Guidance on Principal Investigator responsibilities

I. Oversight of the conduct of a clinical trial:

The Principal Investigator (PI):

- commits her/himself to personally conduct and/or supervise the clinical trial,
- is accountable for the participants' safety, and for the quality and integrity of the trial data generated by the Site,
- is responsible for providing adequate oversight of those to whom tasks are delegated,
- is accountable for regulatory violations resulting from failure to adequately oversee the conduct of the clinical study,
- is expected to apply risk-based oversight principles and maintain a compliance culture at the Site. This includes proactive identification of risks to participant safety, data quality, and Protocol adherence.

II. What is adequate oversight?

Agreements should clearly define the roles, activities and responsibilities for the clinical trial and be documented appropriately.

- Principal Investigator: who has oversight responsibilities for the Site. The primary oversight responsibility should not be delegated.
    - A Sub-Investigator should report directly to the Principal Investigator.
- Sufficient time to oversee the Site activities.
- Appropriate level of oversight, which should be proportionate to the importance of the data being collected and the risks to trial participant safety and data reliability.
- Oversight also covers third-party providers (e.g., laboratories, pharmacies, imaging services, home healthcare, etc.). Where activities have been transferred or delegated to

service providers, the responsibility for the conduct of the trial, including quality and integrity of the trial data, resides with the Sponsor or Investigator, respectively.

- The Investigator/Institution should implement appropriate measures to protect the privacy and confidentiality of personal information of trial participants in accordance with applicable regulatory requirements on personal data protection.
- The oversight must be continuous (not only at trial initiation).

III. Factors that may affect proper oversight:

- Inexperienced Site staff;
- Non-study related workload;
- Large number of patient population (standard of care);
- Involvement of the PI in multiple, parallel study conduct;
- Complexity of the clinical trial(s), such as (not exhaustive list):
    - Large Site staff teams (e.g., more than ~10 delegated Site members, for example in oncology centers);
    - Multiple Site locations (physically separate “satellite sites”) under the oversight of a single Principal Investigator or other location(s) within the Institution, where trial-related activities are conducted and they are overseen by another person (e.g., Head of Department);
    - Number of participants enrolled and their statuses (e.g., in screening, under treatment, discontinued, in follow-up, etc.);
    - External Service providers (not part of Institution) where isolated Protocol specified activities are performed (e.g., Radiology, Laboratory, etc.);
    - Multiple digital systems, tools utilized in the trial (e.g., electronic Investigator Site File [eISF], electronic Patient Reported Outcomes [ePRO], eDiary, wearables, etc.).

IV. Plan for appropriate oversight:

The Principal Investigator should develop a plan to ensure the appropriate supervision and oversight of the clinical trial during the trial conduct and after the closeout of the Site.

- Routine meetings with staff to review trial progress.
- Routine meetings with the Sponsor's (or delegate's) Monitors.
- A procedure for:
    - Timely correction and documentation of issues identified by Study personnel, Monitors, Auditors, or other parties involved in the conduct of the clinical trial,
    - Reviewing and documenting the performance of delegated tasks in a satisfactory and timely manner,
    - Timely resolution of data queries and discrepancies identified by the delegates of the Sponsor (e.g., study Monitor, Data Management representatives, Medical team representatives, etc., as applicable).
- Risk Based Quality Management (RBQM) from the Sponsor's side also contributes to efficient PI oversight.

  Centralized monitoring simultaneously draws attention to possible errors and flags the issues, while remote monitoring ensures continuous and effective communication with the Sponsor via the responsible Monitor. This also makes issue management and resolution much more efficient and easier for the PI.
- Newsletters containing study/data status based on validated system reports, issued by the Sponsor.

V. Examples for evidence of Principal Investigator's proper oversight (non-exhaustive list):

- PI acknowledged Site Standard Operating Procedures (SOPs) to ensure adherence to Good Clinical Practice (GCP) and local regulatory requirements, including local procedure on PI oversight,
- Site staff meeting minutes with a documented confirmation of the PI's attendance,
- Documented presence at the Qualification and Initiation visit (Qualification and Initiation Visit Report, Training log),
- PI delegated tasks and responsibilities to qualified and trained personnel, prior to the qualified staff member performing the delegated task and this delegation is adequately documented (Note: Standard of care activities may not be required to be delegated unless they are related to critical data and processes in the trial. Discuss critical data and processes for the trial with the monitor at initiation, as applicable.),
- Timely and appropriate management of the study Delegation log (e.g., delegating or stopping study personnel, updating list of delegated tasks, etc.),
- Documented presence at Monitoring visits or availability for monitoring visit related remote follow-up discussion (verbally [phone call, teleconference] or in written communication [e-mail]),
- Oversight of third parties and other departments (e.g., Radiology, Pharmacy, etc.) involved in the conduct of the study. The Sponsor may facilitate the identification of service providers for some Investigator responsibilities, but the final decision and ultimate responsibility is with Investigator,
- Follow-up letters addressed to the PI with documented acknowledgement (e.g., Follow-up letter signed and dated as confirmation for the review),
- Review and documented acknowledgement of safety information issued by the Sponsor (e.g., Investigator's Brochure updates, periodic safety reports, urgent safety letters),
- PI is involved in issue management and risk assessment (establishment of escalation pathway, awareness, resolution, prevention; review & documented acknowledgement of Protocol Deviations/Major issues),
- Personal involvement in one or more of the following:
    - Patient selection (recruitment, review of eligibility),
    - Informed consent process (PI signature on the Informed Consent Form),

  - Documented and timely review of the results of imaging / laboratory / other assessments,
  - Investigational Product dosing decisions and/or other medical treatment decisions,

- Documented medical oversight (including the assessment of causality) demonstrated over Adverse Events and Serious Adverse Events, that occurred for the participants enrolled by the Site. Safety reporting activities may be delegated, but ultimately the PI is responsible for the safety of participants and reporting requirements,
- Evidence of ongoing data review (e.g., documented oversight in the electronic Case Report Form [eCRF] system, for example with regular signoff process for the data reported in the eCRF [Signing of batches of workbooks is not suited to ensure high data quality and undermines the purpose of timely and thorough data review]; procedures for review of trial-specific data, audit trails and other relevant metadata should be in place),
- PI is also a treating Investigator of any subject within the study,
- PI attended or supervised any subject visit, and this is documented,
- Documented communication between PI and the local Regulatory Authority, if applicable (e.g., local RA Inspections),
- Documented communication between PI and the Local Ethics Committee (Institutional Research Ethics Committee = Intézeti Kutatásetikai Bizottság, IKEB),
- Therapeutic Area specific meetings (e.g., “onco team” meeting) in the Institution, where further treatments are discussed,
- PI led trainings (e.g., refresher after Investigator’s Meeting, brief GCP training).