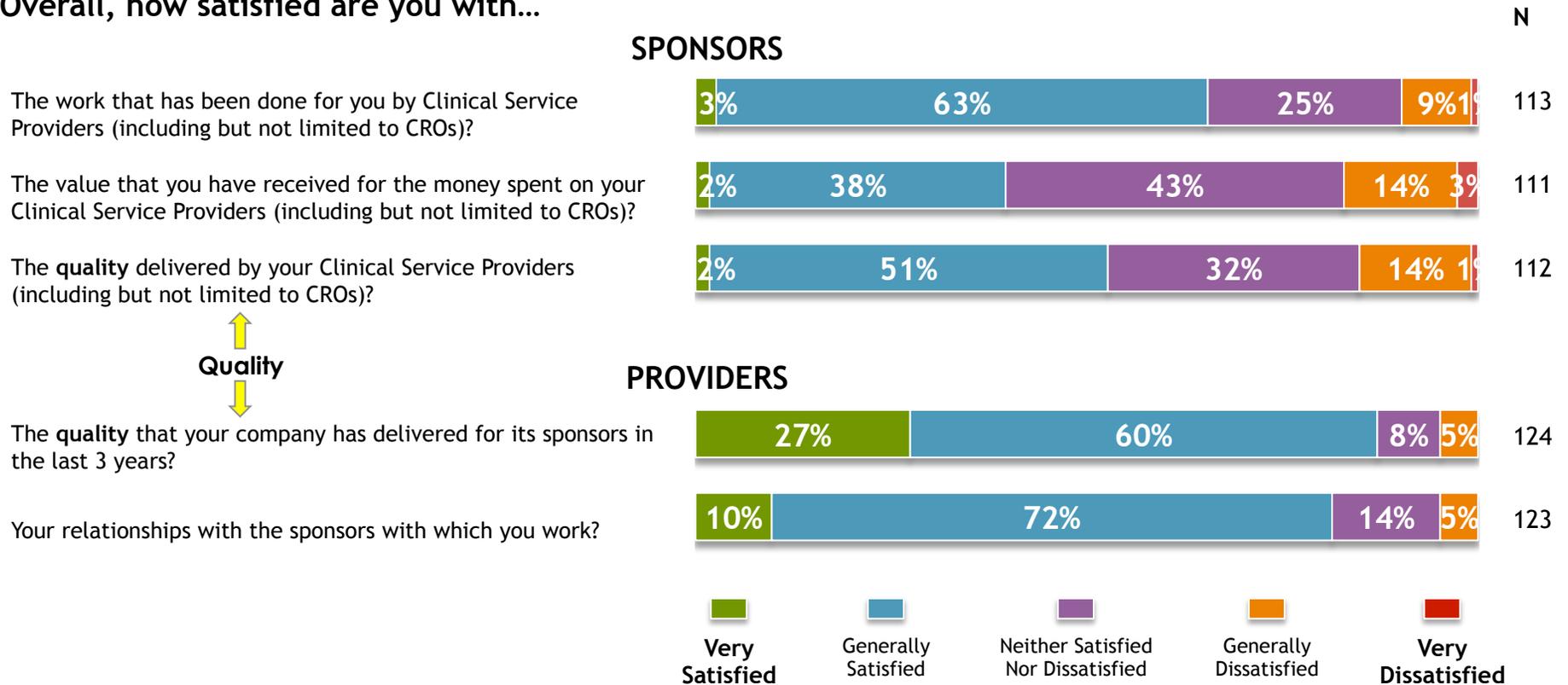
Overall Satisfaction

Sponsor and Provider
Perceptions

Satisfaction Levels: Sponsors vs. Providers

Respondents from Sponsor organizations reported lower levels of satisfaction than Provider respondents in several areas examined, including overall quality. This suggests that some personnel at Provider organizations may be overestimating the quality of their company's service when viewed from the perspective of Sponsors.

Overall, how satisfied are you with...



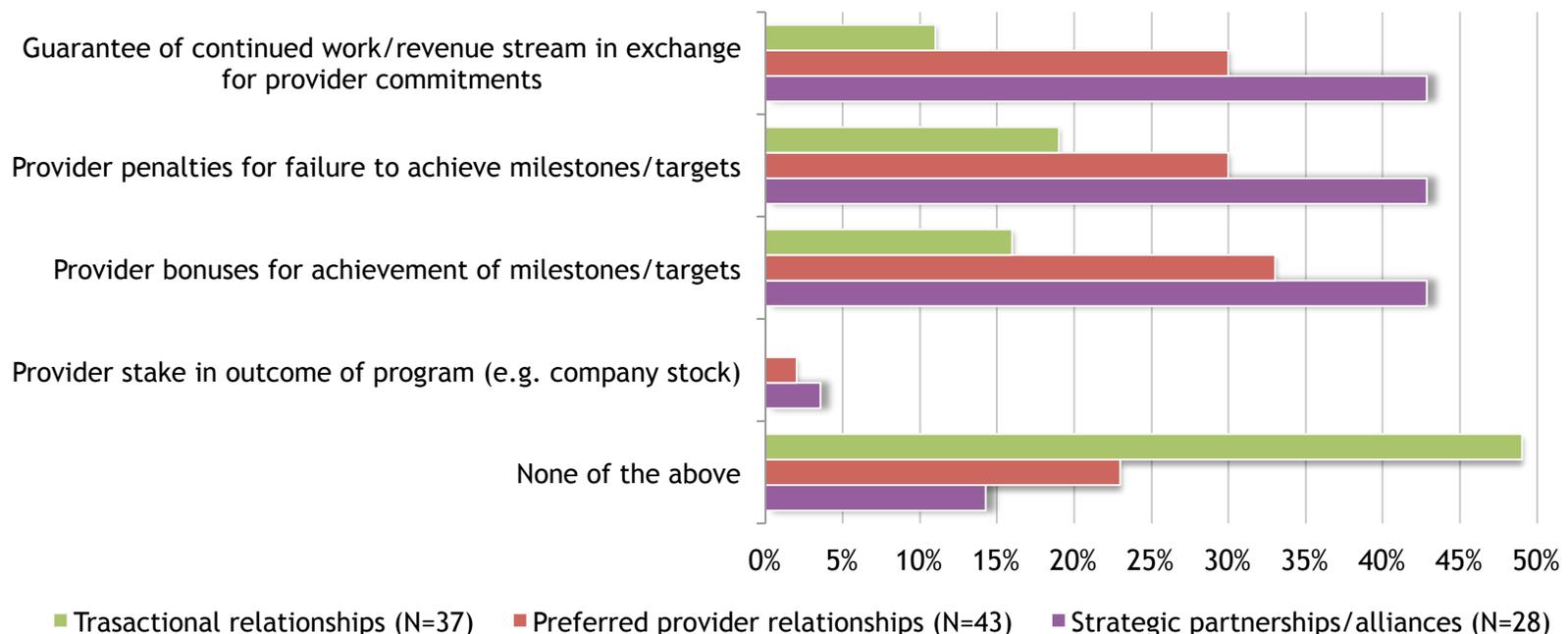
Risk-Sharing Models

Sponsor and Provider
Perceptions

Sponsor Risk-Sharing Model Usage

Respondents from Sponsor organizations that have deeper relationships with Providers were more likely to report having used risk-sharing models. Several models have been used by a similar proportion of respondents.

Risk-Sharing Models Used by Type of Relationship

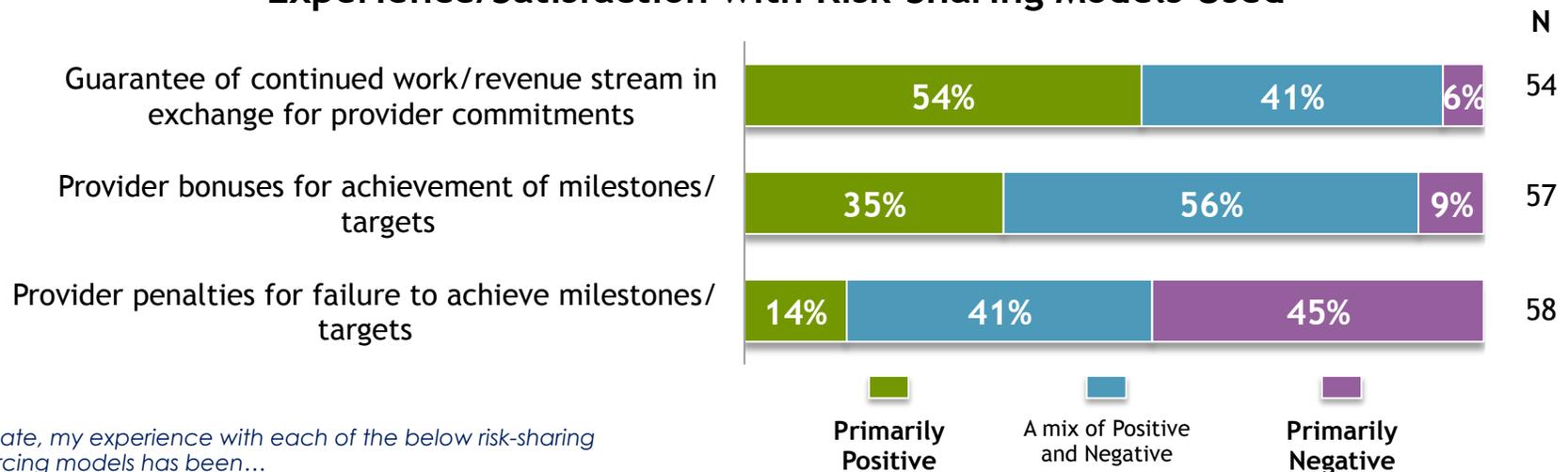


Q: For each of the types of outsourcing relationships listed in the column(s), which of the risk-sharing models listed in the rows has your company used?

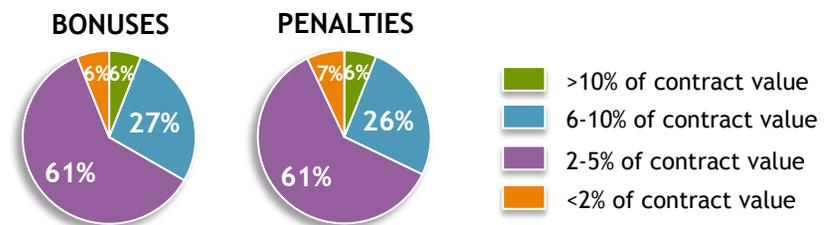
Sponsor Risk-Sharing Model Success

Sponsor respondents reported having the most positive experience with the use of guaranteed revenue streams in exchange for provider commitments, while the use of penalties drew significantly more negative responses. When respondents' companies employ risk-sharing models they are typically a low percentage of the contract value.

Experience/Satisfaction with Risk-Sharing Models Used



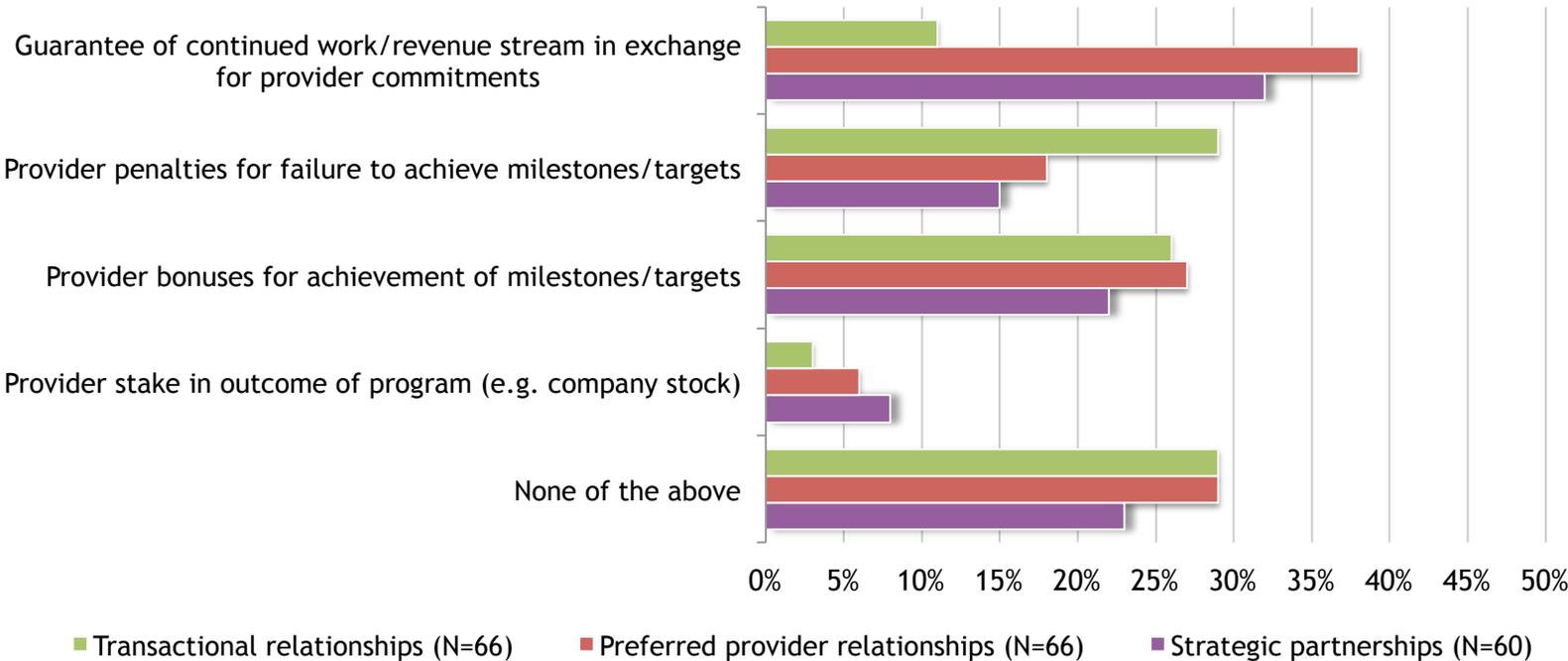
Q: When _____ are used as part of your company's risk-sharing arrangements, what is generally the magnitude of the maximum possible bonus/penalty?



Provider Risk-Sharing Model Usage

Usage of the different types of risk-sharing models evaluated varied among Provider respondents that have preferred provider relationships or strategic partnerships with Sponsors and those that have transactional relationships.

Risk-Sharing Models Used by Type of Relationship

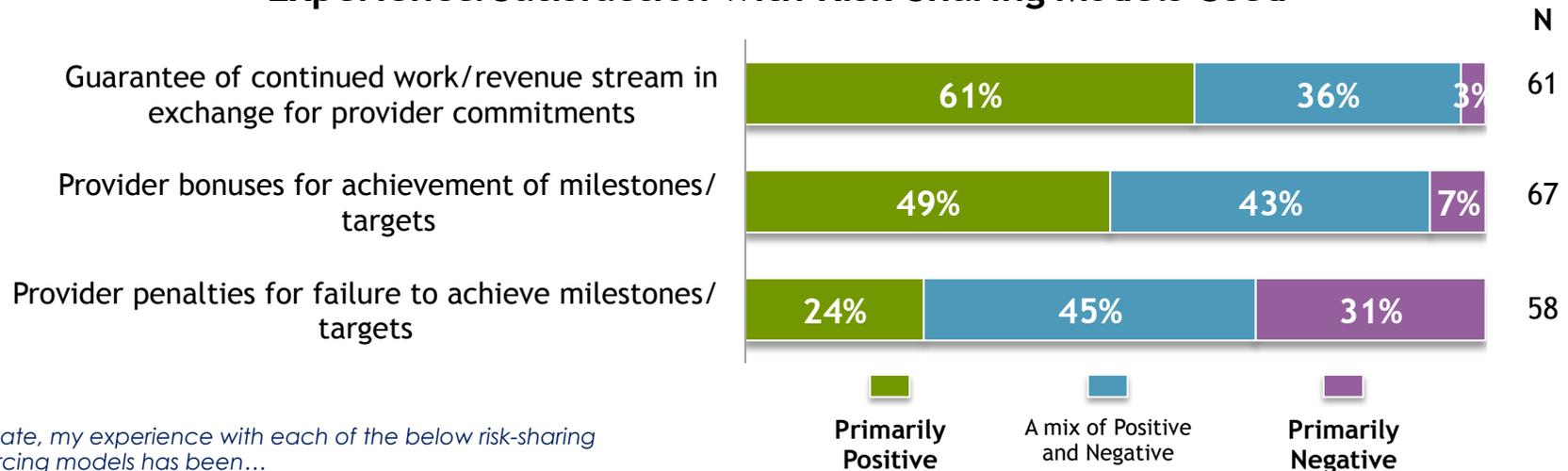


Q: For each of the types of outsourcing relationships listed in the column(s), which of the risk-sharing models listed in the rows has your company used?

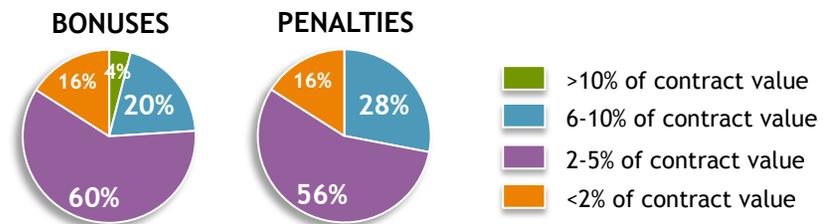
Provider Risk-Sharing Model Success

Providers perceptions align with Sponsors' with respect to having the most positive experience with the use of guaranteed revenue streams in exchange for Provider commitments and the most negative experience with the use of penalties. Overall, Provider perceptions of risk-sharing models were slightly more favorable.

Experience/Satisfaction with Risk-Sharing Models Used



Q: When _____ are used as part of your company's risk-sharing arrangements, what is generally the magnitude of the maximum possible bonus/penalty?



Elements of Risk-Sharing Relationships

Investing time to ensure both parties have a clear understanding of expectations at the beginning of a relationship and establishing and implementing effective Communication Plans appear critical to successful risk-sharing relationships.

In your experience, what is key to a successful approach to risk sharing?

Sponsor Themes:

- Trust
- Clear expectations
- Commitment on both sides
- Good communication
- Openness/Transparency
- Good relationship

Provider Themes:

- Trust
- Common expectations/goals
- Good communication
- Clear milestones
- Openness/Transparency
- Up-front planning

In your experience, what pitfalls should be avoided in an approach to risk sharing?

Sponsor Themes:

- Unrealistic expectations
- Poor planning
- Poor communication
- Cannot be one-sided

Provider Themes

- Unclear expectations
- Too much time
- Poor communication
- Cannot be one-sided

Risk Assessment and Management

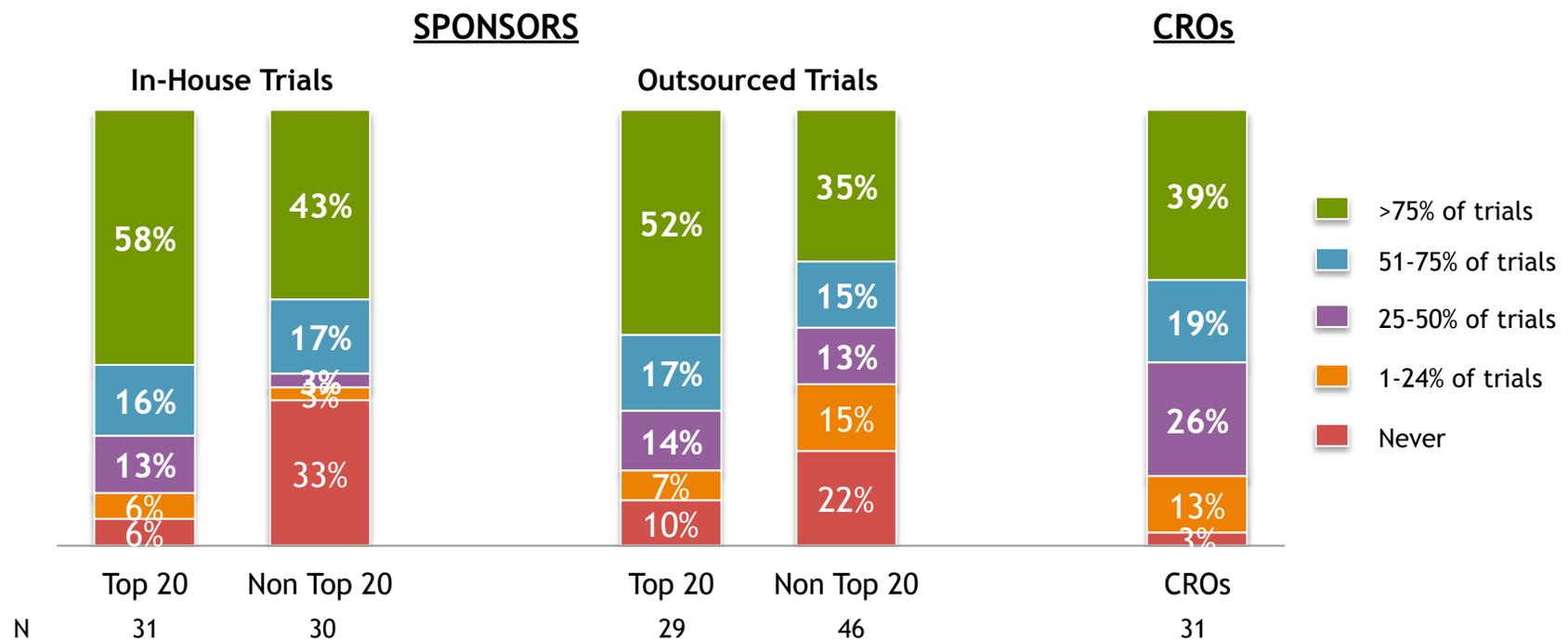
Sponsor and Provider
Perceptions



Systematic Risk Assessment Frequency

As a group, Sponsor respondents from Top 20 firms were more likely to report frequent use of systematic risk assessment processes for clinical trials than were those from Non-Top 20 firms, for both in-house and outsourced trials. The distribution of responses from CRO respondents was intermediate between those seen for different sized sponsors (for outsourced trials).

Usage Frequency of Systematic Risk Assessment Processes

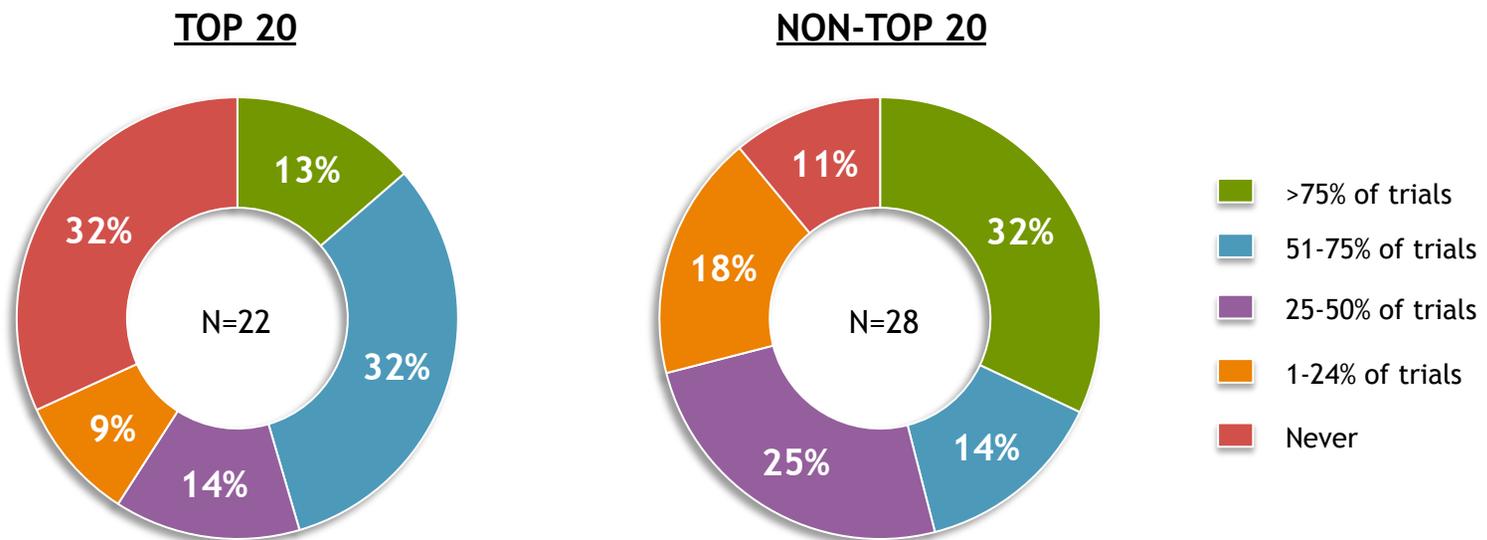


Q: How often do your company's project/program teams use a systematic risk assessment process for clinical trials managed and conducted by in-house teams?
 Q: How often do your company's project/program teams (including the CRO partners) use a systematic risk assessment process for outsourced clinical trials?

Systematic Risk Assessment Usage

While respondents from Top 20 companies were more likely to report frequent use of systematic risk assessment processes, respondents from Non-Top 20 firms were more likely to report frequent use of the information to drive the level of CRO oversight.

Use of Risk Related Information to Determine CRO Oversight

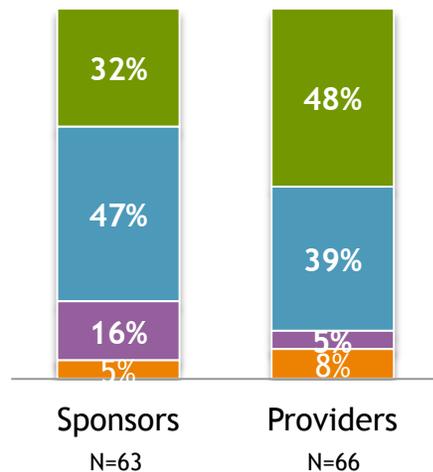


Q: How often do your teams use risk-related information to determine the level and/or type of sponsor oversight that you will employ for your CRO partners?

Systematic Risk Assessment Contributors

Both Sponsor and Provider respondents often reported that risk assessment was performed jointly; however, those who felt that it was performed primarily by one party were much more likely to report their company was primarily conducting the assessment than the other party. A variety of functional groups were reported to be involved in the process.

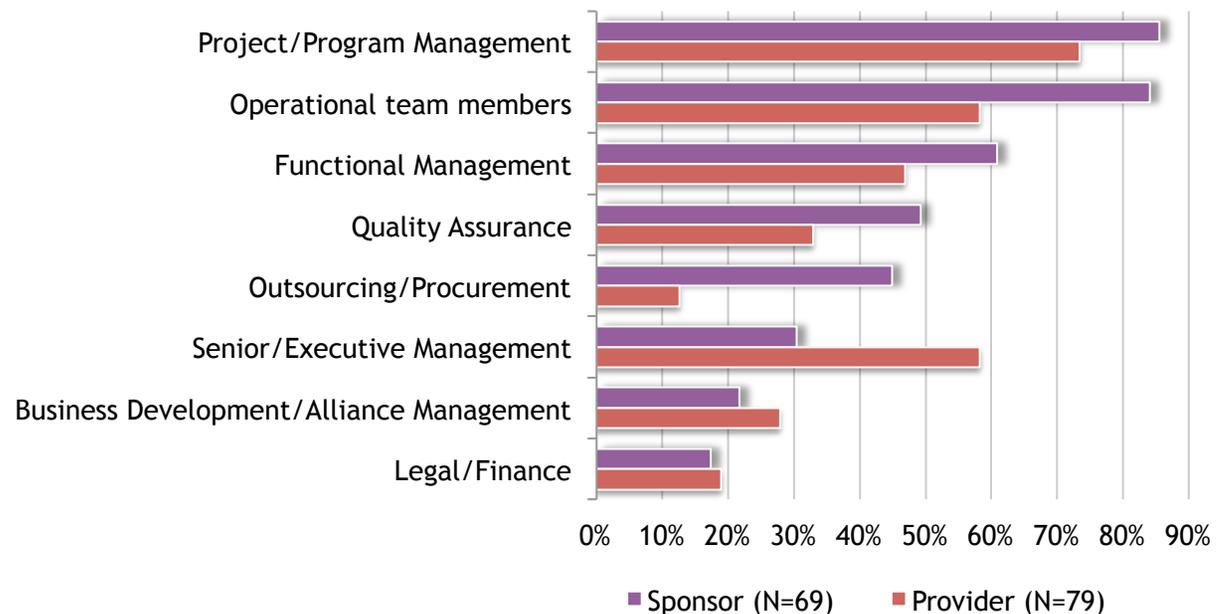
Involvement in Conducting Systematic Risk Assessment



Risk assessment is generally:

- Performed primarily by my company
- A joint CRO/Sponsor process
- Conducted primarily by the other party
- It depends

Functional Groups Involved in Risk Assessment

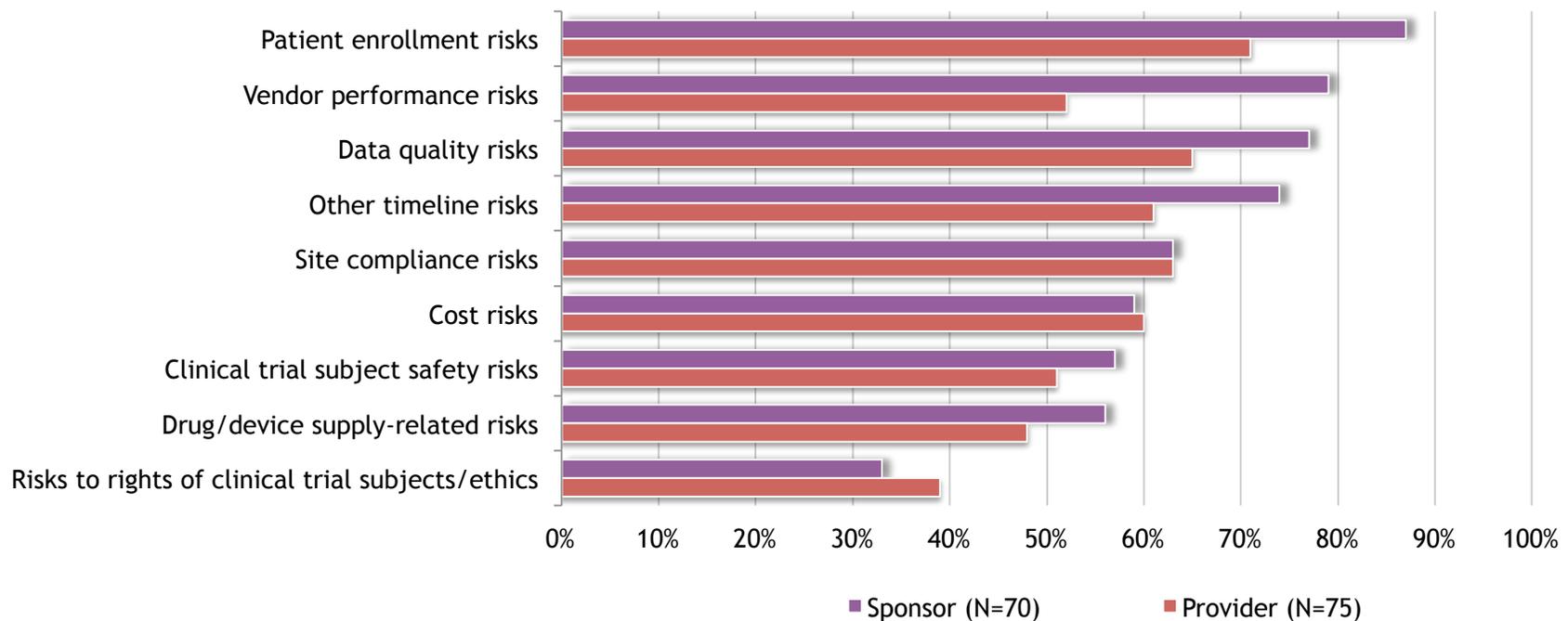


Q (Sponsor): For outsourced clinical trials, to what extent is the CRO generally involved in the systematic risk assessment? Q (CRO): To what extent is your company generally involved in the systematic risk assessment? Q: What functional groups and roles are generally involved in the risk assessment process?

Systematic Risk Assessment Components

Multiple risks are typically included in systematic assessments, with patient enrollment as the one most frequently cited by respondents. Regarding the features of each risk that are assessed, both groups reported evaluating risk probability, severity, ability to proactively reduce risk and ability to remediate risks as common elements.

Types of Risks Assessed During Formal Reviews

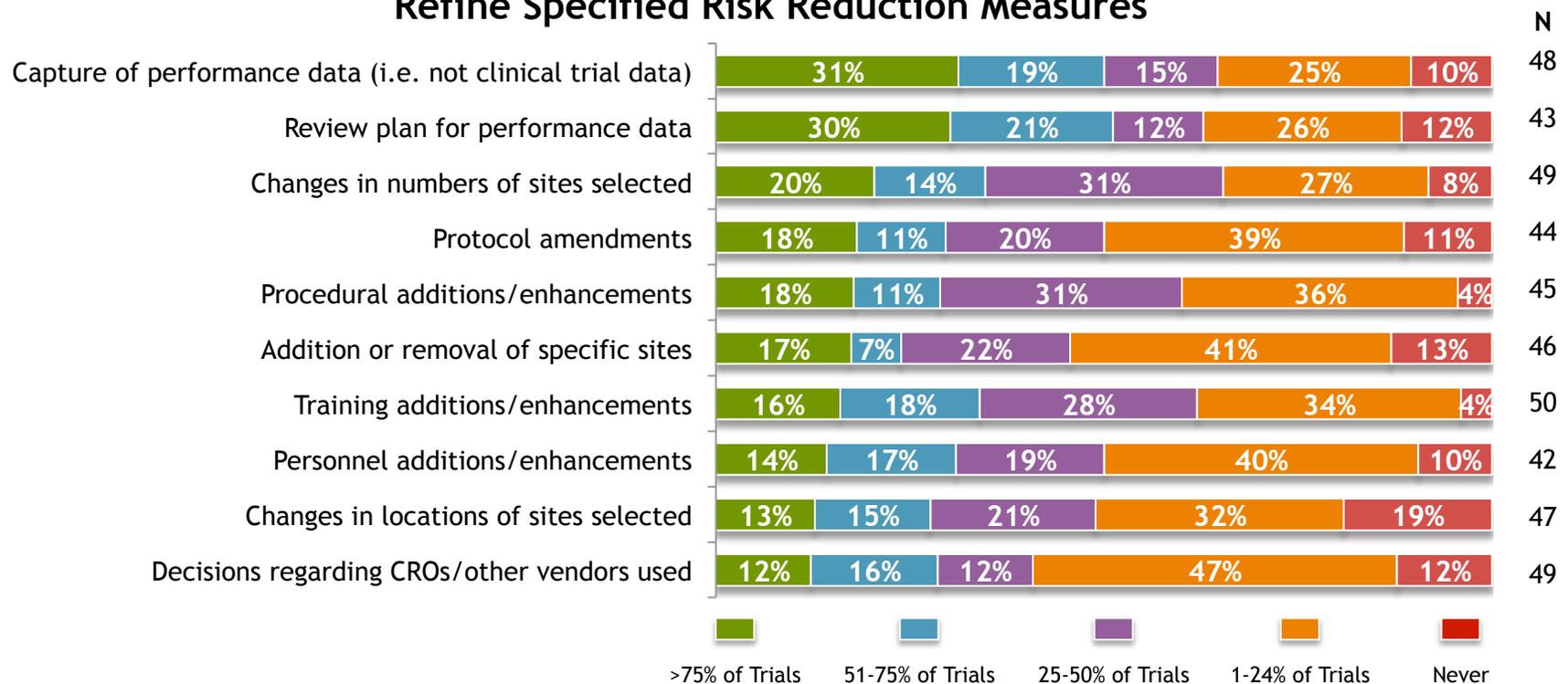


Q: When a systematic risk assessment is performed for projects conducted by your company, which of the following risks are typically formally assessed?
Q: When a systematic risk assessment is performed, what features of each risk are generally assessed?

Risk Assessment Utility: Sponsors

Sponsor respondents reported using risk assessments in various ways, with the introduction or refinement of proactive measures related to performance data used by the greatest percentage of respondents on a majority of trials. It is not common for risk assessments to affect the providers that are used.

Frequency With Which Risk Assessments Lead Sponsors to Introduce or Refine Specified Risk Reduction Measures

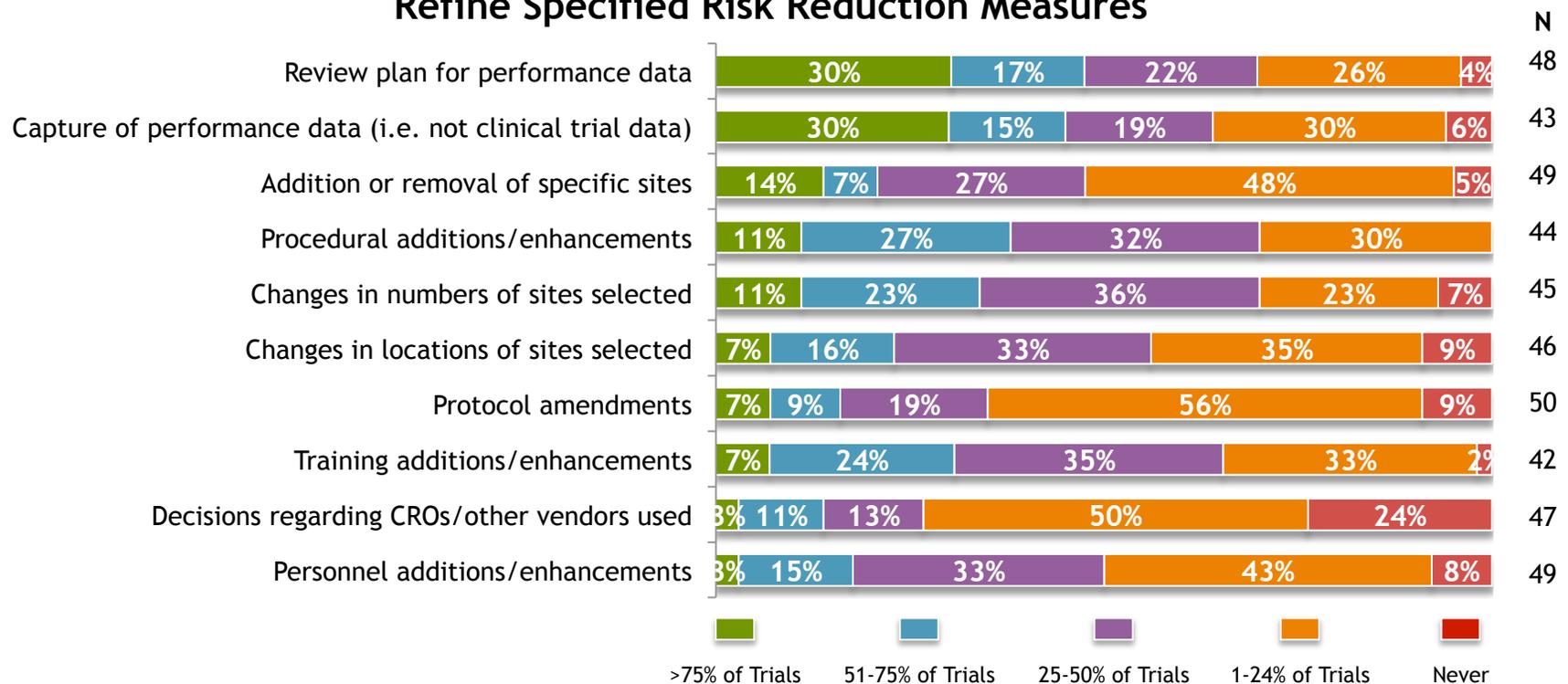


Q: How often does your risk assessment process lead to the introduction or refinement of each of the following proactive measures designed to reduce risk?

Risk Assessment Utility: Providers

Provider respondents reported using risk assessments in similar ways as Sponsors, with enhanced measures related to performance data used by the greatest percentage of respondents on a majority of trials.

Frequency With Which Risk Assessments Lead Providers to Introduce or Refine Specified Risk Reduction Measures



Q: How often does your risk assessment process lead to the introduction or refinement of each of the following proactive measures designed to reduce risk?

Risk Assessment Satisfaction

Sponsor respondents expressed higher levels of satisfaction with their in-house teams than with their CROs and other service providers on every attribute evaluated. CRO respondents provided higher satisfaction ratings for their own performance than did Sponsors, suggesting a perception gap with respect to performance.

Performance Satisfaction Ratings

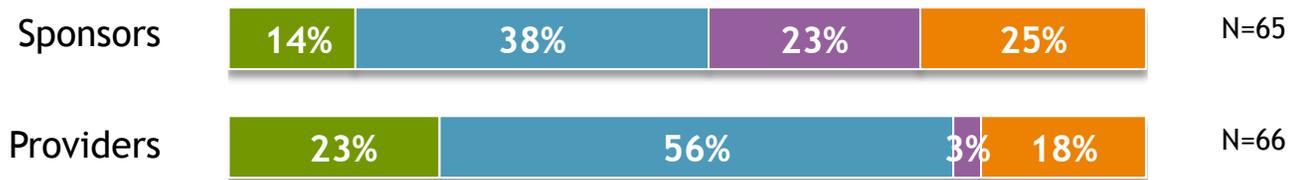
| 1 = Very Dissatisfied, 5 = Very Satisfied | SPONSOR RATINGS | | | CRO RATING | Sponsor/CRO Satisfaction Gap on CRO Performance |
|---|----------------------|---------------------------|--------------|---------------------|---|
| | In-house Teams | Non-CRO Service Providers | CRO Partners | CRO Self Assessment | |
| <i>Q: In general, how satisfied are you with the performance of each of your in-house teams, your CRO partners, and your other service providers with respect to each of the following.</i> | | | | | |
| Appropriateness of measures suggested or taken in reaction to risk-related information | 3.5 | 2.5 | 2.9 | 3.6 | -0.7 |
| Communications regarding risk-related trial information | 3.4 | 2.5 | 2.8 | 3.5 | -0.7 |
| Compilation of risk-related trial information during a trial (observations, trends, etc.) | 3.4 | 2.3 | 2.8 | 3.5 | -0.7 |
| Frequency of review of risk-related trial information | 3.5 | 2.5 | 3.0 | 3.6 | -0.6 |
| Overall performance on risk assessment and management related activities | 3.5 | 2.5 | 2.8 | 3.6 | -0.8 |
| Proactive identification of potential risks | 3.8 | 2.6 | 3.0 | 3.8 | -0.8 |
| Proactive risk analysis and evaluation | 3.4 | 2.5 | 2.8 | 3.5 | -0.7 |
| Rigor of review of risk-related trial information | 3.3 | 2.2 | 2.6 | 3.5 | -0.9 |
| | N (min)= N (max)= | 52 56 | 21 25 | 48 53 | 55 57 |

Systematic Risk Assessment Results

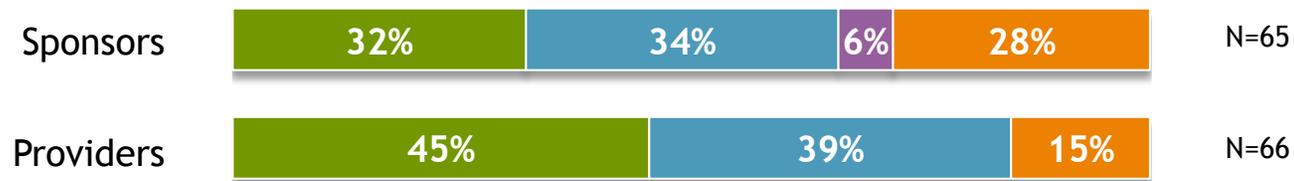
Risk management approaches appear to be yielding some benefits, particularly with respect to increased quality, but most respondents were not willing to provide a definitive “yes” to the questions, particularly those from Sponsor organizations.

In general, have your risk assessment and management approaches resulted in...

More efficient use of resources for your company and/or sponsor partner?



Increased quality?



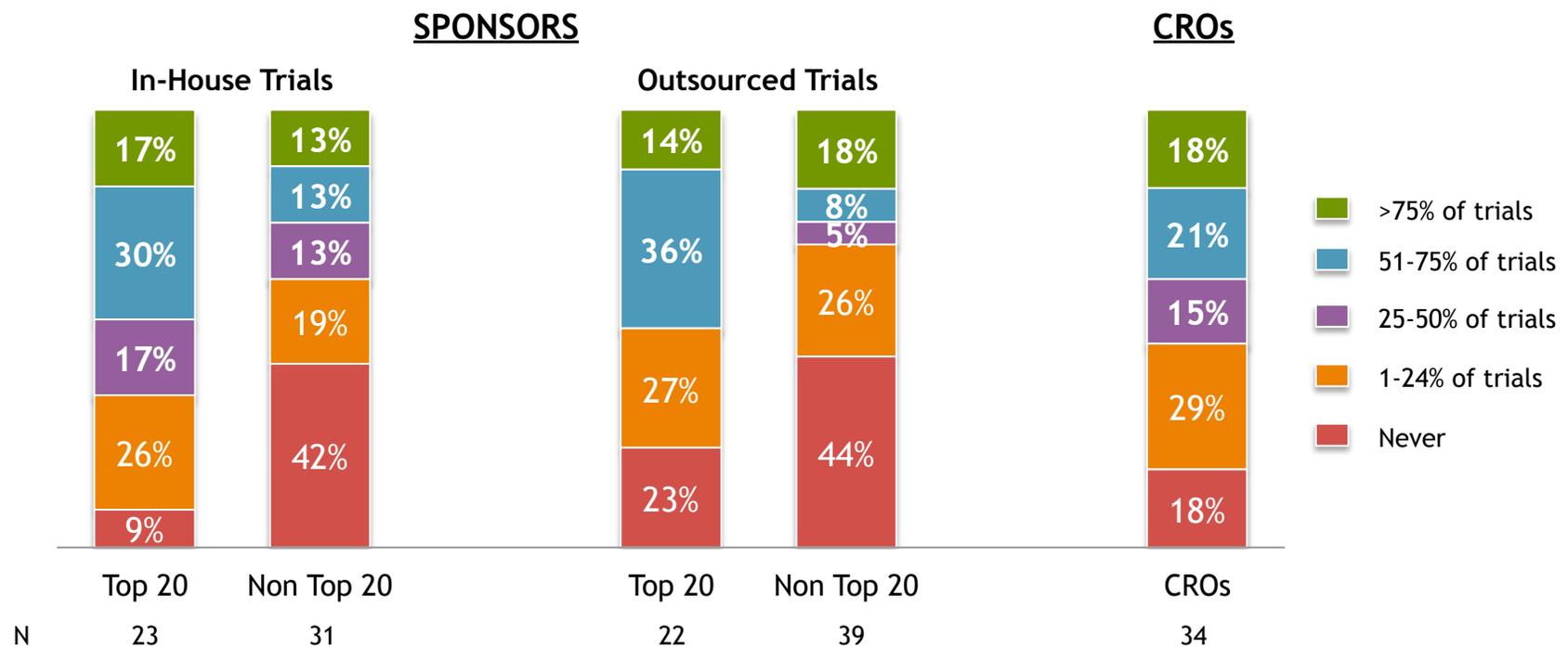
Risk-Based Monitoring

Sponsor and Provider Perceptions

Risk-Based Monitoring Frequency

As a group, Sponsor respondents from Top 20 firms were more likely to report frequent use of risk-based monitoring of investigative sites than were those from Non-Top 20 firms, for both in-house and outsourced trials. The distribution of frequency of RBM use among CROs seems to be intermediate between the two sponsor groups.

Usage Frequency of Risk Based Monitoring of Investigative Sites



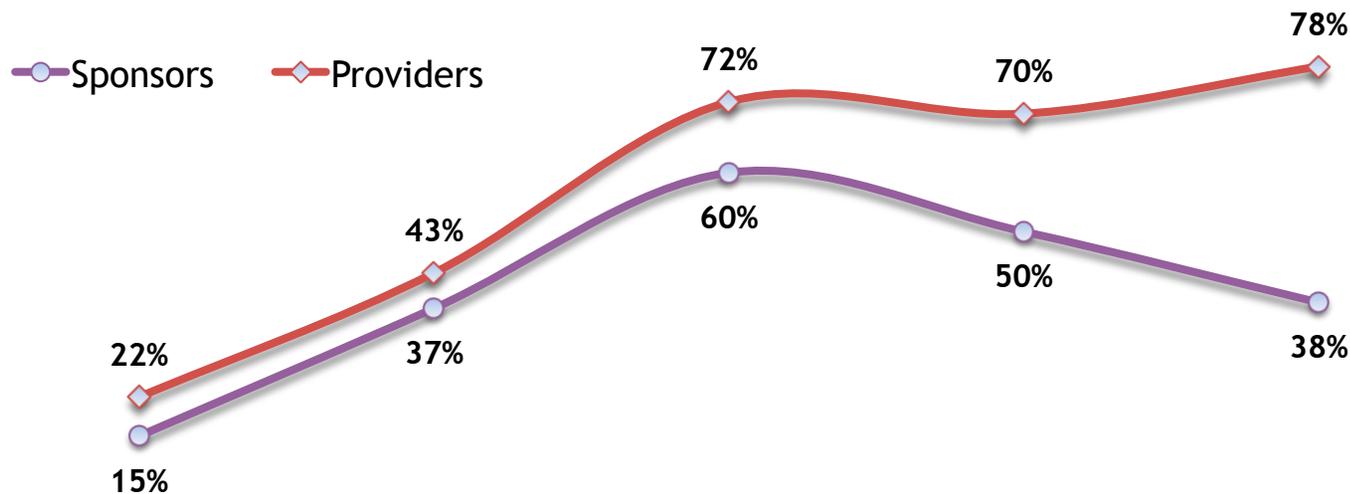
Q: How often does your company use a risk-based approach to the monitoring of Investigative Sites for clinical trials managed and conducted by in-house teams? Q: How often do your project/program teams (including the CRO partners) use a risk-based approach to the monitoring of Investigative Sites for outsourced clinical trials? Q (CROs): How often does your company use a risk-based approach to the monitoring of Investigative Sites?

Risk-Based Monitoring by Phase

A greater proportion of Provider respondents reported having used risk-based monitoring of sites for each phases of clinical development compared to Sponsor respondents. The difference is particularly pronounced in later phases of development.

Use of Risk-Based Monitoring by Clinical Study Phase

% of Respondents that Have Used RBM



Phase I Phase II Phase III Phase IIIb Phase IV

| | | | | | |
|------------|----|----|----|----|----|
| Sponsor N | 39 | 46 | 48 | 46 | 37 |
| Provider N | 37 | 42 | 46 | 43 | 41 |

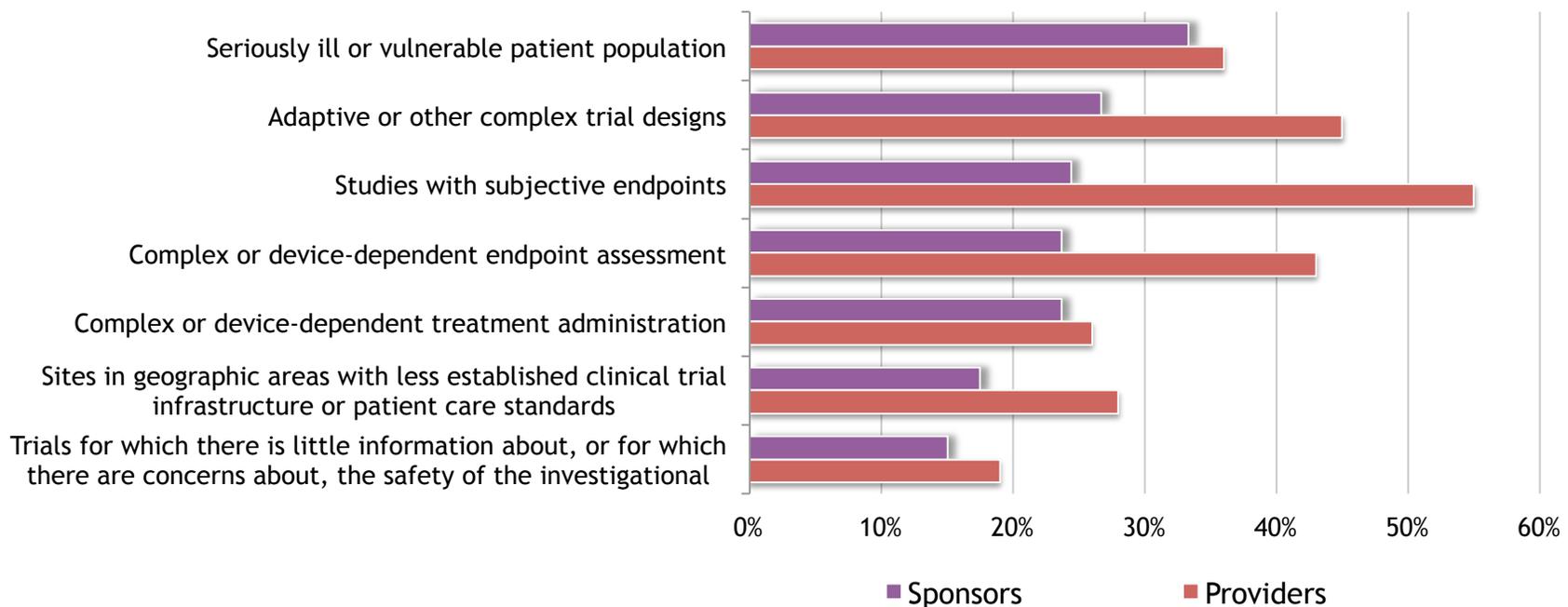
Q: For what phases of clinical studies have you used, or would you consider using, a risk-based approach to investigative site monitoring? (only "have used" shown)

Risk-Based Monitoring by Trial Type

A greater percentage of Provider than of Sponsors respondents reported having used risk-based monitoring for each of the types of trials listed in the survey. The difference was especially pronounced for studies with subjective endpoints, complex endpoint assessments and adaptive/complex trial designs.

Use of Risk-Based Monitoring by Type of Clinical Trial

% of Respondents that Have Used RBM

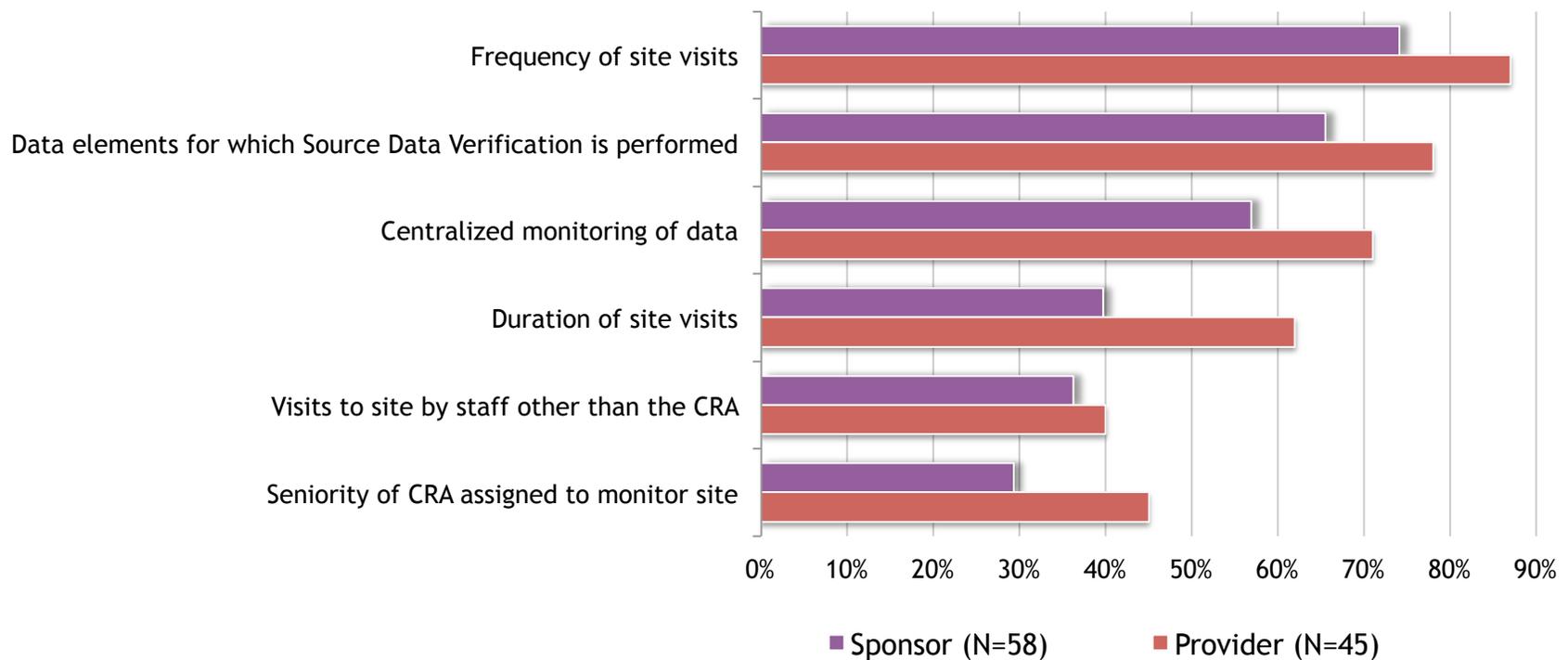


Q: For which of the following types of clinical studies have you used, or would you consider using, a risk-based approach to investigative site monitoring? (only "have used" shown)

Risk-Based Monitoring Implications

Across the samples, various adjustments were reported when using risk-based approaches to monitoring sites. The frequency of site visits and aggressiveness of data monitoring of data were adjusted by the greatest percentages of respondents.

Trial Elements Adjusted According to Risk-Based Monitoring Approach



Q: When you use a risk-based approach to monitoring, which of the following do you adjust depending on the level of assessed risk?

Risk-Based Monitoring Satisfaction

Satisfaction among Sponsor respondents with their CRO partners' RBM expertise and ability to deliver quality studies using an RBM approach was below the satisfaction ratings CRO respondents awarded their own companies, suggesting that the two groups may have different views on standards of satisfaction.

Performance Satisfaction Ratings

| | Very Dissatisfied | | | Very Satisfied | | Avg | N |
|--|-------------------|-----|-----|----------------|-----|-------------------------------------|-------------|
| | 1 | 2 | 3 | 4 | 5 | | |
| <i>1 = Very Dissatisfied, 5 = Very Satisfied</i> | | | | | | | |
| SPONSORS: Satisfaction with CRO partners' experience/expertise with RBM | 2% | 28% | 35% | 28% | 7% | 3.1 | 40 |
| CROs: Satisfaction with own company's experience/expertise with RBM | 2% | 9% | 38% | 33% | 18% | 3.6 | 45 |
| | | | | | | Sponsor/CRO Satisfaction Gap | -0.5 |
| SPONSORS: Satisfaction with CRO partners' ability to efficiently deliver a quality study using RBM | 6% | 18% | 49% | 24% | 3% | 3.0 | 33 |
| CROs: Satisfaction with own company's ability to efficiently deliver a quality study using RBM | 0% | 3% | 30% | 46% | 21% | 3.9 | 37 |
| | | | | | | Sponsor/CRO Satisfaction Gap | -0.9 |

Q: Overall, how satisfied have you been with [your CRO partners' / your company's] level of expertise and experience regarding risk-based monitoring?

Q: Overall, how satisfied have you been with [your CRO partners' / your company's] ability to efficiently deliver a quality study using risk-based monitoring?

Conclusions and Takeaways

Risk-Sharing Models,
Risk Assessment and
Risk-Based Monitoring

Conclusions and Takeaways

- There appears to be a disconnect between Sponsors and Providers regarding perceptions of the overall quality of service that is being delivered, as 87% of Provider respondents reported being “very satisfied” or “generally satisfied” vs. 53% of Sponsor respondents.
- As a group, Sponsor respondents from Top 20 firms were more likely to report frequent use of systematic risk assessment processes for clinical trials than were those from Non-Top 20 firms, for both in-house and outsourced trials.
- A majority of respondents from both Sponsor and Provider organizations reported that their companies had used at least one type of risk-sharing model. Respondents from both groups were much more likely to report having had positive experiences using guaranteed revenue streams in exchange for provider commitments than using penalties for failing to achieve milestones/targets.
- Based on respondents’ answers to open-ended questions, investing time to ensure that both Sponsors and Providers have a clear understanding of expectations at the beginning of a risk-sharing relationship and establishing/ implementing effective Communication Plans appear to be critical elements of success in risk sharing.

Conclusions and Takeaways

- While respondents from Top 20 firms were more likely to report frequent use of systematic risk assessment processes by their companies, respondents from Non-Top 20 firms were more likely to report frequent utilization of the information to drive the level of CRO oversight.
- Multiple risks are typically included in systematic assessments, with patient enrollment as the most frequently cited by respondents. Regarding the features of each risk that are assessed, both Sponsors and Providers reported evaluating risk probability, severity, ability to proactively reduce risk and ability to remediate risks as common elements
- The vast majority of respondents reported at least sometimes changing aspects of clinical trial design, execution, or management based upon information gathered from risk assessments, but most of the possible changes addressed by the survey were made by most respondents for only a minority of clinical trials.
- Sponsor respondents expressed higher levels of satisfaction with their in-house teams than with their CROs and other service providers on every risk assessment attribute evaluated. CRO respondents provided higher ratings of their own performance than Sponsors did, suggesting a perception gap with respect to CRO performance.

Conclusions and Takeaways

- Risk management approaches appear to be yielding some benefits, particularly with respect to quality, as one-third of Sponsor respondents confirmed that quality had increased and another one-third reported that quality had increased some of the time.
- As a group, Sponsor respondents from Top 20 firms were more likely to report frequent use of risk-based monitoring of investigative sites than were those from Non-Top 20 firms, for both in-house and outsourced trials. The distribution of frequency of RBM use among CROs seems to be intermediate between the two sponsor groups.
- Across the samples, various adjustments were reported when using risk-based approaches to monitoring sites. The frequency of site visits and aggressiveness of data monitoring of data were adjusted by the greatest percentages of respondents.
- Satisfaction among Sponsor respondents with their CRO partners' RBM expertise and ability to deliver quality studies using an RBM approach was below the satisfaction ratings CRO respondents awarded their own companies. This is consistent with other findings on overall quality and the ability to successfully perform risk assessments, suggesting that some CRO respondents may overestimate the extent to which they are meeting Sponsors' needs.



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