Clinical Site Monitoring

Purpose and Scope

To describe the goals, expectations, and general processes involved in the on-site and remote monitoring of clinical trial enrollment sites by the SIREN Clinical Coordinating Center (CCC). The goals of site monitoring are quality assurance and improvement, enhanced bidirectional communication between sites and trial leadership, reinforcement of training, and regulatory compliance inclusive of verification of source documents, protocol adherence, and necessary documentation. In SIREN, site monitoring is distinct from central data monitoring performed by the SIREN Data Coordinating Center (DCC). This scope of this SOP does not include central data monitoring, which is described in SOPs maintained at the DCC.

Responsible Individuals

Effective site monitoring is a shared responsibility of the SIREN CCC (including site monitors and leadership), and the enrollment sites being monitored (including site research coordinators, site Principal Investigators, and the associated Hubs and Award Hubs of a Spoke being monitored). The SIREN DCC provides resources in WebDCU to support the planning, conduct, and documentation of site monitoring.

Definitions

Site Monitoring	Review of an enrollment site performed by a site monitor from the CCC for purposes of data quality assurance and improvement, improved communication and transparency, reinforcement of protocol training, and regulatory compliance.
Central Monitoring	Reviews of data patterns and aberrancy, logic checks, and other parameters across a clinical study performed by a data manager or statistician from the DCC for purposes of quality assurance and improvement and detection of anomalies requiring further investigation.
Monitoring Visit	One episode of site monitoring. A designated period of time (scheduled with the site monitor and the site) during which a site monitor performs a review of the site's data, source documents, regulatory documents, and/or facilities. Visits may be on-site or conducted remotely.
Site Monitor	A qualified research professional employed (or contracted) by the CCC to conduct monitoring visits.
Award Hub	An institution or group of institutions awarded a grant by the NIH to organize and support Hubs and Spokes that serve as enrollment sites in SIREN.
Hub	An institution that contracts directly with the CCC to enroll at their own site and at one or more Spokes with whom they subcontract
Site	Any institution or entity that enrolls in SIREN trials
Spoke	An institution that contracts with a Hub to enroll at their own site

Abbreviations

CCC	Clinical Coordinating Center at the University of Michigan (UM)
CIRB	Central Institutional Review Board.
CRF	Case Report Forms
CTMS	Clinical Trial Management System
DCC	Data Coordinating Center at the Medical University of South Carolina (MUSC)
DCR	Data Clarification Request
EHR	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
NIH	National Institutes of Health
RSDV	Remote source document verification
SDV	Source document verification
SIREN	The Strategies to Innovate Emergency Care Clinical Trials Network
WebDCU	The CTMS used by SIREN, created and managed by the DCC

Processes

1. **Good Clinical Practice**
   SIREN site monitoring is performed consistent with the goals and practices outlined in ICH GCP E6 (R3 September 2025) section 3.11.4.

2. **Protocol-specific Site Monitoring Plan**
   The parameters of site monitoring are tailored to each clinical trial or study based on the scientific needs, regulatory framework, and available resources for each project. These parameters should be described in sufficient detail in a free-standing site monitoring plan or as part of a larger Data Safety Monitoring Plan. The plan should describe:
   a. Frequency and timing of monitoring visits - Monitoring visits may be planned based on a variety of parameters including time (e.g. at least one visit per year), enrollments (e.g. at least one visit per a certain number of enrollments), or a combination of these (e.g. within 4 months of a first enrollment). A plan may also allocate visit frequency using risk-based tools (e.g. lower visit frequency based on accumulated data quality metrics). The timing and frequency of visits should be sufficient to ensure adequate data quality, integrity, and participant safety within the context of the specific trial.
   b. Scope of site monitoring - Specific data items, regulatory documents, and/or facilities to be inspected should be described. Typically this involves specifically identifying the highest priority CRFs and the data items within those CRFs requiring SDV. Data collected for operational purposes, or without planned primary analytical purposes may not require SDV. Similarly, data for which the CRF itself is likely to be the source document, (e.g., when data are observed by the study team and directly and contemporaneously entered on the electronic CRF as the first

place the information is recorded) and for which there is unlikely to be another source, typically should be designated as not requiring SDV. For regulatory documents, it is common to designate that consent forms will be reviewed. For facilities, the plan may designate inspection of the ED or other place of enrollment, the pharmacy storing study drugs, or the location where study equipment or records are stored.

c. Sampling - Monitoring may be accelerated using sampling strategies if allowed in the trial-specific plan. Sampling can be specified by participant (e.g. 50% of participants enrolled at each site will undergo SDV) or by items (e.g. a specific CRF may only be SDV in 50% of those enrolled). If a sampling strategy is employed, it is preferable to ensure the sampling is random rather than selected by convenience (e.g, not just those with readily available source data) or time (e.g. not just the first year of enrollment). The DCC may help provide sampling targets.
d. Extra monitoring for-cause and not-for-cause - The study leadership, Award Hub, Hub, or Spoke leadership may request monitoring more frequently than otherwise planned for cause when an investigation of quality is indicated. Time and resources permitting, additional monitoring may also be performed not-for-cause. Monitors may review a broader scope of items than what is prioritized or designated in the plan, or may perform visits more frequently than planned at their own discretion or as directed by leadership.

3. Site Expectations and Responsibilities for monitoring visits

a. Preparing for a monitoring visit - In preparation for an upcoming monitoring visit, sites need to be responsive in scheduling, expedite access to records, pre-review their CRFs to correct as many errors and missing data as possible prior to the visit, and prepare to be able to direct site monitors to the appropriate sources for each CRF.
    i. Scheduling Responsiveness: Sites should respond in a timely manner to monitoring visit scheduling requests to facilitate compliance with the sponsor's monitoring plan.
    ii. Access to Records: Sites must ensure that study monitors are granted efficient access to medical records, regulatory files, and any other required documentation for source data verification whether on-site or remote. Sufficient planning and time must be allotted to ensure monitors have all necessary permissions and privileges prior to the visit. Source documents external to the EHR must also be organized and accessible for monitoring. To share source documents external to the EHR, the site (or the monitor) may establish a HIPAA-compliant shared folder or secure repository.
    iii. Case Report Form (CRF) Preparation: Sites should pre-review all CRFs prior to the visit, correcting errors and resolving missing or inconsistent data to the extent possible.
    iv. Source Documentation Navigation: Sites should prepare to direct monitors to the appropriate source documentation supporting each CRF entry, in alignment with ICH GCP E6 (R2) Section 4.9.
b. During a monitoring visit - Sites need to be available to answer questions (greater availability may lead to fewer DCRs). The study staff and site PI should be available to meet during the visit. For on-site monitoring visits, the site should be available to accompany inspections.

c. After a monitoring visit - Sites need to promptly reply to DCRs and address any identified action items. Sites document their responses to action items in WebDCU. The site PI needs to review and sign off on the monitor report in WebDCU.

4. Site Monitor Expectations and Responsibilities for monitoring visits

a. Preparing for a monitoring visit - Correspond with the primary study coordinator to determine the location and time of the monitoring visit. The site monitor will provide the site with a Pre-Visit letter including an agenda of activities, a list of participants to be monitored, and confirmation that EHR access and sources needed to conduct the visit are available. This should be sent to the Primary Study Coordinator and Site PI once the visit is confirmed. Monitors use the WebDCU monitoring module to plan, track, and report their monitoring visits.

b. During a monitoring visit - Near the onset of a monitoring visit, the site monitor will meet with the site study staff and review the plans for the visit. The site monitor and study team may also discuss screening and enrollment strategies, any subject discontinuation, and identify any challenges at the site. Data quality metrics in WebDCU will be reviewed together, so that the site can benchmark their performance against other sites. The monitor will then review the content of the monitoring visit as described below. Clarifications may be addressed immediately with the study team if available, or through DCRs generated in WebDCU. Toward the end of the monitoring visit, the site monitor will again meet with the site study staff and the site PI (whenever possible) to review findings of the review and any action items that will be included in the subsequent report.

c. After a monitoring visit - Site monitors will complete a monitoring report in WebDCU including whether the visit was on-site or remote, the list of participant CRFs reviewed, findings of the review and action items.

5. Content of the monitoring visit and items that may be reviewed by the site monitor

a. Regulatory binders and files - Both the site e-binder in WebDCU (which contains all essential records) and any physical regulatory binders maintained (for on-site monitoring visits only) may be inventoried for completeness and missing or expired materials. These reviews typically include confirmation of appropriately completed and signed informed consent documents.

b. Source document verification - Most of the effort of a monitoring visit is directed toward verification that data reported in the CRF is consistent with and completely represents that in the source documentation. The source documentation in SIREN trials and studies is usually the electronic health record (EHR). Given the complexity of the conditions under study and the CRFs in most SIREN trials, monitors will typically require direct view access to the EHR to properly conduct SDV whether on-site or remote. Alternative strategies such as reproduction of parts of the EHR in a secure shared folder, or over-the-shoulder reviews may be acceptable for simpler trials with few source documents, or under other exceptional circumstances.

c. Protocol adherence - The site monitor will also review reported and potentially unreported protocol deviations (including eligibility deviations) through review of the completed CRF casebook, source documents, and discussions with the site study staff. The site monitor will

assess familiarity and understanding of the protocol by the site study staff and facilitate and reinforce training as needed.

d. Safety reporting - The site monitor will also assess for potentially unreported adverse events through review of the completed CRF casebook, source documents, and discussions with the site study staff.
e. Inspection of facilities - For on-site monitoring visits, the study monitor may inspect site facilities to assess proper storage of research records or equipment. When applicable the site monitor will review pharmacy storage conditions and records. The monitor will reconcile investigational product local inventory with that in WebDCU and ensure that inventory marked as disposed and destroyed product is no longer present.

6. Documentation of Monitoring Visits and findings

a. Documentation of monitoring visits is completed in the WebDCU monitoring module.
b. The monitoring report template and the included fields are shown below. The template is provided for illustrative purposes only and may be revised and evolve over time.
c. The site monitor will generate a report for every monitoring visit completed.
d. The site PI is notified of the completed report, reviews the report (including action items) and signs off on the report in WebDCU.
e. Sites document responses to action items in the monitoring report in WebDCU.
f. The national trial PIs are notified of the completed report as well. A national trial PI reviews the report and signs off on the report in WebDCU.
g. All monitoring reports are retained in WebDCU.

Monitor Visit Report Template and Content

No.	Item Description	Data Value
	Section A: Site Monitoring Visit Summary Information	
2	Site Name	
3	Monitor	
4	Visit Type	On-site *Remote*
5	Start Date	
6	Stop Date	
7	Total Subjects Reviewed	
8	Total CRFs Reviewed	
9	Total CRFs Verified	
10	% CRFs Verified	
11	Total CRFs Queried	
12	Previous Visit Date	
13	Next Visit Date	
14	Monitoring Visit Report Data Freeze	
14	Monitoring Visit Report	XXX.pdf

19	Site Study Personnel Attended the Monitoring Visit		
No.	**A. Name**	**B. Role**	**C. Comments**
19-1		PSC	

Section B1: Site Trial Operation Monitoring Results

Findings for certain auto check points in the table below are derived from WebDCU. Before completing section B1, click 'Save'. Then click 'Refresh Monitor Checklist'.

20	Site Monitoring Check List						
No.	**A.**	**B.**	**C.**	**D.**	**E.**	**F.**	**G.**

	Monitoring Check Point	Check Type	Check Point Passed	Findings	Site Response Required	Site Response	Case Closed
20-1							
20-2							

Section C: Case Report Form Data Monitoring Results

30	CRF Data Review Summary by Form					
No.	A. CRF No.	B. CRF Name	C. CRF Reviewed	D. CRF Verified	E. % CRF Verified	F. CRF Queried
30-1						
30-2						

31	CRF Data Review by Subject						
No.	A. Subject ID	B. Start Visit	C. End Visit	D. CRF Reviewed	E. CRF Verified	F. % CRF Verified	G. CRF Queried
31-1							
31-2							

32	Rule Based Protocol Violation Summary			
No.	A. Form	B. Rule ID	C. Protocol Violation	D. Count
32-1				
32-2				

33	Monitor Data Clarification Request Query						
No.	A. CRF No.	B. CRF Name	C. CRF ID	D. Subject ID	E. Monitor Query	F. Site Response	G. Status
33-1							
33-2							

900	General Comments	

SIREN CCC PI Sign-off: _____ Robert Silbergleit 2025.12.12 14:34:29 -05'00'

SIREN DCC PI Sign-off: _____ Valerie Durkalski-Mauldin Digitally signed by Valerie Durkalski-Mauldin Date: 2025.12.12 15:56:50 -05'00'

NIH Administrative PO Sign-off: _____ GRETCHEN C. SCOTT -S Digitally signed by GRETCHEN C. SCOTT -S Date: 2025.12.15 07:33:11 -05'00'