The following risk assessment tables are used by SROS Monitoring to help generate the initial and subsequent Clinical Monitoring Plans for study participant monitoring.

The initial CMP is required before a study is activated. CMPs are regularly assessed and updated during the study.

The following assessment tables should be considered as guidelines. Utilized assessment factors may change from those listed if OSRO deems it warranted.

Note: This form is used for clinical studies filed to an IND or IDE; it is not required for a study using only an NSR device.

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1. Initial Clinical Monitoring Plan (prior to study activation)

The initial CMP uses information from the IRB-approved protocol, supporting documentation, and site history (if available).

The risk score calculated in Table 1 is used to determine the CMP assigned to the protocol. The three initial CMP options are listed in Table 3. The plans set the percentage of study participants to be monitored and the frequency of site visits during the trial.

Table 1: Initial Protocol Monitoring Assessment

Monitoring Factor	Monitoring Assessment	Score	Risk Score
Protocol Phase	Phase II or III	3	
	Phase 0, I or I/II	6	
Site Monitoring Index	*Refer to Table 2 in Section 1.1*		
Expected accrual[1]	Slow	1	
	Fast	2	
Known CAPAs for this site[2]	No	0	
	Yes	2	
FDA or Sponsor initiated hold(s)[3]	No	0	
	Yes	2	
Multi-center study	No	0	
	Yes	2	
Minimal Risk Score: 4 **Median Risk Score: 21** **Maximal Risk Score: 38**		***Total Risk Score =***	

[1] Use the yearly/monthly accrual as described in the statistical section of the protocol.
- Slow: Less than two study participants per month
- Fast: Two or more study participants per month

NOTE: If the protocol statistical section does not clearly describe the expected accrual rate, assume slow accrual.

[2] Consider any CAPA requests from the Sponsor within the past 2 years.

[3] Consider any FDA or sponsor-initiated holds within the past 2 years.

1.1. Site Monitoring Index

The Site Monitoring Index (Table 2) is assessed based on data from monitoring observations, specifically, "monitoring activity type: action items" within the monitoring visit reports for this **site (The NIH Coordinating Center if the study is multi-institutional)**.

The **initial** site monitoring assessment is based on all **available monitoring reports across all protocols for the site** (where site is defined as the PI and Branch) conducted **over the last 24 months**.

If monitoring report data for the site is insufficient or not available, the site is given an automatic risk score of 12.

Table 2: Site Monitoring Index Assessment

Monitoring Activity Types	Action Items	Action Items Assessment Criterion	Monitoring Index	
eCRF Completion	Percentage of **monitored participants** with findings across **all monitored studies** at this site. **Note:** *system generated queries are excluded*	< 5%	0	
		≥ 5% and < 10%	1	
		≥ 10%	3	
Eligibility Criteria	Percentage of **monitored participants** with findings across **all monitored studies** at this site.	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Protocol non-adherence	Percentage of **monitored participants** with findings across **all monitored studies** at this site.	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Informed Consent	Percentage of **monitored participants** with findings across **all monitored studies** at this site.	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Safety Reporting	Percentage of **monitored participants** with findings across **all monitored studies** at this site.	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Source Documents	Percentage of **monitored participants** with findings across **all monitored studies** at this site.	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	

Monitoring Activity Types	Action Items	Action Items Assessment Criterion	Monitoring Index	
PI Involvement	Number of findings across **all monitored studies** at this site.	< 5%	0	
		≥ 5 and < 10	1	
		≥ 10	3	
Essential Documents	**Average number** of action items initiated within the last 24 months across **all monitored studies** at this site.	< 1	0	
		≥ 1 and < 15	1	
		≥ 15	3	
Minimal Site Monitoring Index: 0 **Median Site Monitoring Index: 12** **Maximal Site Monitoring Index: 24**		***Total Monitoring Index =***		

Table 3: Initial CMP selection based on the Total Risk Score (from Table 1)

CMP #	Risk Score	Parameters	Active Phase[1] Monitoring Visit Intervals	Follow-Up Phase[2] Monitoring Visit Intervals
Ini-1	4 - 15	• **First 2** enrolled participants, and thereafter, **25%** of those enrolled over the duration of the study based on random selection • All participants with SAEs	• First interim visit within **4 – 6 weeks** after the first enrollment • Interim visits **every 12 – 16 weeks** (3-4 months)	Interim visit every **6 – 8 months** based on protocol follow-up visit schedule (at least twice a year)
Ini-2	16 - 26	• **First 2** enrolled participants, and thereafter, **50%** of those enrolled over the duration of the study based on random selection • All participants with SAEs	• First interim visit within **4 – 6 weeks** after the first enrollment • Interim visits every **8 – 12 weeks** (2-3 months)	Interim visit every **3 – 6 months** based on protocol follow-up visit schedule
Ini-3	27 and over	• **First 3** enrolled participants, and thereafter, **75%** of those enrolled over the duration of the study based on random selection • All participants with SAEs	• First interim visit within **4 – 6 weeks** after the first enrollment • Interim visits every **8 – 10 weeks** (2-3 months)	Interim visit every **3 – 6 months** based on protocol follow-up visit schedule

[1] Enrollment and Treatment phases.
[2] Begins after Treatment phase has been monitored.

2. Subsequent Clinical Monitoring Plans (updated during the study lifecycle)

When a periodic review of the active CMP triggers updating the CMP, the following tables and figure are used as guides in determining new CMP parameters for percentage of participants to be monitored and the visit frequency.

A new risk score calculated in Table 4 is used to determine the new CMP (Table 6) assigned to the protocol. The seven (7) subsequent CMP options are listed in Table 6.

Table 4: Subsequent Protocol Monitoring Assessment

Monitoring Factor	Monitoring Assessment	Score	Risk Score
Protocol Phase[1]	Phase II or III	3	
	Phase 0, I or I/II	6	
Protocol Monitoring Index	*Refer to Table 5 in Section 2.1*		
Actual accrual[2]	Slow	1	
	Fast	2	
Known CAPAs for this site[3]	No	0	
	Yes	2	
FDA or Sponsor initiated hold(s)[4]	No	0	
	Yes	2	
Multi-center study	No	0	
	Yes	2	
Minimal Risk Score: 4 **Median Risk Score: 21** **Maximal Risk Score: 38**	***Total Risk Score =***		

[1] If the Phase I portion of a Phase I/II study has been completed, then consider the protocol as Phase II and give a risk score of 3.

[2] Calculate from enrollment data since the enrollment of the first participant:
- Slow: Less than two study participants per month
- Fast: Two or more study participants per month

[3] Consider any CAPA requests from the Sponsor within the past 2 years **for all sites of this protocol**.

[4] Consider any FDA or sponsor-initiated holds within the past 2 years **for the product, the study or any of site of this protocol**.

2.1. Protocol Monitoring Index

- The Protocol Monitoring Index is assessed using data from monitoring observations, specifically, the "monitoring activity type: action items" within the monitoring visit report(s) for **this protocol**.
- The **index** is based on all **available monitoring reports for this protocol and across all active sites** (for multi-center studies) conducted **since the previous CMP review.**

Table 5: Protocol Monitoring Index Assessment

Monitoring Activity Types	Action Items	Action Items Assessment Criterion	Monitoring Index	
eCRF Completion	Percentage of **monitored participants** with findings across **all monitored sites for this protocol.** **Note:** *system generated queries are excluded*	< 5%	0	
		≥ 5% and < 10%	1	
		≥ 10%	3	
Eligibility Criteria	Percentage of **monitored participants** with findings across **all monitored sites for this protocol.**	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Protocol non-adherence	Percentage of **monitored participants** with findings across **all monitored sites for this protocol.**	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Informed Consent	Percentage of **monitored participants** with findings across **all monitored sites for this protocol.**	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Safety Reporting	Percentage of **monitored participants** with findings across **all monitored sites for this protocol.**	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
Source Documents	Percentage of **monitored participants** with findings across **all monitored sites for this protocol.**	< 5%	0	
		≥ 5% and < 20%	1	
		≥ 20%	3	
PI Involvement	Number of findings across **all monitored sites for this protocol.**	< 5	0	
		≥ 5 and < 10	1	
		≥ 10	3	
Essential Documents	**Average number** of action items initiated within the last 24 months across **all monitored sites for this protocol.**	< 1	0	
		≥ 1 and < 15	1	
		≥ 15	3	
Minimal Protocol Monitoring Index: 0 **Median Protocol Monitoring Index: 12** **Maximal Protocol Monitoring Index: 24**		***Total Monitoring Index =***		

2.2. Revised CMP # Selection

2.2.1. The new risk score and the participant monitoring level of the current CMP are used in selecting the new CMP #. A decision tree (Figure 1) aids the selection.

2.2.2. The percentage of monitored participants and the frequency of monitoring visits, as determined by the current CMP # (initial or previously revised), will be revised only if the protocol has been monitored at least once over the past 12 months.

2.2.3. The decision tree in Figure 1 and the revised CMP # in Table 6 are guidance provided by the Sponsor. The Sponsor will make the final decision about the appropriate level of monitoring for each protocol and as such monitoring percentages can be increased or decreased as well as the frequency of monitoring.

2.2.4. The 7 revised CMP # options are listed in Table 6. A decision tree (Figure 1) assists in selecting the appropriate revised CMP #.

- The selection of the revised CMP # is based on the percentage of participants to be monitored per the current CMP and the risk score calculated in Table 4.
- For protocols with either a) 25% monitored participants and a risk score over 26 or b) 75% monitored participants and a risk score of 4-15, the Sponsor is consulted in selection of the revised CMP # options.

2.3. Decision Tree

Select the row corresponding to the percentage of participants monitored in the current CMP, locate the new risk score then identify the revised CMP #.

Figure 1: Decision tree for selecting a revised CMP

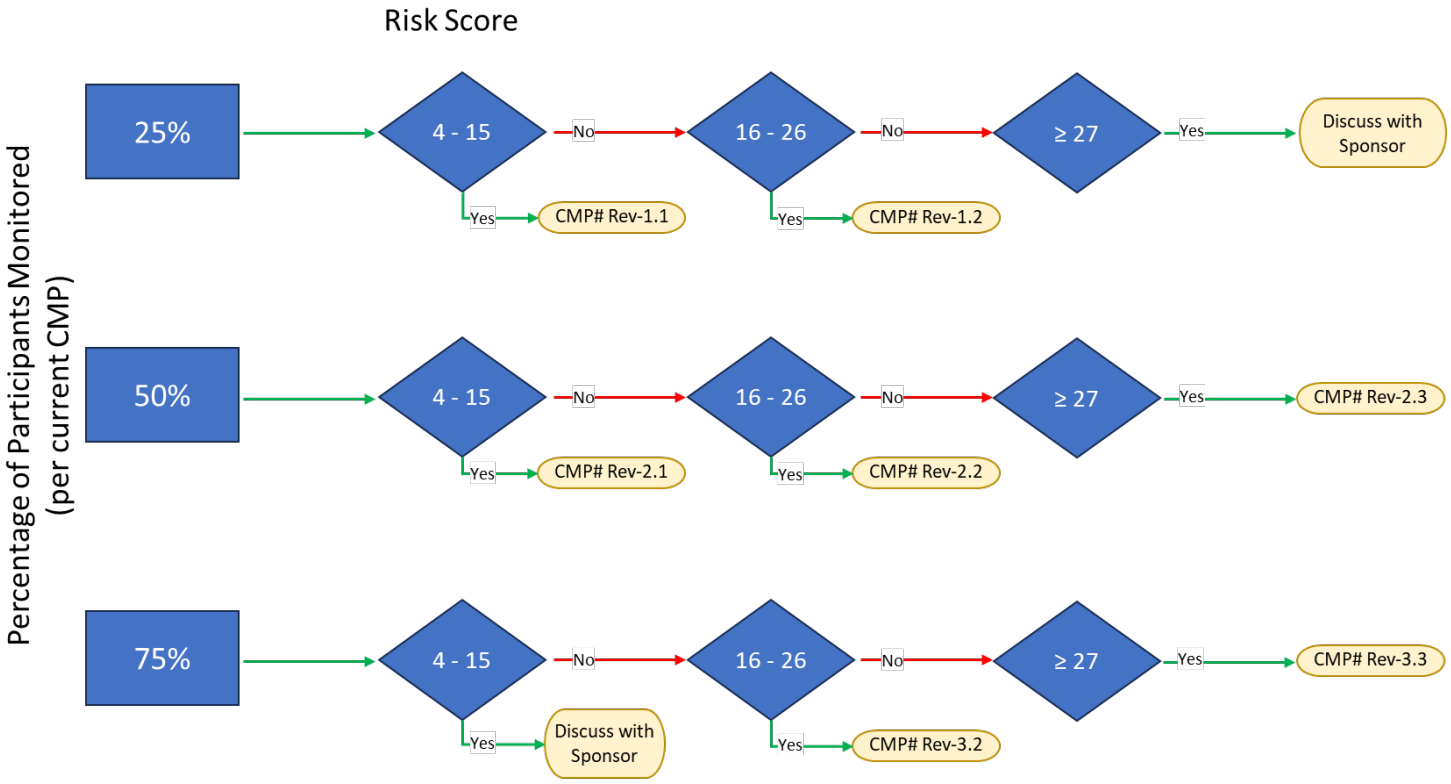

Table 6: Revised CMP selection based on the Total Risk Score (from Table 4)

CMP #	Active Phase Monitoring Visit Intervals	Follow-Up Phase Monitoring Visit Intervals	Parameters
Rev-1.1	Interim visits **every 12 – 16 weeks** (3-4 months)	Interim based on protocol follow-up visit schedule (at least twice a year)	• **First 2** enrolled participants, and thereafter, **25%** of those enrolled over the duration of the study based on random selection • All participants with SAEs
Rev-1.2	Interim visits **every 8 – 12 weeks** (2-3 months)		
Rev-2.1	Interim visits every **12 – 16 weeks** (2-3 months)	Interim based on protocol follow-up visit schedule (at least twice a year)	• **First 2** enrolled participants, and thereafter, **50%** of those enrolled over the duration of the study based on random selection • All participants with SAEs
Rev-2.2	Interim visits **every 8 – 12 weeks** (2-3 months)		
Rev-2.3	Interim visits **every 8 – 10 weeks** (2-3 months)		

CMP #	Active Phase Monitoring Visit Intervals	Follow-Up Phase Monitoring Visit Intervals	Parameters
Rev-3.2	Interim visits **every 8 – 12 weeks** (2-3 months)	Interim based on protocol follow-up visit schedule (at least twice a year)	• **First 3** enrolled participants, and thereafter, **75%** of those enrolled over the duration of the study based on random selection • All participants with SAEs
Rev-3.3	Interim visits **every 8 – 10 weeks** (2-3 months)		

Please Note: The decision tree in Figure 1 and the revised CMP # in Table 6 are guidance provided by the Sponsor. The Sponsor will make the final decision about the appropriate level of monitoring for each protocol and as such monitoring percentages can be increased or decreased as well as the frequency of monitoring.