REMOTE INVESTIGATOR SITE AUDIT (RISA)

CONFIDENTIAL

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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.)

Objective:

Remote Investigator Site Audits (RISA) can be conducted as part of a sponsor's risk-based approach to auditing. The RISA can provide a level of confidence in the GCP compliance status of the site.

An assessment phase will be introduced to devise an approach to the RISA 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.

If support for the RISA is available at the site, Option 1 will be followed, otherwise Option 2 instructions apply.
Should the outcome of the RISA combined with other signals available to the sponsor (e.g. statistical analysis central monitor review, etc) fall below the level expected, an on-site audit should be considered at a later date.
If Option 1 is followed and the confidence level is as expected an on-site audit would not be required.
If Option 2 is followed a reduced scope on-site audit to perform SDV/SDR should be considered at a later date.

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.

Confidentiality for RISAs conducted via video or other visual technology:
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).
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, CRA and/or the PI (to cover the site staff involved in the video section of the audit at the site)

Option 1) Audit activities involving the site possible:

A thorough review of essential documents will need to be performed during the preparation using the eTMF. This will leave the conduct phase of the RISA to identify, through interview and demonstration where possible, whether gaps exist.

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 CRF 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.

RISA Assessment includes:

- 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 rules for remote auditing in the appendix to this document
- 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)
- Agreement on CRA and/or site staff time required and dates for conduct phase of RISA

- Agreement with sponsor on content and distribution of deliverables
- Agreement with sponsor to progress to RISA preparation

RISA Preparation includes:

- Preparation of a detailed draft agenda/plan describing the scope of the RISA and how this will be achieved, reference standards, date and time of RISA conduct, and the deliverables
- Request for comments/approval by the sponsor to the agenda/plan
- Prepare and issue confidentiality agreement if required by one or more party
- Finalisation of agenda/plan and issue to agreed distribution as appropriate (CRA, auditee, sponsor)
- Gain access to all required electronic systems with sufficient lead time to perform steps below.
- Full review of (electronic) documents and available data related to site:
  - Standard Operating Procedures of sponsor and auditee are fully understood
  - eTMF: site file section of the eTMF, country file for documents related to site, sponsor level for documents related to site to include but not limited to:
    - Clinical Study Protocol, Amendments (all implemented at site)
    - Informed Consent Forms (all implemented at site)
    - Relevant parts of Investigator Brochure (implemented at site)
    - approvals (Regulatory Authority and IEC/IRB).

        - Guidance documents given to CRA and site (monitoring plan, pharmacy manual etc)
        - Known site deviations
        - SAEs that have occurred at site– collect full details of SAEs
        - Site staff – delegation log
        - Documented training (GCP, study specific i.e. eSystems)
        - Documentation related to site equipment
        - Correspondence
        - etc
    - All monitoring visit reports
    - Site eCRF data if available to check critical data compliance with protocol
    - IVRS or other electronic system to have reports ready for the accountability during the conduct phase
    - Check that subject consent (where applicable) has been obtained as advised during the assessment phase of the RISA to allow the agreed method of audit
    - etc

Evaluating the available documents and data, the auditor should tailor the planned review of source data with the site (and the comparison versus the CRF) to the areas of highest risk.

RISA Conduct includes:

- 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 noted during preparation phase i.e.
        - gaps in documentation noted during preparation phase
        - gaps in training noted during preparation 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 RISA activities include

- Providing a short summary of the audit results via email to sponsor QA prior to the audit report
- Writing of draft audit report
- Distribution of draft audit report to nominated person(s)
- Finalisation of audit report and preparation of audit follow-up template
- Review of CAPAs suggested by auditee, and confirmation of acceptability of suggested actions.
- Issue of audit certificate to the auditee(s) upon request of sponsor

Option 2) Audit activities involving the site NOT possible

N.B. In this instance a project or protocol level assessment may also be considered. If access to sponsor data and systems allow, the auditor can analyse whether there are trends in the targeted site compared to other sites also conducting the clinical trial.

RISA assessment phase includes:

- Introduction of auditors to the contacts for the RISA (Sponsor, CRA, site staff – as applicable)
- Telecon with the contacts to perform feasibility of approach to the RISA and to assess the scope that will take place and who will be involved:
- Agreement on time CRA required and dates for conduct phase of the RISA
- Agreement with sponsor on deliverable content and distribution
- Agreement with sponsor to progress to RISA preparation

RISA Preparation includes:

- Preparation of a detailed draft agenda /plan describing the scope of the RISA and how this will be achieved, reference standards, date and time of RISA conduct, and the deliverables
- Request for comments/approval by the sponsor
- Finalisation of agenda /plan and issue to agreed distribution as appropriate (CRA, auditee, sponsor)
- Gain access to all required electronic systems with enough lead time for conduct phase

RISA Conduct includes:

- Full review of (electronic) documents related to site:
  - Standard Operating Procedures of sponsor and auditee are fully understood
  - eTMF: site file, country file for documents related to site, sponsor level for documents related to site to include but not limited to:
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    - Informed Consent Forms (all implemented at site)
    - Relevant parts of Investigator Brochure (implemented at site)
    - approvals (Regulatory Authority and IEC/IRB).
    - Guidance documents given to CRA and site (monitoring plan, pharmacy manual etc)
    - Known site deviations
    - SAEs that have occurred at site– collect full details of SAEs
    - Site staff – delegation log
    - Documented training (GCP, study specific i.e. eSystems)
    - Documentation related to site equipment
    - Correspondence
    - etc
  - All monitoring visit reports
  - IVRS or other electronic system to have reports ready for the accountability during the conduct phase
  - Interview with CRA and other staff from CRO or sponsor as necessary
  - etc

Post RISA activities include

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Points for consideration:

Prior to the audit

1. Determine the time difference between you and the auditees accurately and consider it while drafting the audit agenda. If you and the auditees are in different time zones, indicate both times for each session in the audit agenda. It is possible that different members of the auditee team may be in different time zones.
2. Test the line of audio / video communication including screen-sharing with the site prior to the audit (mention this in the audit notification letter). Allow sufficient lead time for the test to ensure the audit can go ahead as planned. Ensure you have a redundant telephone / internet line available at the time of audit, just in case, the main line fails during the audit.
3. Consider parallel use of different systems (video conferencing and remote document access).
4. Keep available IT support contact details handy during the audit. Suggest the site inform their IT department (where applicable) of the audit dates and duration.
5. If video communication line is being used, dress as if you are attending the audit in person.

Audit Conduct

6. Open the line of audio / video communication 10 minutes prior to the scheduled audit start time. This will give time to resolve issues with the communication line, if any, and start the audit on the scheduled time.
7. As far as possible ensure that you (and the auditees at site) are in a silent and noise-free surrounding during the audit. If required, request the auditees, in advance, to ensure the availability of a dedicated room for the audit duration.
8. Remind each person involved in the audit that recording of audio or video communication is prohibited by law.
9. Take attendance of each member on the call. If any key contributor (auditee) - who is required on the call and has confirmed attendance - is not present, check if he/she is going to join. If not, confirm the time when the member will be available.
10. Explain the reasoning for the remote audit approach at the beginning.
11. Discuss slowly but clearly.
12. Try to build rapport with the auditees by introducing yourself and holding a brief conversation. This will also help to get adjusted to the language / accent of the auditees. Remember, it's difficult to build rapport remotely.
13. While discussing the agenda, explain the duration of each session and the arrangement for breaks – to keep the line on mute or to disconnect and re-connect after the break.
14. Describe the process for interrupting the communication line and leaving or joining the call. Request each member to inform you when they leave or re-join the call.
15. Confirm the process for receiving additional documents from the auditees during and post-audit. Convey and confirm your contact details while requesting additional documents, if any. Suggest an agreed timeline for any requested documents to be provided to the auditor and make a note of when to expect the document.
16. Address each question to a particular attendee if more than one auditee is on the call. Ensure that the questions are succinct and understood by the auditee (questions on a call are sometimes easily misunderstood!).
17. Responses to questions, indicating noncompliance and potential audit finding, should be re-confirmed with the auditees during the discussion.

18. Check with each interviewee after the discussion if they have any question for the auditor.
19. In case of live video tour of facilities, determine the important facility area and request the auditees to take you through those area only. Discuss and agree on the sequence in which the facility tour should be conducted. If areas, devices and/or (emergency) equipment are critical for trial (safety, endpoints, etc.), and the scope of audit, request a floor plan with manual entry of location of areas/devices/equipment, together with brand names, serial numbers, etc. to allow full traceability of relevant equipment.
20. Follow the audit agenda as far as possible. Remember, this is a remote audit limiting the flexibility to re-arrange sessions, if required.
21. Remember not to take remote access control of any auditee computer system (even if offered by the auditee) unless you can log into it using your access details.
22. During document review, ask for time out and let the auditees continue their routine work with an agreed time to reconvene.