SITE LEVEL RISK ASSESSMENT CONSIDERATIONS
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Introduction
The TransCelerate Risk Assessment and Categorization Tool (RACT) provides a quantifiable way of identifying and assessing protocol level risk. The Site Level Risk Assessment Considerations provides examples to help demonstrate possible alternatives for quantifying initial and ongoing site level risk. Developing meaningful ways to measure site level risk will advance Risk Based Monitoring (RBM) generally and the development of ancillary technology.

This document provides examples to help demonstrate various methods a sponsor might use in quantifying risk metrics and ensuring consistency across the data that a sponsor could use to evaluate risk at the site level. These examples are provided for illustrative purposes and are not meant to suggest the criteria that sponsors must use or should use in assessing site level risk.

General Principles
Different approaches that can be used to assess site level risks are illustrated in more detail in the subsequent sections, however, the following should be considered:

» A trial should have a completed RACT and Integrated Quality Risk Management Plan (IQRMP)
» The TransCelerate Risk Indicator Library can be used as a source for risk indicator definitions
  - Risk indicators can be used to set thresholds and weighting to assess overall risk as well as site level risk
» Data sources and types should be considered carefully when defining risk indicators
» Site level risk assessments should be performed prior to subject enrollment as well as on an ongoing basis
» Risk indicators would only provide an indication of a possible issue at a site; a root cause analysis to further understand, confirm and manage risks would be required
» Mitigations/proposed actions should be pre-defined whenever possible
Site Level Risk Identification Methods Illustrated

The first step in risk assessment occurs at the clinical study level. The RACT, or other similar tools, provide a mechanism to facilitate risk assessment at the protocol level. This can be used to set an overall risk level to determine the baseline monitoring activities, how the risks impacting critical data and processes are handled, as well as, the impact on functional plans housed within the IQRMP.

Once risk has been assessed at the protocol level, some additional method would have to be applied to assess risk at the site level. This would determine the appropriate level of individual site monitoring activities and detail possible mitigation strategies for emerging site risks.

TransCelerate has compiled a risk indicator library grouped into eight categories. This library can be used by a sponsor to select those risk indicators most applicable in identifying and assessing risks within the specific clinical study at both a protocol and site level. Additional trial specific risks should also be considered and applied if required. Although the Risk Indicator Library has extensive examples, typically around 10 to 20 risk indicators are deemed appropriate for most studies. Each chosen risk indicator will require pre-determined thresholds to be set and possible mitigation actions defined for when a threshold level is exceeded.

Color coding, using a traffic-light paradigm, can be applied so that when reviewing the risk indicators those with threshold breaches can be easily identified. A green color would indicate risk indicators with a current low-risk, yellow for medium risk and red for high risk. However, other rating systems showing a numeric value, categories (e.g. low, medium or high) or a combination of all three methods could be used.

It is then possible to assign an overall site risk level by aggregating the individual indicators. The aggregate scores can then be grouped for each of the risk categories (e.g. Data Quality, Safety etc.) for that site. Again, color coding can be applied to ease review. This allows a reviewer to quickly identify high risk sites and then further assess which category or categories are driving this risk level. By assigning a weighting to each risk indicator and its different thresholds, the calculation of an overall site risk score can then account for differing levels of importance of each indicator (if applicable). If this approach is adopted, it is important to carefully consider each risk indicator weighting and how they would impact the overall risk level for a site. It is worth noting that a site with a high-risk score is not necessarily indicating poor performance. Site level risk scores can be useful in directing additional monitoring efforts to sites with increased need, such as sites that are high enrollers.
Figure 1 below provides an example, purely for illustrative purposes, of how a company might set thresholds for a risk indicator and apply color coding and weighting to whatever thresholds might be set. Thresholds and therefore any related weighting for a particular indicator will vary, perhaps widely, depending on circumstances such as protocol-specific risks. A sponsor therefore will not only need to make its own determination with regard to which risks indicators would be relevant to the particular study but also what thresholds to set and how to weight the relevant risks.

**Figure 1: Example of a risk indicator with possible thresholds and weightings applied**

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Indicator</th>
<th>Thresholds</th>
<th>Signal Color</th>
<th>Weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Quality</td>
<td>Timeliness of data entry</td>
<td>Low 5-9 calendar days from visit</td>
<td>Green</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medium 10-19 calendar days from visit</td>
<td>Yellow</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High &gt;=20 calendar days from visit</td>
<td>Red</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Consideration of Data Type

A variety of clinical and operational data can be utilized when performing site level risk assessments. When choosing risk indicators to perform site assessments, it is important to consider the availability of the data as well as its limitations and type.

In theory, any data source can be utilized to assess risk as long as these data are able to be collected and integrated for use as an input to the risk assessment. Clinical data collected via Electronic Data Capture (EDC) and uploaded from external vendors (such as laboratory results) are the obvious choice for inclusion to an ongoing risk assessment. However, data collected via an issue management system and/or other operational databases should be considered as potential data sources.

Practically it may not always be possible to access and integrate all data sources. Surrogate measures for assessment may be required when this is the case. Some data are historical in nature and will not change once collected. Although these data are useful in assessing site risk, their ongoing impact on a site level risk should be considered. For example, a change in site staff could increase the risk at a particular site. This risk would typically reduce over time as the staff member becomes familiar with the clinical study protocol and completes any required training. Therefore, when defining this risk indicator, a timing element should be included. This would reduce the risk indicator after a pre-determined period of time.

Lastly, it is useful and may be necessary to consider whether the actual type of data is qualitative or quantitative in nature. Methods to quantify qualitative information may need to be applied to ensure data is reconcilable. This can be achieved by the use of targeted questions with pre-defined choices for completion or by providing a framework for assessment. It is worth noting that such measures of quality do not necessarily indicate an actual issue at a site, but when combined with other data sources could indicate the need for further monitoring efforts and investigation. Either approach should be combined with training and guidance to those roles performing the assessments.

The examples below are provided purely for illustrative purposes to demonstrate how one might go about quantifying and thus making useable for purposes of site level risk assessment information or data that is subjective in nature. These examples are not meant to suggest that sponsors rely on the particular criteria used in the examples to assess site level risks or that other criteria may not or should not be used in such an assessment. Rather, the examples merely are meant to provide guidance on how a sponsor might be able to incorporate useful and meaningful qualitative information into a risk assessment, but do so in a way that allows for consistency in how the data is collected and evaluated throughout a study and across sites.
**Example 1: Using qualitative site assessments**

Qualitative evaluations assessed during interactions with a site could be used in assessing site risk. A site’s organization, workload, staff behavior etc. that are observed during these interactions can be just as important as the quantitative metrics used to evaluate site performance.

Given the subjective nature of a qualitative assessment, instructions should be provided to site-facing roles to provide them guidance on how to assess the site. Two examples on how this guidance could be collected are detailed below.

**Illustration A:** provide a list of questions which could be included in a site contact/visit report that a Clinical Research Associate would complete. The type of responses should be pre-defined, either specifying yes/no responses or multiple choice responses if further granularity is required, for example:

- **Staffing, Facilities and Supplies:**
  - Does the investigator have sufficient time to properly conduct and supervise the clinical trial?
  - Does the investigator maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated?

- **Essential Documents:**
  - Are the investigator/institution necessary documents in the appropriate files?
  - Is there Dated, documented approval/favorable opinion of institutional review board (IRB)/independent ethics committee (IEC) of the protocol and any amendments?

Each response would be assigned a numeric value that could be summed and then a threshold applied as with quantitative risk indicators.

**Illustration B:** Figure 2 below demonstrates how one might assess and give a site rating, as well as an example of how to quantify a score. The score can then be included into the calculation of the site level risk.

![Figure 2: Illustration B example of a qualitative framework](image)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No issues or only small issues (e.g. low number of data points missing data)</td>
</tr>
<tr>
<td>1</td>
<td>Site has Protocol Violation impacting data or concerns over the amount of missing/incorrect source data in the records.</td>
</tr>
<tr>
<td>2</td>
<td>Multiple Protocol Violations or those impacting critical data, or documentation of investigational product supply or informed consent issues.</td>
</tr>
<tr>
<td>3</td>
<td>Serious Adverse Event (SAE) missing in eCRF or in source</td>
</tr>
<tr>
<td>4</td>
<td>Misconduct or potential fraud; other significant monitoring issues</td>
</tr>
</tbody>
</table>

Either method selected would enable a more consistent assessment allowing for integration into the site level risk assessment.
Initial Site Level Risk Assessment

The RACT provide an overall risk level for the study that can be used as baseline for all sites. However, an initial site level risk assessment can be performed at site identification, selection, or prior to study site initiation. This allows for the setting of a baseline risk level which then determines the initial monitoring approach for each individual site. This provides the sponsor the opportunity to apply mitigation strategies limiting potential risks and maintain compliance standards immediately.

Input to the baseline site risk will differ from data that would be used to assess site risk during the conduct phase of a study. The initial assessment would be based upon information available prior to study start rather than observations and data collected during the course of the study. Examples of the risk indicators used for an initial site assessment could include the amount of experience the investigator and site has in the therapeutic area, familiarity with working with the sponsor, anticipated size of enrollment, and site facilities. The sources for these risk indicators may include:

» Feasibility assessment/pre-initiation visit
» Recent historical data if available (including central team feedback)
» Prior audit/inspection history

Information gathered during feasibility assessments should be collected in a manner that allows for a quantitative assessment to be made based on responses.

The result of the initial risk assessment should lead to the implementation of any mitigating actions and a monitoring visit frequency strategy for each site. The mitigation actions used will depend on the specific identified. Examples of mitigating actions from the initial risk assessment could include:

» Gated recruitment
» Higher monitoring frequency
» Higher level of Source Data Verification (SDV)/Source Document Review (SDR)
» Additional site support
» Training or provisioning of resources/ facilities

The purpose of the mitigating actions is to provide additional support to the site and help with early identification and management of potential issues. For example, gated recruitment can ensure that the site is assessed at an additional on-site visit after a pre-specified number of subjects have been recruited before additional screening is allowed.

Any mitigation strategies or monitoring approaches implemented based on the initial risk assessment should be documented.
Ongoing Site Level Risk Assessment

Once sites begin enrolling subjects, the site risk level may change based on actual observations and data collected during the study. Site risk levels can therefore decrease, stay static, or increase based on the continued collection of data. Data used to continuously assess site level risk can include items that were used to establish the baseline risk level as well as additional categories / factors (e.g. Adverse Event (AE) reporting or time to query resolution).

This way, changes in site risk from baseline over time can be evaluated, and site monitoring mitigations and actions can be adapted accordingly.

To ensure that a site’s performance can be compared to other sites in the study, qualitative assessments, such as site contact assessments, can be combined with quantitative metrics. This will allow for a more holistic profile of the site. Examples showing how metrics could be used to assess site risk and how the metrics might be used to determine what actions could be followed when a threshold is reached can be seen in figure 3. As above, this example is provided for illustrative purposes only and is not meant to suggest what criteria a sponsors should use in assessing site level risk.
### Figure 3: Examples of data categories, thresholds and proposed actions

<table>
<thead>
<tr>
<th>Category</th>
<th>Sub-Category/Risk indicator</th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
<th>Examples of proposed actions when threshold is met</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data Quality</strong></td>
<td>CRF Completion / Timeliness of data entry</td>
<td>Meets pre-defined threshold for data entry timeliness e.g. &lt;10 days</td>
<td>Does not meet pre-defined threshold for data entry timeliness e.g. 10-19 days from visit</td>
<td>Does not meet pre-defined threshold for data entry timeliness e.g. 10-19 days from visit</td>
<td>Verify if required site staff resources in place to manage data entry. Ensure staff are aware of expectations. Discuss a plan for getting into compliance. Consider increasing frequency of off-site monitoring; and providing regular feedback to site for missing data. Consider increasing frequency of on site monitoring and level of SDV/SDR to be performed. Escalation to the Investigator (if not aware) and Line Manager may be necessary. Data entry timelines to be reiterated in central communication e.g., study newsletter.</td>
</tr>
<tr>
<td><strong>Issue Management</strong></td>
<td>Protocol Compliance / Protocol deviation (PD) rate</td>
<td>Lower than average PD rate / number of ICH issues per site / time to issue resolution</td>
<td>Average PD rate / number of ICH issues per site / time to issue resolution</td>
<td>Higher than average PD rate / number of ICH issues per site / time to issue resolution</td>
<td>Follow up to ensure Correction/Corrective Action has been implemented. Consider scheduling a more frequent monitoring visit as follow up, especially if the study is still in the recruitment phase. Escalate any concerns to Management: consider controlled recruitment until the site is back in compliance. Study-wide site and/or CRA re-training or consider need for protocol amendment depending on deviation trends. Consider central communication to sites regarding common PDs.</td>
</tr>
<tr>
<td><strong>Subject Recruitment and Discontinuation</strong></td>
<td>Enrolment / Enrolment rate / screening rate / discontinuation rate / screen fail rate for the site based on the expected enrolment per site</td>
<td>Average enrolment or below average enrolment / screening rate / discontinuation rate / screen fail rate for the site based on the expected enrolment per site</td>
<td>Higher than average or below average enrolment / screening rate / discontinuation rate / screen fail rate for the site based on the expected enrolment per site</td>
<td>Higher than average or below average enrolment / screening rate / discontinuation rate / screen fail rate for the site based on the expected enrolment per site</td>
<td>High Enrolment: Contact site to verify if required resources are still available, and if site has enough supplies based on projections. May consider enrolment hold depending on other risk triggers. May need to increase off-site monitoring frequency for high enrolment. Assess whether a higher on-site monitoring visit frequency is needed, or triggered intervention visit. Low Enrolment: Consider re-training needs on applicable protocol requirements for staff after a long period of no or low enrolment. Flag site for potential closure if non-enrolling. Evaluate need for onsite visit to review eligibility for screened subjects.</td>
</tr>
</tbody>
</table>
Site level risk assessments should be performed throughout the study. The timing of ongoing site risk assessments may vary but should be evaluated/reactively as issues arise (on an as needed basis), as well as proactively at fixed time points (to re-assess a site’s current risk in the absence of issues) to ensure the risk level is still aligned with the site’s performance and workload. The assessment of site risk is dependent upon the availability of contemporaneous data. The availability of real or near real-time data allows for quicker identification of risks at each site. This allows for the more targeted use of onsite monitoring resources, the ability to confirm the existence of issues at a site, and the implementation of any required activities to minimize the risks to study subjects or quality.

**Other Considerations**
Displaying a site’s overall risk level over time, including the risk levels of the contributing risk categories, is a useful mechanism to identify trending in risk. Coupled with an ability to group sites by country or region this could further the ability to spot potential issues impacting the clinical study. For example, if all the sites in a region are trending towards a higher risk level, this could be indicative of potential issue impacting the sites outside of the sites control (e.g. investigational product supply or a lack of sponsor guidance for that particular geographic location).

Recognizing that an investigational site may participate in multiple clinical studies for a sponsor is important. If a site is actively participating in more than one study simultaneously, potential identified issues arising from a site level risk assessment in one study could be valuable input into setting the risk level in the other active studies. This is especially true if a study is early in the conduct phase and currently has limited data available.

**Summary**
Performing risk assessments at a site level allows for increased sponsor oversight and more targeted use of monitoring resources focusing on those areas of higher risk. It is understood that each sponsor company has distinct differences in systems, data infrastructure, clinical operating models, and even Risk Based Monitoring implementation strategies. For this reason, the considerations addressed above are meant to provide general guidance to assist sponsor companies in developing a method for gauging and managing site level risk that each sponsor can tailor to its own individual circumstances despite the various differences among sponsors.