A Risk-Based Approach to Auditing Implementing RISA and SALSA

Introduction

The ongoing COVID-19 pandemic and the accompanying restrictions on travel and on-site visits are just one set of exceptional circumstances that can force sponsors to re-evaluate their annual audit plans. The decision on how to handle each individual audit, whether it be postponement, removal from the audit plan altogether, or conduct of a full or abbreviated remote site audit must be justified and documented by QA.

GXP Engaged has developed a risk-based approach to support sponsors in deciding, first, which audits can be postponed or removed from the plan, and second, how to apply a stepwise approach to remote auditing that balances the need for confidence in GCP compliance with the practical limitations that may exist. This approach incorporates the use of The Engaged Database's newly developed analysis tool SALSA (Statistical Assessment Layer for Site Audits).

SALSA: Objective Evidence to Support Decision-Making

The Engaged Database's newly developed tool SALSA can be used to provide objective, data-based evidence to support decisions to postpone or cancel individual audits, or to convert to a remote auditing approach, as a response to the COVID-19 pandemic or other exceptional circumstances requiring changes to a sponsor's annual audit plan. These decisions must be made based on factors defined in the sponsor's risk-based quality management approach and justified by QA. As the reason(s) for selecting the site for inclusion in the annual audit plan in the first place will probably not have changed (e.g. high enrolment, inexperienced site, high monitor turnover, etc.) the decision to modify the original plan may be additionally backed-up by evidence of acceptable data quality and integrity at the site. SALSA can be used to review and compare the data from several sites to prioritize those with potential issues. Based on the analysis, some sites may be prioritized, some may be taken off the schedule altogether, some may be selected for deferment to a later time point, and some may be considered good candidates for a full or abbreviated remote audit.

For a full description of the functionality of the SALSA tool please refer to The Engaged Database's concept paper: *SALSA - A statistical approach for data-driven site auditing.*

Risk-Based, Stepwise Approach to Remote Investigator Site Audits (RISA)

Remote Investigator Site Audits (RISAs) can be conducted as part of a sponsor's risk-based approach to auditing. GXP Engaged's concept paper on RISAs describes our general strategy and methodology for a full RISA, analogue to an on-site audit, which we believe yields audit results comparable to a routine on-site audit.

However, in certain circumstances, a full RISA may not be possible or even required. RISAs can also be conducted in a stepwise manner, with varying level of involvement of CRO and site personnel, ranging from no involvement (data and document review only) to involvement of one or both parties. This reduces the burden on site staff while providing a level of confidence in the GCP compliance status of

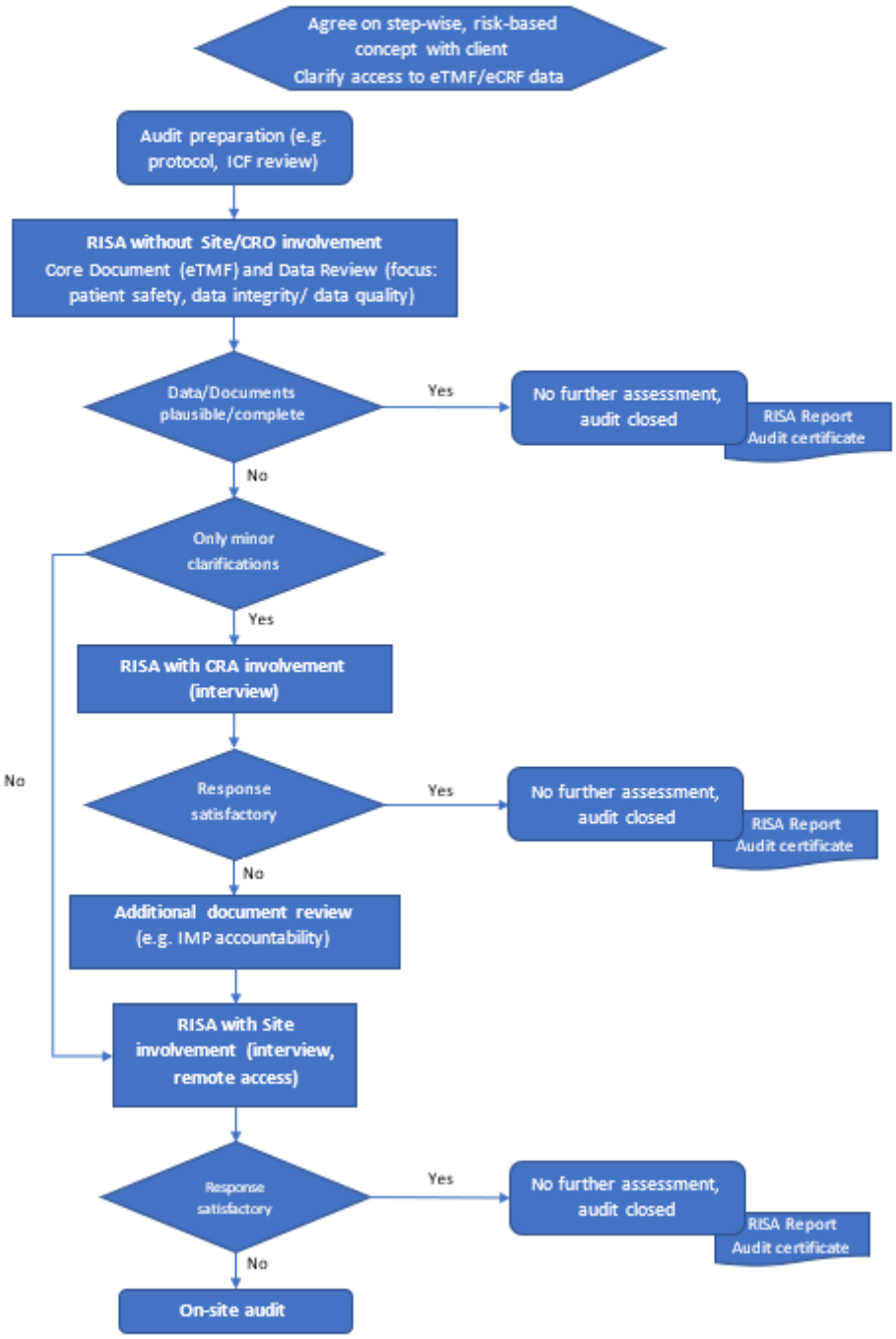
the site. This enables a flexible approach that can be tailored to the specific circumstances of each individual audit.

As part of our risk-based, stepwise approach, the RISA begins with a remote review of the site's documentation and data. It continues with interviews with CRO and site staff only if and to the extent necessary to clarify issues that cannot be resolved through data and document review.

At the beginning of RISA planning an assessment phase is conducted to introduce the concept of risk-based RISA to the sponsor and discuss the various approaches. Based on these discussions, the sponsor may decide to conduct a full RISA with CRO and site involvement, or the stepwise approach described here.

The figure below illustrates our stepwise approach.

Figure 1: Risk-based, step-wise RISA concept including SALSA



Stepwise RISA: Step 1 – Document and Data Review: No site or CRO involvement

The first step of the RISA is a remote review of the site's documentation and data. No involvement of the CRO or site staff is necessary.

Document review includes a remote review of study and site-specific documentation available in the eTMF of the study.

Data review comprises a review of patient data recorded in the Electronic Data Capture (EDC system). The SALSA tool can be utilised in order to get an understanding of the site's overall data quality and integrity and in order to select the data sample for subsequent EDC data review. The SALSA report allows a rapid analysis and visualisation of selected study data in order to identify data patterns and statistical abnormalities for selected sites and individual subjects. Based on the SALSA result, individual data are picked for further review in the electronic data capture (EDC) system itself.

Preparation, conduct and reporting of a RISA without site and/or CRO involvement are described in detail below:

RISA Preparation:

- Preparation of a detailed draft agenda/plan describing the scope of the audit and how this will be achieved, reference standards, date and time of audit conduct, and the deliverables
- Request for comments/approval by the sponsor to the agenda/plan
- Finalisation of agenda/plan and issue to agreed distribution as appropriate
- Gain access to all required electronic systems and access to Trial Master File (TMF) and EDC data for SALSA analysis with sufficient lead time prior to the planned audit date
- Review of Clinical Study Protocol, Amendments (all implemented at site) and Informed Consent Forms (all implemented at site)

Conduct

As the audit is conducted without planned involvement of site and/or CRO staff no opening or closing meeting with site staff are held. The RISA consists of:

- Conduct of a SALSA analysis and review of the resulting report to identify unusual data patterns and outliers for individual subjects or data points.
- Review of data in the EDC system following up on data points identified during the SALSA analysis and other study specific data of interest not included in the SALSA report
- A review of core documents from the eTMF focusing on patient safety, data integrity and quality, including
    - Monitoring Reports
    - Protocol Deviations
    - IRB/IEC and CA Submission and approvals
    - SAEs
    - Study specific topics (e.g. known issues)

Post Audit activities:

A short summary of the audit results is provided via email to sponsor QA prior to the audit report and discussion about further steps to be taken. The following possibilities exist at this point:

If the data and documents reviewed were plausible and complete and no issues or questions to be followed-up were identified, no further audit activities will be planned and the audit can be completed without site staff or CRO involvement. In this case the audit process proceeds with writing of draft audit report, distribution of draft audit report to nominated person(s), finalisation of audit report and preparation of follow-up templates, review of CAPAs suggested by auditee, and confirmation of acceptability of suggested actions, issuance of audit certificate to the auditee(s) upon request of the sponsor.

If minor issues or questions are to be followed-up prior to audit closure, an interview with the CRA responsible for the site is planned (see below RISA Step 2 – Interview with CRA)

If major concerns have been identified, an additional interview with site staff (see below RISA Step 3 - Site Involvement) and additional document review in the eTMF are planned.

Stepwise RISA: Step 2 (if needed): Interview with CRA

Preparation:

- Preparation and execution of confidentiality agreements (auditor, CRO/CRA), if necessary. Should one or more of the parties require a separate confidentiality agreement that captures the prohibition of recording, GXP-Engaged has a template available for use between the Auditor and CRA.
- Agreement on time and date CRA available for conduct phase of audit
- Definition of communication methods:
    - Audio: communication between participants via audio only (telephone line, computer audio). Via this method documents would be sent via email, placed in shared area only etc.)
    - Audio-visual: communication using Webcon/Video Includes ability to see participants being interviewed allowing the visual sharing of documents, to have direct “viewing” access via the interviewee to computerized systems (i.e. via screen sharing).
- Enduring continued access to eTMF and EDC for the time planned for the CRA interview
- Based upon the nature of the questions and/or issues to be discussed sharing of the topics to be discussed during the interview with the CRA

Conduct:

Remote interview with the CRA to follow-up on/clarify the open questions and issues resulting form the data and document review. If necessary the CRA can approach the site team in order to clarify any pending items after the interview. To facilitate discussion and clarification of issues screen sharing to discuss data points or documents is encouraged, but it should be noted that recording of audio or video (including any kind of recording outside the software being used i.e. voice recording, screen

shots, screen printing, photo taking of the screen, etc.) of all or part of the RISA by all parties is prohibited by national data privacy and protection regulations (for example, GDPR).

The remote interview can be complemented by review of additional documentation in the eTMF not reviewed previously and/or request of documentation not (or not yet) available in the eTMF to confirm information provided during the interview.

Post Audit activities:

If all open questions and issues could be answered satisfactorily no further audit activities will be planned and the audit completed without site staff involvement. In this case the audit process proceeds as described above with audit report writing and subsequent activities.

If issues or questions could not be answered satisfactorily or if new issues were identified, interview with site staff (see below RISA with Site involvement) and additional document review in the eTMF are planned.

Stepwise RISA: Step 3 (if needed): Site Involvement

RISA with Site Involvement

General Considerations

Preparatory activities include an assessment phase to devise an approach to the RISA with Site Involvement conduct phase. A RISA should be planned to place as little extra burden on the trial site as possible. The results of this assessment phase will be agreed with the Sponsor, CRA and Site (as applicable) before moving to the next phase of the RISA with Site Involvement.

Definition of communication methods:

- Audio: communication between participants via audio only (telephone line, computer audio). Via this method documents would be sent via email, placed in shared area only etc.)
- Audio-visual: communication using Webcon/Video Includes ability to see participants being interviewed allowing the visual sharing of documents, to have direct "viewing" access via the interviewee to computerized systems in use by the auditee (i.e. via screen sharing), or to see computer screens where screen sharing is not possible (e.g. X-Ray, Ultrasonic systems etc.) or via video transmission using a camera at auditee's site giving the auditor direct sight via live camera link, of auditees, equipment, materials, rooms etc.
- Direct Access to systems: auditor's direct access to auditee's validated system (where permissible by local regulations) using their own unique access and password (i.e. eTMF, IXRS, EMR, CTMS etc.)

Informed consent:

In general, there is no need for additional subject consent where the methodology for the RISA remains the same, no access (EMR or Visual) is proposed and therefore the only change is to the audit location.

Where access to the site EMR remotely is permissible via local regulations/ethics, subject consent may be required according to local regulations/ethics. Local regulations/ethics may consider verbal consent sufficient.

Where visual sharing of subject's notes or completed consent forms via video with the CRA/Site staff is permissible via local regulations/ethics, consent from the subject may be required to cover additional data protection regulations.

Where additional consent is needed, the auditor should leave enough time between the assessment and the conduct of the RISA for the site to contact the subjects.

Based on local authority, ethics committee and/or site requirements the conduct phase of the RISA may take place via:

- direct access to site systems (for example EMR, pharmacy system, document repository, etc)
- via audio-visual link with the CRA or site staff (e.g. non-medical team members like Study Coordinator) and/or
- telecon with the CRA or site staff (e.g. non-medical team members like Study Coordinator)

Consideration should be given to whether technology that allows a non-encrypted exchange is available.

Review of source data:

Source data verification (SDV) and review (SDR) by definition are not possible if direct access to the subject source data is not possible. However, methodologies that allow the auditor to understand the recording in the subject source notes and compare the data captured in the eCRF can be considered an acceptable alternative to providing a level of confidence in the GCP compliance status of the site. For example, the CRA or site staff member may read the notes recorded in the subject's records, similarly to an over-the-shoulder method. Selection of the data sample per SALSA is highly recommended in order to allow efficient source data review during the interactive part of the audit.

RISA with Site Involvement Assessment:

- Review of additional documentation in the eTMF (e.g. IMP accountability documentation, randomization information)
- Introduction of auditors to the auditee(s)
- Telecon with CRA and a telecon with the auditees to perform feasibility of approach to remote audit (access via EMR, video link, telecon etc) and to assess which of the following will take place, how they will occur, who will be involved and how much time of the CRA/Site time is needed:
    - Understanding of the subject source notes: Can this be performed via EMR, visually through video or other means. (See consent section above) or via telecon with the CRA or site staff reading the notes (similarly to the over-the shoulder method).
    - Understanding of the facility: Can a tour via video take place? Can a floor plan be provided to help? or will this simply be via telephone interview?

- Drug accountability: What can be accessed/provided up front? Where is the IMP stored? Are there separate site accountability forms that can be provided? Can this be conducted via video, or simply though telecon interview
- ICF review: Can a list of the consents signed and when be provided upfront (if not accessible via TMF/IVRS) Can a spot check of the completed ICFs be reviewed via video (see consent section regarding data protection above)? Or will this be performed via telecon interview only?
- ISF: Will the ISF check be performed purely on what is in the eTMF? How up to date is the filing in the eTMF? Can a spot check of hard copy documents that do not contain personal data be viewed via video? Or will this be conducted via telecon interview only? Who can be available for fielding questions related to the ISF?
- General interviews with the PI and other key staff: Will interview with the PI and other key staff be possible? Can a site delegation log be provided upfront to understand the site set up?
- Discuss general rules and best practices for remote auditing
- If the use of video is agreed, remind all parties of the need to adhere to legal requirements to refrain from recording of all or part of the RISA. A template for a separate confidentiality agreement is available if required
- Gain agreement on time for test of approach to be used during conduct phase (i.e. test of access to EMR, video link with CRA and, where required, site)
- Evaluate whether eCRF data can be used to tailor the scope of the audit (sampling for data or document review using SALSA)
- Agreement on CRA and/or site staff time required and dates for conduct phase of RISA

RISA with Site Involvement Preparation

- Preparation of a detailed draft agenda/plan describing the scope of this part of the RISA and how this will be achieved, reference standards, date and time of RISA conduct
- Prepare and issue confidentiality agreement if required by one or more party
- Ensure continued access to all required electronic systems
- Gain access to all site's electronic systems (e.g. EMR), if applicable

RISA with Site Involvement Conduct:

- Opening meeting: remind of confidentiality of RISA conduct (recording prohibited), confirmation of approach, communication of the scope and confirmation of agenda
- Ensure that subject consent has been obtained (where applicable) as advised during the assessment phase of the RISA to allow the agreed method of audit to continue
- Interviews with PI to understand site set up and processes.
- Interviews with key staff identified on the agenda to further understand:
  - site processes
  - answer questions and discuss issue identified during previous audit phase

- Facility tour where feasible (e.g. areas for study specific treatment, storage of study drugs, devices used for trial conduct including status of maintenance and calibration – refer to those covered during preparation)
- Review of signed informed consents (for the sample agreed and using the means agreed during assessment phase)
- Review of source data and compare vs eCRF (using means agreed during assessment phase)
- Drug accountability (using means agreed during assessment phase)
- Debriefing including communication of findings and comments to agreed site staff.

Post Audit activities:

Providing a short summary of the audit results via email to sponsor QA prior to the audit report and discussion about the outcome of the RISA and possible additional steps (e.g. on-site audit), writing of draft audit report, distribution of draft audit report to nominated person(s), finalisation of audit report and preparation of follow-up templates, review of CAPAs suggested by auditee, and conformation of acceptability of suggested actions, issuance of audit certificate to the auditee(s) upon request of the sponsor.