Revision Table		
Version of the document	**Edited paragraphs**	**Change description**
V1.1	5.2.1	Previous paragraph 5.2.1 has been renamed 5.3.9
	5.3.9	Previous paragraph 5.3.9 has been renamed 5.3.10
	5.3.9	- "Subject Identification Log" FRM 33-17 has been corrected to FRM 33-18 - "Drop Out Log" FRM 33-19 has been corrected to FRM 33-24 - "Study Site Duty Delegation Log" FRM 33-14 has been corrected to FRM 33-20 - "Site visit Log" FRM 33-18 has been corrected to FRM 33-19 - "Site Training Log" FRM 33-15 has been corrected to FRM 33-21

1 INTRODUCTION

To assure quality during the study, monitoring oversight activities will be managed by a Monitoring Plan (MP). Quality within clinical trials is defined as the ability to effectively and efficiently answer the intended question about the benefits and risks of a medical device, while assuring protection of human subjects. Risks may be defined as those things that may potentially cause a loss, in this case a loss that affects data integrity or subject safety.

The Monitoring Plan (MP):

- Is designed to support all applicable members assigned to a clinical trial either conducted or supported by Limacorporate S.p.A, in fulfilling their responsibilities during study planning, conduct, and closeout in accordance with ICH GCP Guidelines, ISO 14155 Guidelines and contractual obligations, and to ensure that all trial procedures are being performed in accordance with protocol requirements.
- Should be aligned with the study protocol and other documents developed for the study.
- Is a living document that will be maintained throughout the course of the clinical study; If the MP is updated, the new version number and date will be clearly identified on the front page of the MP; all updates are filed in the Trial Master File.

This monitoring plan is a project-specific operating plan during the conduct of H-34 DELTA Revision study.

2 ISSUE ESCALATION

This section describes the issue escalation process. The escalation pathway is considered to be a critical study management process and should be referred to when resolving study and site issues.
This section describes the escalation process in case a significant non-compliance with clinical investigation plan, SOPs, GCP and/or applicable regulatory requirements by an investigator/institution/member of study staff is discovered during the study monitoring.

According to the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH GCP), non-compliance can be described as: “Non-compliance with the protocol, Standard Operating Procedures (SOPs), GCP and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor’s staff”
Non-compliance’ includes, but is not limited to the following:

• Research duties undertaken by staff without appropriate experience and education;
• Delegation of responsibilities unclear and undocumented throughout the conduct of the research;
• Undertaking research without obtaining a favorable Regulatory or ethical opinion from an Ethics Committee;
• Failure to comply with the current approved research protocol (protocol deviation);
• Failure to obtain the necessary approval(s) for any amendment to the protocol or patient documentation (except in the case of Urgent Safety Measures);
• Failure to take informed consent properly and in line with applicable regulatory requirements and EC-approved consent forms and patient information sheets;
• Deficiencies in the accuracy, completeness, legibility and timeliness of data reported to the Sponsor in Case Report Forms (Limes) and in all required reports;
• Failure to manage data securely, in line with applicable legislation and good practice standards;
• Improper record-keeping and failure to retain Essential Documents in the Trial Master File and/or Investigator Site File;
• Failure to retain research documentation for the appropriate retention period;
• Failure to submit periodic progress and safety reports to the relevant bodies;
• Failure to record, assess and report Adverse Events (AEs) in the prescribed format;
• Failure to comply with the SOPs of the Sponsor/CRO/Institution;
• Neglecting to provide final reports to the appropriate bodies.

The following non-compliance categories have to be considered used:

• Critical: a critical non-compliance presents a significant business risk and may result in significant regulatory action if not corrected immediately. A critical non-compliance may require that operations are halted until corrective action is complete. A critical non-compliance is a significant and unjustified departure(s) for applicable legislative requirements with evidence of at least one of the following:
- Safety or well-being of trial subjects has been or has significant potential to be jeopardised;
- The clinical investigation data are unreliable;
- There are a number of major non-compliances (as defined below) indicating systemic quality failure.

• Major: a major non-compliance represents a systemic and/or significant business and/or compliance risk. A major issue requires prompt corrective action although operations can proceed. A Major non-compliance is a significant and unjustified departure from applicable legislative requirements that may not have developed into a critical issue but may have the potential to do so unless addressed.

• Minor: a minor issue requires corrective action to improve the quality of existing documentation or data, and/or preventive action to enhance or modify existing processes or procedures. Minor non-compliance is a departure from one or more of the following has occurred but it is either critical or major:
- Legislative requirements;

- ICH GCP guidelines;
- Procedural requirements.

Escalation procedure:
Critical/Major: The Clinical Research Associate (AJCL/AMCL/ASCL) or designee informs the sponsor via email or phone contact within 24h of detection of the issue. The initial reporting to CMCL/RMCL should be done by email and should include:
• Investigator's name and investigational site where the issue has been detected;
• Clinical investigation number and title;
• Summary of the NC;
• Initial corrective actions;
• initial evaluation of the impact on the safety of the subjects and integrity of the data.
The sponsor will give a feedback about classification of issue and corrective action. The resolution of the issue should be provided within 10 working days since the issue detection. The AJCL/AMCL/ASCL or designee documents the issue in the visit report together with the CAPA (corrective action and preventive action).
Minor: the AJCL/AMCL/ASCL or designee documents the issue in the visit report indicating the category and the corrective action and in the study specific "Protocol Deviation Form" (FRM 33-23) Form. The Form is reviewed periodically by CMCL/RMCL in order to consider if the monitoring plan and risk management plan has to be update or if a specific action has to be undertaken in order to guarantee a good overview of the study in general. The issue is monitored till the resolution.

3 PURPOSE

The purpose of the MP is to provide guidance and study specific instructions to ensure completeness and consistency in study monitoring and site management activities throughout the conduct of the study.
The plan describes the tasks performed during the types of monitoring site visits as well as follow up activities related to the site visits. The plan includes a list of minimum acceptable criteria and does not replace an understanding of adherence to the requirement contained in the approved study protocol, applicable regulation, guidelines or SOPs.

4 SCOPE

The Clinical Research Associate (AJCL/AMCL/ASCL) or designee shall review the MP periodically throughout the study. If the MP is updated, the new version number and date should be clearly identified on the front page of the MP. Updates to the MP include any revisions or updates made to the appendices. The description of changes is documented in the Revision Table section of the MP. All versions will be filed in the Trial Master File.

The MP for study in object H-34 DELTA Revision
has been created to provide instruction to be followed during all the periods of the study. Please refer to the sections below.

5 TABLE OF MONITORING VISITS

The monitoring frequency defined in the table below serves as a guideline and may be changed if there are significant monitoring issues at the site that requires follow up. The

AJCL/AMCL/ASCL or designee will use good judgment when scheduling Monitoring Visits (MVs) to ensure that maximum efficiency is utilized on site (e.g., an MV may be delayed for a reasonable time if it is understood that additional data can be monitored later).

site Qualification Visit (SQV)	An SQV will occur following review of the Feasibility Questionnaire and the Confidentiality Agreement on expressed interest by the investigator and the need to qualify the site
Site Initiation Visit (SIV)	An SIV will occur prior to the first subject Screening Visit at site. The SIV will occur after all the approvals are in place.
Monitoring Visit (MV)	MVs should be scheduled based on quality across the program at site. Visits should not be scheduled unless there is enough data backlog to warrant a visit or a visit is required for a specific reason. The following general indications should be ensued: • First MV should be scheduled within 2/4 weeks after 4 patients were enrolled. • Monitor every 2-4 months during enrolment period depending of enrolment rate at the site. • Monitor every 3-6 months during follow-up period until Last Patient Last Visit (LPLV). • Contact sites every 2 weeks during enrolment period. • Contact sites monthly during follow-up period until LPLV. • MV frequency may be increased to ensure Quality. Every MV needs to be approved by the sponsor via email.
Close-out Visit (COV)	COV will be scheduled upon closure of one site.

Table 1

5.1 Site Qualification Visit (SQV)

This section describes the activities to be performed during the Site Qualification Visit visit and the SOP/WIN to be followed.

SQVs are to be scheduled and conducted in accordance to the reference Work Instruction (refer to WIN-33-1-05). SQV may be conducted either on-site or remotely via telephone/WebEx in case the Site has already performed a trial with the Company o or in case of specific justified circumstances (e.g. like but not limited to COVID restrictions),.

Activities for each SQV includes, but are not limited to (refer to Table 2):

SQV ACTIVITIES
• Evaluation of the Site's ability to conduct the study, including qualification of investigator and other study personnel, scientific knowledge and experience in patient care and in the use of MD and adequacy of clinic facilities and ensure the investigator

is aware of, and comply with, GCP-ICH, ISO 14155 and the applicable regulatory requirements; the investigator shall be a person exercising a profession which is recognised in the Member State concerned as qualifying for the role of investigator on account of having the necessary scientific knowledge and experience in patient care. Other personnel involved in conducting a clinical investigation shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks.
• Review of the Study Protocol, Investigator's Obligations per ICH-GCP and ISO 14155 with Investigative Site personnel;
• Assess Investigative Site's ability and expectation regarding subject recruitment;
• Discuss IRB/EC procedures and potential issues (including review of ICF requirements, IRB/EC approvals of required documents, IRB/EC meeting and submission schedule, and IRB/EC Roster / General Assurance Number);
• Discuss source document requirements including review of standard clinic/hospital records to determine adequacy and accessibility of source documents for this Study and discussion of Good Clinical Practice (GCP) guidelines related to retention of study documents. Determine the location and types of source documents maintained by the site (e.g., Electronic records, hard copy files, etc.);
• Discuss the "Feasibility Questionnaire" (FRM 33-07) Form;
• Discuss responsibilities of Study personnel;
• Discuss experience of Investigators and site staff using the product/device subjected to study;
• Anticipate using of an electronic Case Report File (eCRF) – Limes and set expectations on: • entering subject data into eCRF on a timely basis; • site payment schedule based upon complete and timely entry of data; • training required of all site personnel using the system - training provided by the Company or a designated person; • evaluate site's receptiveness to using eCRF; • evaluate site's technical capabilities about conducting eCRF trials (e.g. secured computer with high- speed internet connection); • assess site for equipment availability and training needs per protocol; • discuss and asses Site's ICF process and Site's SOPs; • evaluate and discuss ICH/GCP compliance and documentation; • discuss previous regulatory inspection and findings;

Table 2

5.1.1 SQV report

The "Site Qualification Visit Report" (FRM 33-08) Form has to be finalized within a total of ten (10) business days from the last day of the site visit and the Follow-up Letter has to be finalized and sent to the site within ten (10) business days from finalizing the SV Report. The "Site Qualification Visit Report" (FRM 33-08) Form and Follow-up Letter are completed in accordance to the reference Work Instruction (refer to WIN-33-1-03).

AJCL/AMCL/ASCL or designee is responsible to fill the "Site Qualification Visit Report" (FRM 33-08) Form. Once completed the report, AJCL/AMCL/ASCL sends it to

CMCL/RMCL or to the designee for review and the follow-up letter is sent to the Investigative Site. Both the approved Report and Follow-up letter, are files by by AJCL/AMCL/ASCL/CMCL/RMCL in the TMF and in the SharePoint in the folder "MONITORING" in the respective clinical site.

The "Site Qualification Visit Report" (FRM 33-08) Form and Follow up letter have to be written in English.

5.2 Site Initiation Visits (SIV)

This section describes the activities to be performed during the site initiation visits (SIV). Note that prior to the SIV, the SQV report and follow-up letter is reviewed to identify any outstanding action items, including outstanding documents for retrieval at the SIV.
Also, prior to the SIV, AJCL/AMCL/ASCL/CMCL/RMCL or designee confirms that the site has received all required study supplies including the investigational devices if applicable and that all the authorizations (ethic and administrative) have been obtained.

SIVs are conducted in accordance with the reference Work Instruction (refer to WIN 33-1-05).

Every effort must be made to conduct the SIV after all required regulatory and contractual obligations have been met.

SIV will be performed when:

- SQV has been conducted
- Principal Investigator's (PI) signed Confidentiality Agreement has been obtained
- Clinical Trial Agreement (CTA) is finalized and signed. RMCL may approve the conduction of the SIV prior to CTA fully execution if the CTA is in good faith negotiation and only pending final signatures.
- Site has been approved by EC/IRB for participation.
- Appropriate approvals from any local/institutions, if applicable, have been received.
- Additional region and trial-specific criteria have been fulfilled, where applicable.

Site's unconditional EC/IRB approval, a fully executed CTA and all site regulatory/essential documents must be obtained and approved before starting enrolment of patients. Thus, the SIV Follow-up letter must contain language to remind the PI and site staff that no study procedures can be done, and no subjects may be enrolled until the site is fully activated.
The PI and site staff will be informed that they will receive written notification by LimaCorporate via email when it is acceptable to begin the screening of patients.

During the SIV, the activities that will be performed, but are not limited to:

SIV Activities
Complete information on the SIV in Site Visit Log, filed in the ISF
Review the Study Protocol and IFU
Discuss investigator's and site staff's obligations as per protocol and guidelines (e.g. ISO

14155, ICH-GCP)
Discuss responsibilities to be delegated to certain members of the site staff by the PI and ask to complete Site Signature and Duty Delegation Log (SSDDL)
Discuss EC/IRB issues including review of requirements for documentation of informed consent, requirements for periodic EC/IRB review and re-approval, and ongoing EC/IRB reporting requirements (e.g. protocol deviations, adverse events, etc.).
The AJCL/AMCL/ASCL or designee will also provide review of general instructions for eCRF (Limes) completion. Procedures for correction/revision of recorded data should also be covered.
Discuss the Randomisation procedure as per protocol, confirm that the site received sealed envelopes.
Discuss maintenance of ISF (e.g. completion of Drop-out Log, Screening & Enrolment Log)
Discuss EC/IRB approved ICFs and patient materials (Informed Consent Form, Questionnaires)
Review of Adverse and Serious Adverse Event (AE/SAE), device deficiencies procedures and requirements for reporting procedures, including SAEs, deaths, pregnancies, relationship with device and outcomes
Discuss schedule and procedures for routine monitoring visits
Discuss procedures and requirements for retention and access of study documents.
Discuss screening and enrolment (focus on inclusion and exclusion criteria)
Discuss expectations set by LimaCorporate regarding source document requirements as per ICH-GCP and ISO 14155
Determine the location and types of source documents maintained by the site (e.g., electronic records, shadow chart, etc.), and AJCL/AMCL/ASCL or designee proper access to all source. The information will be documented in the SIV report.
Verify the site's facilities during the visit.

Table 3

AJCL/AMCL/ASCL or designee:

- Obtains Principal Investigator's (PI) signed Confidentiality Agreement and protocol signature page;
- ensures that the applicable Independent Ethics Committee/Institutional Review Board (IEC/IRB) approval documentation are obtained;
- Ensures all local requirements for regulatory submissions are satisfied;
- Obtains the Investigator/institutional financial contract signed and dated;
- Ensures that all required documentation is obtained;
- Completes, signs the "Greenlight Approval For Site Activation" (FRM 33-22) Form and transmits it to CMCL and RMCL for approval.

Once Greenlight Approval For Site Activation" (FRM 33-22) Form has been reviewed, approved and signed by CMCL/RMCL, the site can be activated and can start the enrollment activities.

SIV report:

The AJCL/AMCL/ASCL or designee shall send a confirmation on the scheduled visit to the site no less than 5 business days prior to the visit, containing an agenda on topics to discuss and actions to be taken if applicable.

The initial SIV must be onsite, in case of circumstances (e.g like but not limited to COVID restrictions) the SIV can be done remotely only after sponsor decision and approval. If a PI is unable to attend the onsite SIV meeting, the AJCL/AMCL/ASCL or designee shall schedule a phone meeting within 7 days to review the protocol and PI responsibilities and any pertinent key study information.

The SIV Report must be finalized within a total of 10 business days of the last day of the site visit and the Follow-up Letter must be finalized and sent to the site within 10 business days of finalizing the SIV Report. The SIV Report and Follow-up Letter are completed in accordance with WIN-33-1-05.

The SIV Report will be send to the RMCL/CMCL or designee for review and the follow-up letter will be sent to the Investigative Site. Both approved SIV Report and Follow-up letter need to be filed in the TMF and in SharePoint in the folder “MONITORING” in the respective clinical site.

Approved SIV Report, as well as the Follow-up letter, need to be filed in the ISF on site.

SIV Report and Follow up letter are obliged to be written in English.

5.3 Monitoring Visit (MV)

5.3.1 Informed Consent Process (ICF)

This section describes the minimum recommendations concerning a proper Informed Consent Process, as per GCP and applicable standard and regulation (refer to par.2):
AJCL/AMCL/ASCL/CMCL or designee:

- Ensures the approved Informed Consent Form (ICF) is correctly signed and dated by every subject recruited since the previous monitoring visit. Each ICF must be signed and dated by the Investigator or staff member designated according to the “Study Site Duty Delegation Log (SSDDL)” (FRM 33-20) Form who is conducting the informed consent discussion, prior to the commencement of any study procedures. The signed ICF should be filed in the Investigator Site File, or if otherwise the location should be specified with a file note;
- The process for obtaining Informed Consent is to be described in the subject files;
- Any observed deficiency in the ICF management process at site have been discussed as a priority topic with the site staff and an action plan is implemented to solve the pending issues and prevent their recurrence;
- The Investigator or designee has informed the subject of new information and any ICF revisions implemented have been signed and dated by ongoing subjects;
- Appropriate information has been provided to all vulnerable subjects (incapacitated adults and minors);
- If the subject is not able to give informed consent (e.g. incapacitated adult), then his/her Legal Representative must sign and date the ICF on the subject’s behalf, in

addition to documenting their name, relationship to subject and the reason why. The process must be approved by the IRB/IEC and be documented in the subject files;

- In the case of clinical trials for minors, the informed consent of the parents or Legal Representative must be obtained. All attempts should be made and documented in subject's file, to have the subject signature on ICF for minors as well, depending on local requirements;
- All ICFs are obtained prior to conducting any study related procedures. If consenting and screening occur on the same date, it needs to be stated that the patient was given adequate time to review and give consent;
- All subjects can read and understand the language of the ICF that is being used;
- All subjects are provided ample time to review the ICF and ask questions;
- The site may provide a copy to take home for review prior to completing the consent process;
- Signature and date of the person obtaining consent and explaining the process have to be recorded on the ICF;
- Site staff who obtained the informed consent have been delegated this responsibility by the PI, indicated on the SSDDL;
- All ICFs are signed and personally dated by site personnel and subjects;
- The consent process is clearly documented in the subject's source documents, including documentation to support that the subjects have received a signed copy of the ICF.

5.3.2 Safety

This section describes the minimum recommendations concerning a proper safety monitoring and reporting, as per ICH-GCP §4.11, ISO 14155 §7.4, §9.2.5, §10.8 and Annex F and MEDDEV 2.7/3.

All subjects will be monitored throughout the study for AEs/ADEs/UADEs/SAEs/SADEs/USADEs, from the time of the surgery till the final follow-up visit and/or till the resolution of event whichever occurs first.
Verify that PI and/or delegated Sub-I have performed assessments of causality and severity of every AEs/ADEs/UADEs/SAEs/SADEs/USADEs as per clinical Investigation plan
When an AEs/ADE/UADE/SAE/SADE/USADE occurs, the necessary information collected must include: - Type of event (event term and classification) - Date of onset - Date of resolution - Outcome - PI/Sub-I assessment of severity and causality to device and study procedure - Seriousness criteria - Action taken
If an Event changes in severity throughout the study, the existing AE should be updated to indicate the highest severity and should be SDV'd as such.
All SAEs/SADEs/UADEs/USADEs and device deficiency that have led to a serious

adverse device effect will be reported to sponsor Lima within 24 hours after investigator site study personnel's awareness of the event.
All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the sponsor.
Ensure that the AEs/SAEs/SADEs/UADEs/USADEs and device deficiencies that could have led to a serious adverse device effect are reported to the EC according to EC guidelines and national regulations.

Table 4

AJCL/AMCL/ASCL/CMCL or designee:

- Checks for any Adverse Events (AE) and SAEs for all subjects/patients, since last monitoring visit. In addition to reviewing the subject notes and CRF/eCRF, asks the site staff if any new SAEs/AEs occurred;
- Ensures that the Investigator is aware that the subject must obtain medical care until resolution of the AE. If the AE is not under the Investigator's expertise, he should refer the subject to a qualified physician;
- Ensures that any new SAEs since last monitoring visit have been sent or reported to the sponsor, and that follow-up questions relating to previously reported SAEs have been completely addressed. If a SAE has not been reported within 24 hours, asks the Investigator to report the SAE immediately by completing the Clinical Study SAE Report Form;
- Reminds the Investigator of the correct procedure and of his obligations according to the CIP, GCP and local requirements, in regards with safety reporting;
- Checks the information on the Clinical Study SAE Report Form against the source data and the CRF/eCRF entry;
- Clarifies any observed inconsistencies with the Investigator and requests the site to resend a follow-up SAE form with updated information if required;
- Ensures that any SAEs/SADEs/DDs have been reported to Independent Ethics Committee/Institutional Review Board (IECs/IRB), if required, or that reason for not doing so is documented.

5.3.3 Source Data Verification and Source Data Review

This Monitoring Plan emphasises a difference between Source Data Verification (SDV) and Source Data Review (SDR).

SDV is defined as comparing available data in the source document to the data collected on the Limes (eCRF) to ensure data has been recorded accurately, e.g. transcribed accurately.

SDR involves on-site review of source documentation to review protocol compliance, ensure the source is adequate and meets the ALCOA+ principles (= attributable, legible, contemporaneous, original and accurate + complete, consistent, enduring, available), to ensure investigator involvement and appropriate delegation and assess compliance to other areas (e.g. ISO 14155, ICH-GCP).

SDR is not comparison of source data against eCRF data.

5.3.4 Activities to be performed during the monitoring visit

AJCL/AMCL/ASCL/CMCL or designee:

- Verifies that source documents and other trial records are accurate, complete, up-to date and securely maintained;

• Checks the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other;

• Reviews data in the CRF/eCRF for completeness, consistency, legibility and protocol compliance as detailed in the Monitoring Plan and/or in the eCRF completion guideline.

• Informs the Investigator and/or authorized site staff of CRF entry error, omission or illegibility and ensures that appropriate corrections, additions, or deletion are made, dated, explained and initialled by authorized site staff personnel. The corrections must be completed either by the Investigator or by an authorised member of staff as documented in the SSDL;

• In the case of major issue noted during CRF review, the AJCL/AMCL/ASCL or designee should be informed CMCL/RMCL immediately and appropriate action taken

The Table 5 defines the main activities to be performed during the monitoring visit:

Check the informed consent process has correctly been reported on the SD and verify all Subjects who signed the ICF are documented on the internal Site Subject identification log
Check that any new ICFs have been duly signed and dated by subjects and delegated staff i.e PI/Sub-Inv
Check that the original ICFs are duly filed in the ISF
Check if changes to the site staff have been made. If yes, check if information in ISF (e.g. SSDDL, CV available, Certificates available, training log) are coherent and collect copies for the TMF.
Verify that the PI or designee is providing required training to site staff
Verify training documentation is present and that on-going training is documented and filed in the ISF. Training documentation should be checked against the SSDDL
Verify site staff are performing specified functions in accordance with the protocol and as delegated by the PI on the Site Signature and Duty Delegation Log (SSDDL)
Check status of open action items indicated by the MVR's CAPA section of previous MVs
Check if the correct patients have been enrolled (i.e. fulfil all inclusion and no exclusion criteria. Cases of incorrect enrolment should be discussed with the PI, reported in the MVR CAPA section and escalated to LimaCorporate immediately (see 5.3.8.)
Informed Consent withdrawals revealed during the monitoring visit should be discussed with the site personal
Emphasise to the site the need to minimize the number of patients lost to follow-up
Check if all AEs, ADEs, SAEs, USADEs and SADEs were reported in a timely manner and report to the sponsor as per section 5.3.2
Questions on new potential A(D)Es and SA(D)Es should be asked.
New reported SAEs need to be reviewed and it shall be checked whether follow-up information on previous reported SAEs are available
Check if data entry quality with respect to ALCOA+ principles are met (i.e. time of data entry, comprehensibility of information provided, legible, person delegated on procedure

by SSDDL)
Discussion on data entry timelines
Check protocol adherence and upon identifications of deviations, discuss with the PI, agree on an action plan and report in the MVR CAPA section
Check if questionnaires (HHS,OHS) were completed according to protocol
Check if X-rays scan with AP and lateral views were performed as per protocol.
Discuss pending queries status
Check if latest version of essential documents is filed (e.g. EC approval, Protocol, IFU, Insurances, CE-Certificate). If not, report in the CAPA section of the MVR
Complete information of the MV in Site Visit Log, filed in the ISF, collect a copy for the TMF

Table 5

5.3.5 Responsibilities concerning SDV

For H-34 study, a reduced SDV is performed, through a mixed approach, since data quality check is supported by centralized remote monitoring.
100% SDV must be performed for the following data: ICF, Eligibility, baseline data, implant data, date of visit, primary endpoint, and safety. Reduced % of SDV during the MV for each section of the Limes (eCRF) should be performed as per the following table

	Pre-operative visit	Intra-operative visit	Discharge	FU 2 months (+/- 30 days)	FU 6 months (+/- 60 days)	FU 1 year (+/- 6 months)	FU 2 years (+/- 6 months)	SFU 3 years (+/- 6 months)	SFU 4 years (+/-6 months)	SFU 5 years (+/- 6 months)
Verify Inclusion/Exclusion criteria	100%									
Obtain informed consent	100%									
Demographics	100%									
Obtain medical history Note: all the medical history needed for the evaluation of the eligibility criteria and all medications/complications related to the pathology, joint, or any condition that could interfere with the study procedures and evaluations must be reported.	100%									
Physical examination	50%		0%	0%	0%	0%	0%			
Surgery and implant data		100%								
Date of visit			100%	100%	100%	100%	100%	100%	100%	100%
OHS	100%		0%	10%	10%	10%	100%	20%	20%	100%
HHS	100%		0%	20%	20%	20%	100%			

X-rays	100%		100%	100%	100%	100%	100%			
Radiographic evaluation	10%		100%	0%	0%	0%	100%			
Concomitant Medication all medications /complications related to the pathology, joint, or any condition that could interfere with the study procedures and evaluations must be reported.	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Evaluation and reporting AE/SAE		100%	100%	100%	100%	100%	100%	100%	100%	100%

Table 6

When source data verification is required at 50%, every other patient have to be checked. When source data verification is required at 10%, one every five patient has to be checked.

When source data verification is required at 20%, one every ten patient has to be checked.

Inconsistencies and/or deviations need to be reported in the respective section of the MVR. It is required to complete respective information into the CAPA section.
If significant issues are identified during SDV, error rate assessment is evaluated by the Sponsor and SDV % may be increased.

Indicatives on which subjects, respective visits and data have been checked during the visit, shall always be provided in the MVR in section “Source Data Verification”.

5.3.6 Responsibilities concerning SDR

Medical records of all enrolled patients will be reviewed to ensure compliance with inclusion/exclusion criteria.

For all enrolled patients, the AJCL/AMCL/ASCL or designee is obliged to provide crucial information within the MVR in the section “Source Data Review” on:

- Diagnosis as per medical records, confirming indication for treatment Date of consent for H-34
- Date of signature on ICF of both the patient and name of delegated site staff who obtained informed consent from the subject
- Version of all (if applicable) ICFs signed per patient
- Whether there is indicative information on informed consent process available in the source data

AJCL/AMCL/ASCL or designee shall review patient’s medical record for presence of unreported SAEs or AEs.

The AJCL/AMCL/ASCL or designee shall prioritize the visit activities to ensure ICF and eligibility of subjects have been checked, status of SAEs have been reviewed.

Via reviewing relevant parts of source documentation/study documentation of patients who have been documented as withdrawn consent, the AJCL/AMCL/ASCL or designee ensures the patient indeed withdrew consent.
For patients who are documented lost to follow up, the AJCL/AMCL/ASCL or designee should confirm that due diligence has been completed by site to collect information on status of the patient.

5.3.7 Corrections to source data

The incorrect entry should have a single horizontal line marked through it in a manner that leaves the incorrect entry legible. Correction fluid or correction tape shall not be used. The correct entry is written next to the incorrect entry. The correction is initialled and dated by the person who makes the correction. Only authorized site personnel designated on the SSDDL may do corrections to the source data.

5.3.8 Escalation of ineligible subjects and protocol deviations

In case of ineligible subjects AJCL/AMCL/ASCL/CMCL or designee shall inform RMCL immediately (see 2.0: Issue escalation). A discussion with the PI on reasons or rational needs to be held. If applicable, internal discussion at the Company should include the Medical consultant, on possible prematurely discontinuation of the identified patient's participation.
Comprehensive documentation shall be ensured via the CAPA section of the "Monitoring Report" (FRM 33-10) Form.

AJCL/AMCL/ASCL/CMCL or designee shall discuss and document any deviation with protocol or GCP and any other issues detected at each visit, emphasising the Investigator's responsibility to maintain subject safety and welfare. Any deviation must be documented in the "Monitoring Report" (FRM 33-10) Form and in the "Protocol Deviation Log" (FRM 33-23) Form.
AJCL/AMCL/ASCL/CMCL or designee shall forward any deviation and/or issues to the CMCL/RMCL in a timely manner. If deviation is not resolved and/or issue persists then these should be investigated and an action plan implemented to correct the issue and prevent its recurrence.
If a serious breach or misconduct has occurred or is suspected, refer for Handling Cases of Suspected Serious Breach, Misconduct and Fraud and ensures that the RMCL is informed immediately. Ensures the submission of protocol non-compliance to IRB/EC, if applicable.

5.3.9 Maintenance of Essential Documents

AJCL/AMCL/ASCL/CMCL or designee:

- Ensures all supplies for the study are in adequate amount, is within appropriate time range and/or version is up to date during all the course of the study (e.g.: ICF, manuals, patients questionnaires, study specific supplies);

- Ensures the equipment are properly maintained and corresponding documentation is available at site for consultation;
- Ensures the appropriate completeness and maintenance of the "Screening and Enrolment Log" (FRM 33-17 Form, "Subject Identification Log" (FRM 33-18) Form and "Drop-out Log" (FRM 33-24) Form;
- Checks for staff changes since the last visit and ensures Curriculum Vitae have been retrieved for filing in the TMF and ISF and the Study site duty delegation log (FRM 33-20) has been updated;
- Each time a site staff is trained, ensures the completion of the "Site Training Log" (FRM 33-21) Form. Each time that staff change occurs, ensures that a new log is completed and old line is ended with date and signature of PI in SSDL;
- Conducts training or ensures that new staff has been trained on all aspects of the protocol, any protocol amendments and study procedures. Training material and certificate of training must be collected for filing in the ISF and TMF plus the Site Staff Training Log must be updated. If Electronic Data Capture (EDC) is used, authorised new staff must receive training on the EDC system;
- Completes the "Site Visit Log" (FRM 33-19) Form at each monitoring visit and ensures that relevant staffs have signed appropriately;
- Files in ISF copies of all CIPs with related signed protocol signature pages by the Principal Investigator, Amendment forms, Investigator Brochures (IB)s, ICFs and any amendments (if applicable), together with any IEC/IRB and Competent Authority notifications/approvals;
- Collects any outstanding documentation required in the TMF Index and documents it in the monitoring visit report;
- Ensures that the documentation within the ISF is appropriately maintained and updated in accordance with SOPs, ICH GCP and applicable regulatory requirements.

5.3.10 Remote monitoring visit

If due to circumstances (e.g. like but not limited to COVID restrictions), the sponsor or their designee is unable to conduct on-site monitoring, the site will be monitored remotely.
Remote monitoring visits and SDV should occur only when deemed necessary by the sponsor in case the postponement of such activities would put patient safety and data integrity at risk. Monitoring visits can be done remotely only after sponsor decision and approval.
The AJCL/AMCL/ASCL or designee should confirm with the site the possibility to perform remote monitoring visit and if the pseudo anonymized Source documents can be provided.

During the remote monitoring visit the AJCL/AMCL/ASCL or designee should verify with the site:

- The current version of ICF is signed in the proper manner for all the subjects enrolled.
- That all data are entered in eCRF and the eCRF is updated.
- That some issues open from the previous MV are closed (e.g. documents missing related to ISF/TMF that can be shared with the site)
- The possibility to collect pseudo anonymized Source Documents if available only for safety purposes.

All care will be taken to ensure that Source Documents are verified confidentially. Any breach would be reported in the MV report and signalled promptly to the sponsor.

For COVID restriction decision please refer to 6.General Information paragraph.

5.3.11 Monitoring Visit Report (MV Report)

The AJCL/AMCL/ASCL or designee shall send a confirmation of the scheduled visit to the site no less than 5 business days prior to the visit, containing an agenda on topics to discuss and actions to be taken.

If the PI is unable to attend the MV meeting, the AJCL/AMCL/ASCL or designee shall schedule a phone meeting within 7 days to discuss issues identified or give general feedback. In case it is not possible to organize a phone call with PI, an e-mail summarizing the visit can be accepted (i.e FU letter)

The MV Report must be finalized within a total of 10 business days of the last day of the site visit and the Follow-up Letter must be finalized and sent to the site within 10 business days of finalizing the MV Report. The MV Report and Follow-up Letter are completed in accordance with WIN-33-1-05 and WIN-33-1-08.

The MV Report will be sent to the RMCL/CMCL for review and the follow-up letter will be sent to the investigative Site. Both approved MV Report and Follow-up letter need to be filed in the in the TMF and in SharePoint in the folder “MONITORING” in the respective clinical site folder.

MV Report and Follow up letter are obliged to be written in English.

5.4 Close-out Visit

This section describes the close-out visits (COV) to be conducted.

Prior to the visit, the AJCL/AMCL/ASCL or designee may ensure the following:

- Formally document the completion of the trial
- Confirm all documentation is available and can be archived
- Collect remaining trial documentation or request that the site submits outstanding documentation
- Confirm resolution of data queries
- Verify the Principal Investigator (PI) understands their post-trial obligations

COV Activities
Complete information on the COV in Site Visit Log, filed in the ISF
Review previous MVR’s CAPA section on pending/open action items and close them
Check if all queries have been closed, if applicable
Review previous MVR’s SAE section on pending information
Confirm AEs/ADEs/SAEs/SADEs/USADEs and device deficiencies that led to a SADE are

documented and reported to EC, if applicable
Check on status of protocol deviations
Confirm protocol deviations are documented and reported to EC, if applicable
Check if changes to the site staff have been made. If yes, check if information in ISF (e.g. SSDDL, CV available, Certificates available) are coherent and collect copies of the documents for the TMF
Ensure the site personnel stop dates are recorded on the delegation log
Re-confirm that all subjects have completed the trial, if applicable
Ensure that all the Randomization envelopes have been open and filed in the ISF. In case of early termination of the study, ensure that both open and sealed envelopes are filed in the ISF.
Availability and accessibility of subject records for archiving purposes
Discuss archiving responsibilities with PI and site staff
Verify signed Informed Consent is present for each subject and informed consent process complies with LimaCorporate recommendations (see 5.3.1)
Conduct final reconciliation of filed essential Documents in ISF with Trial Master File (TMF): all versions of ICF, latest version of protocol, EC/IRB approval, latest version of IFU, comprehensive insurance certificates from beginning of the study until COV, CE-certificate, Screening and Enrolment-Log, SSDDL, Training logs, Site Visit Log. The originals will be filed in the ISF, final copies will be collected for sponsor archiving in TMF.
Any questions or concerns from the site staff
Check pending payments by LimaCorporate to the Institution

Table 7

COV report

The AJCL/AMCL/ASCL or designee shall send a confirmation of the scheduled visit to the site no less than 5 business days prior to the visit, containing an agenda on topics to discuss and actions to be taken. AJCL/AMCL/ASCL or designee must ensure the PI availability during COV meeting.

The COV Report must be finalized within a total of 10 business days of the last day of the site visit and the Follow-up Letter must be finalized and sent to the site within 10 business days of finalizing the COV Report. The COV report and Follow-up Letter are completed in accordance with WIN-33-1-05. Both approved COV Report and Follow-up letter need to be filed in TMF and in the SharePoint in the folder “MONITORING” in the respective clinical site folder.

The AJCL/AMCL/ASCL or designee ensures the follow-up letter contains unambiguous choice of words, implying the clinical site needs to cease any study related procedures. Notification to the EC on closure of the site need to be sent within 7 business days after forwarding the Follow-up Letter to the investigative site.

COV Report and Follow-up letter are obliged to be written in English.

6 GENERAL INFORMATION

The acronyms used in this document are given in the SQ Site.

Where specific templates/logs are not available (e.g. Follow-up letter, Site Confirmation letter and the protocol deviation log) and the designated AJCL/AMCL/ASCL or designee belongs to a third-party Contract Research Organization (CRO) NAMSA, NAMSA's templates/logs shall be used.

COVID restrictions: during the global pandemic it may not be possible to facilitate on-site monitoring visits. The sponsor can request to perform remote monitoring visits to support oversight of quality assurance activities related to the study protocol (please refer to section 5.3.10).
In case, during the study, the COVID restrictions will not be eased, the sponsor could decide to decrease the percentage of SDV requested. The decision will be made depending of COVID situation and will be promptly communicated to CRO and site.

	Role	Name and Surname	Date	Signature
Written by:	Jr CRA	Lisa Ciuffarin	20/9/2021 | 16:18 CEST	DocuSigned by: Lisa Ciuffarin Signer Name: Lisa Ciuffarin Signing Reason: I am the author of this doc Signing Time: 20/9/2021 | 16:18 CEST 2D5C1223BA1F4EDB9C6206245B0C446
Approved by:	Clinical Research Manager	Federica Azzimonti	20/9/2021 | 21:37 CEST	DocuSigned by: Federica Azzimonti Signer Name: Federica Azzimonti Signing Reason: I approve this document Signing Time: 20/9/2021 | 21:37 CEST E76117269A994B43A353A3F6CBA0F6D