REPUBLIC OF TÜRKİYE
MINISTRY of HEALTH

TÜRKİYE MEDICINES AND
MEDİCAL DEVICES AGENCY

Guidelines on Phase 1 Clinical Trial Centers

Version: 1

Date : 21.06.2019

TABLE OF CONTENTS

INTRODUCTION:

Many studies on the candidate molecule are conducted during the preclinical and clinical phases of the process from discovery to marketing authorisation of the medicinal product for human use. In preclinical studies, generally, the candidate molecule's pharmacodynamic, pharmacokinetic, and toxicokinetic profiles are used to decide the pharmaceutical form to be employed in human trials.

Clinical trials, in which the effects of the candidate molecule on humans are evaluated after preclinical trials, are usually carried out in four successive phases. Phase 1, phase 2 and phase 3 clinical trials are carried out before and phase 4 clinical trials are carried out after marketing authorization. Phase 1 clinical trials are studies in which the candidate molecule is administered for the first time in humans and are generally conducted with a small number of healthy volunteers.

As it is not expected for the volunteers (healthy or patient) participating in phase 1 clinical trials, in which a medicinal product for human use is administered for the first time to humans, to get any therapeutic benefit, the most important consideration at this stage is volunteer safety. In this regard, phase 1 clinical trials may be conducted in places that are designed to conduct such research and suitable for ensuring the safety of the people on whom the research will be conducted, as well as conducting the research in a healthy way, following up and making emergency interventions when necessary, and employing the personnel, equipment, and facilities suitable for the nature of the research.

With the Implementing Regulation on Clinical Trials effectuated after being published in the Official Gazette dated 19 August 2011 and no. 28030, the inspection and certification of centers where phase 1 clinical trials will be conducted became mandatory, and the "Guidelines for Conducting Inspections on Good Clinical Practices Regarding Phase 1 Units" was published in August 2011. The first phase 1 clinical research center inspection was carried out on December 25, 2011, and since 2011, clinical research centers that are established for the purpose of carrying out phase 1 clinical trials have been periodically inspected.

The inspection thus conducted does not cover the entire hospital and hospital staff or the works carried out outside of the inspected unit. While some molecules or compounds to be tested on humans for the first time are deemed "high risk", it should be kept in mind that serious adverse reactions may also occur at later periods in clinical trials. Furthermore, there are also risks arising from study procedures and/or marketing authorised medicinal products for human use utilized as comparator products. Therefore, it is vital that all centers where phase 1 clinical trials are conducted have adequate staff and facilities to deal with emergencies that may arise from the investigational product and/or study procedures.

1. Purpose:

This guidelines document has been prepared to assist sponsors, researchers, and phase 1 clinical research centers in the transition from preclinical studies to early clinical trials and to provide guidance for the inspection of centers.

2. Scope:

This document covers phase 1 clinical trials and the centers where such trials will be conducted.

3. Basis:

Article 11 of the Implementing Regulation on Clinical Trials of Medicinal And Biological Products (Amended: OG-25/6/2014-29041) was effectuated by being published in the Official Gazette dated 13.04.2013 and no. 28617 and served as the basis for the preparation of this guideline.

4. Facilities:

4.1. General Considerations:

Phase 1 clinical research centers should have enough space for activities, equipment, and personnel within the scope of the studies being conducted, and should include the following areas at the least, which should be appropriately separated from one another. These areas are listed below:

- Volunteer registration and screening areas,
- An area for obtaining informed consent from volunteers,
- Clinical,
- Recreation and dining area,
- Investigational product room,
- Sample processing (centrifuge etc.) and storage (fridge/freezer) area,
- For centers not included within a hospital; an intensive care unit with “Level 1” or “Level 3” intensive care standards in terms of minimum equipment, personnel and service standards,
- Management and personnel areas,
- Archive

The layout, building and other general characteristics for Phase 1 clinical research centers are listed below:

i. The lighting and ventilation in the facilities should be adequate, and the surfaces of the floors, walls, and work benches should be easy to clean and disinfect.
ii. Phase 1 clinical trials should be conducted under conditions ensuring adequate safety for the subjects, and the center features should be appropriate to the potential risk of the study to be conducted.
iii. Power should be sufficient and uninterrupted and a backup power supply should be available. In addition, similar measures should be taken for water and medical gases (if any).
iv. In addition to communication tools such as telephone, e-mail, and fax, office equipment such as printers, etc. required to carry out office activities should be available.
v. There should be systems in compliance with the relevant legislation for the disposal of waste.
vi. Doors, corridors, and elevators should have adequate width to allow volunteers to be carried on stretchers in case of emergencies.
vii. Entrances to the center should be controlled and limited, and entry/exit records should be kept.

viii. A system ensuring that the center staff, volunteers, and visitors can be easily recognized should be established (name badges, different colored clothes, etc.).

ix. A monitoring system for key areas and storage systems (investigational product room, archive, refrigerator, fridge/freezer, etc.) should be in place, and relevant records of such system should be kept. There should be an alarm system that will alert the personnel when the temperatures of these areas and storage systems exceed the determined limits. The functionality of the alarm system should be periodically tested and documented.

x. A list of tools and equipment used in the center should be established, and their maintenance, repairs, and calibrations should be tracked and documented.

xi. There should be synchronized clocks in the areas where study-related activities are carried out in the center. Furthermore, computer and hardware clocks must also be synchronized with the system and/or each other.

4.1.1. Volunteer Registration and Screening Area:

i. There should be screening and physical examination areas where necessary procedures will be carried out to assess volunteers' suitability for the study.

4.1.2. Area for Obtaining Individually Informed Consent from Volunteers:

i. Following a general and verbal briefing, the informed consent of the volunteer who decided to participate in the research should be obtained in a separate area reserved for this process, where the volunteer can have a one-on-one interview with the researcher or a physician authorized by them about the research and where the privacy of the volunteer is ensured.

4.1.3. Recreation and Dining Area:

i. In the event the volunteers are required to stay in the trial center under the study protocol, there should be a resting area where the volunteers can spend their free time during the stay.

ii. Recreation areas should be equipped with suitable activities with which volunteers can spend their free time and these areas should be within sight or under the supervision of the center personnel.

iii. The dining area should preferably be separate from areas where clinical activities are located. However, it may be necessary to take the food in the clinical area according to the study protocol. In such cases, there should also be patient overbed tables available.

4.1.4. Sample Processing and Storage Area:

i. There should be a sample processing and storage area where the processing and storage of materials collected from volunteers as defined in the study protocol will be conducted.

ii. In the event of multiple studies being conducted at the same time, necessary measures should be taken to prevent any mixing, contamination and cross-contamination in the sample handling and storage areas.

4.1.5. Management and Personnel Areas:

i. The centers should have the necessary areas for staff such as changing rooms and lockers, personnel rooms, toilets, and showers.

ii. Such designated areas should also be established for the research team such as quality assurance personnel, lead researchers, researchers, field officers, etc. and the administrative staff.

4.2. Clinical:

In case the volunteers participating in the study need to stay/overnight at the center in accordance with the study protocol; the center needs a clinical area with the suitable number of beds for the volunteers, dining and resting areas, as well as shower and toilet facilities. The number of beds required for the clinic depends on the protocol, the type of trial, and/or the investigational product, and the length and time of hospitalization of the volunteers should be specified in the study protocol. Regarding the clinical area:

i. In the event of volunteers staying overnight at the center, there should be a changing room for changing their clothes, and there should be a number of lockers compatible with the number of beds for personal belongings and clothes.

ii. The beds used in the clinic should have wheels and their height and inclination should be adjustable. The distance between the beds should be wide enough to allow the emergency cart/medical equipment to pass.

iii. There should be systems that can detect and record the departure of the volunteers from the center while the study is being conducted.

iv. Volunteers should not be allowed access to kitchen, laboratory and office areas. The doors to such areas should be kept locked when not in use. Volunteers should have restricted access to other areas outside the clinical area.

v. Where more than one study is conducted at the same time, necessary measures should be taken to avoid any disorder, confusion, and contamination.

vi. There should be adequate number of toilets, sinks and showers assigned for volunteer use only. Personnel must be able to open the door from the outside in an emergency. In addition, personnel should be able to limit and control access to toilets so that they can collect urine or feces samples when necessary.

vii. There should be an alarm system to alert the personnel in the event of a medical emergency. Alarms should be placed in every area established for the use of individuals (shower, toilet, bed, recreation area, etc.). Furthermore, the functionality of this alarm system should be periodically tested and documented.

viii. If the volunteers are to be bedridden in accordance with the study protocol, there should be overbed patient table so that they can eat their meals.

ix. Volunteers should be within the sight vision of the staff in the clinical area and in their beds at all times and, as far as possible, from several advantageous points.

4.2.1. Medical Hardware:

The medical equipment required for the centers where Phase 1 studies will be conducted may vary depending on the study, the risks expected from the study and the measures to be taken for mitigating such risks. In addition, regarding the equipment used in the center, the following requirements should be met:

i. A specific person is responsible for the equipment,

ii. All equipment is regularly checked, maintained, and calibrated (for systems that can be calibrated) and all these processes are documented,

iii. Manufacturers or subcontractors who calibrate the equipment issue a certificate guaranteeing that the calibration is performed according to national standards,

iv. All equipment bears a label containing information about the equipment (name, brand/model, serial number, maintenance, and calibration date, etc.).

In addition, the medical equipment that may be required for phase 1 centers are listed, but not limited to, as follows:

- Necessary equipment for resuscitation and emergency cart,
- Necessary equipment for medical intervention,
- A monitoring system for continuous monitoring of variables such as EKG, heart rhythm, oxygen saturation, blood pressure, pulse and fever,
- Electrocardiography,
- Equipment for processing biological samples,
- Coolers, refrigerators and freezer(s) for storage of biological samples, and, where necessary, investigational products.

4.2.2. Medical Emergencies and Intervention:

Phase 1 centers operating inside or outside a hospital should assign an intensive care specialist and/or anesthesiology and reanimation specialist temporarily or permanently, considering any occurrence of medical emergencies. Phase 1 centers operating inside hospitals should allocate a sufficient amount of beds in the intensive care unit. Phase 1 centers operating outside hospitals should have intensive care units with “Level 1” intensive care standards in terms of minimum equipment, personnel, and service standards for studies to be conducted with low-risk investigational products, and “Level 3” intensive care standards for studies to be conducted with high-risk investigational products.

Phase 1 centers operating outside hospitals should have an intensive care unit with "Level 1” intensive care standards for studies to be conducted with low-risk investigational products, as well as an adequate number of beds allocated in the intensive care unit of a tertiary healthcare institution and an agreement with the healthcare provider in question for all relevant services to be provided.

The center should have a conveniently and quickly accessible emergency cart with adequate supplies of suitable equipment and medicines for use in medical emergencies. The contents of the emergency cart may vary depending on the type of study to be performed and the potentially expected risks. With respect to the management and mitigation of risks, the contents of the emergency cart should be checked, approved, and documented by an intensive care specialist or anesthesiology and reanimation specialist. The equipment and medicines that should be found in the emergency cart are as listed below, including but not limited to:

- Monitor,
- Nasal cannula, face mask, and portable oxygen tubes necessary for oxygen therapy
- Airway materials,
- Ventilator with transport feature
- IV catheters, sets, tubes
- Endotracheal tubes
- Laryngoscope kits
- Oral and nasal airways
- Aspiration system
- Bag valve mask (Ambu)
- Defibrillator (both electric and battery-powered if possible)
- Transcutaneous cardiac pacing
- Tracheostomy set and materials
- Emergency medications and IV fluids

Personnel should be assigned with the responsibility for the emergency cart, which should be checked periodically and also after each use in terms of quantity and expiration date, and relevant records should be kept.

To be used in case of any medical emergency, the personnel should have the following:

- Telephone number of the sponsor's medical specialist
- Method and randomization code for reporting serious adverse events
- An alarm system to call for help in a medical emergency (code blue etc.)
- Appropriate methods for responding to highly probable medical emergencies such as fainting, hypotension, anaphylaxis, and cardiopulmonary arrest
- Method of transporting the volunteer to the hospital in case of a medical emergency

All physicians and nurses working in the center should have received training on providing basic life support or advanced life support when necessary and have valid certificates. In case an intensive care specialist or anesthesiology and reanimation specialist experienced in resuscitation is included in the research team and is available at the center during the dosing and follow-up periods, it will be sufficient for the remaining personnel to only have the basic life support training.

A study-specific identity badge must be issued to all volunteers included in the study. The identity badge should include the information that the individual has been included in a clinical trial and a 24-hour available telephone number of the lead researcher, from whom information about the study can be obtained in case of emergency.

All relevant areas designated for use by volunteers should have an alarm system to alert personnel of any medical emergency, and the functionality of this system should be tested and documented periodically.

Center personnel should be trained and ready to detect a serious adverse event or reaction in the subject and respond promptly. Drills should be conducted over scenarios involving possible medical emergencies (cardiac arrest, anaphylaxis, cytokine release syndrome, etc.), and these drills should be planned and periodically repeated, including transfer to hospital/intensive care unit, rush hour in terms of hospital and transportation, and night shifts. In addition, the case of unblinding must be included in these scenarios.

Center personnel should attend these training that include possible medical emergency scenarios, and be involved in various different scenarios (e.g. different events, places, and times) and these processes should be documented and monitored. All aspects of medical emergency scenario training should be defined under a procedure. Any corrective/preventive action taken during the drills should be monitored and documented.

There should be a fire evacuation procedure for the evacuation of volunteers in case of fire in the center. Fire extinguishers should be checked regularly and there should be emergency exits and emergency lights. Periodic drills for fire evacuation should also be performed and documented.

The sponsor should ensure that the relevant study is conducted in phase 1 centers that are compatible with the risk level of the investigational product in terms of personnel, facilities, and equipment.

4.3. Investigational Product Room:

It is the lead researcher's responsibility to receive the investigational products, store them, distribute them in accordance with the written request or research protocol, control the stock, process the surplus, and keep the records in accordance with applicable legislation. (For other responsibilities in terms of investigational product, see GCP Guidelines articles 25-31). The lead researcher may preferably appoint a pharmacist for these procedures. In this context, the center should have a investigational product room with controlled and limited access to which only the

authorized personnel have access to carry out the procedures regarding the investigational product. Entry/exit to the investigational product room should be recorded. The investigational product room should have sufficient space in accordance with the studies conducted. The requirements for the investigational product room will vary depending on the service to be provided as part of the study. Furthermore, procedures and recording methods should be in place for investigational product collection, use, retrieval, and disposal, including off-hours and holidays.

Investigational products should be stored in accordance with the product's specifications and under the conditions specified in the manufacturer's/supporter's instructions. Investigational product room:

- Should have sufficient space for the separate storage of different investigational products as well as a quarantine area,
- Should be temperature and humidity controlled, and there should be an alarm system that will be activated in case of any deviation from the predefined values,
- Should not be exposed to direct sunlight,
- Should be accessible only by authorized personnel.

Furthermore, appropriate medicines should be kept in stock and easily accessible for clinical personnel to manage common adverse events (such as headache and nausea), convulsions, and low blood sugar levels.

The sponsor is responsible for proper packaging of the investigational product, transporting it to the trial site, and ensuring transport under appropriate conditions. The center should document and keep information about the investigational product shipment, delivery, acceptance, storage, distribution, administration, investigational product accounting, returned or disposed quantities, and all such processes should be defined in the relevant procedure.

In case the randomization process is carried out by the center; the processes for generating, distributing, using, and maintaining the randomization list should also be defined in the procedure. A written procedure should be present to allow rapid identification of a 'blinded' investigational product in an emergency. The procedure should be maintained throughout the study but should be readily available, while not allowing the blinding to be broken undetected. In addition, processes related to unblinding in emergency situations, training of relevant personnel, and code-breaking rehearsals should likewise be defined in the procedure.

4.4. Archive:

The center should have an archive area for archiving medical records and the study master file, which is of suitable size for the relevant activities and fire resistant, and where necessary measures are taken in terms of water and humidity, relative humidity is monitored, with appropriate rodent and pest control measures. Measures should be taken towards ensuring that only authorized persons can access the archive and restricting access to everyone other than such persons.

There should be a procedure related to the archive operation, the entries/exits to the archive (personnel and documents) should be recorded, the archiving period of the documents related to the study, including the electronic data and the raw data pertaining to the study, should be in accordance with the relevant legislation, and the temperature and humidity values should be defined. A fire/smoke sensor should exist in the archive area and the alarm system should be periodically checked in terms of functionality.

Essential documents (trial master files) are documents that individually and/or collectively enable the conduct of a study and the evaluation of the obtained data quality. These documents demonstrate compliance of the lead researcher or other researchers, sponsor, and monitor with good clinical practices standards and relevant legislation. Essential documents are defined in the Good Clinical Practices Guidelines (Article 12) under which it is specified which documents should be kept in the trial master file by both the researcher and the sponsor.

Handwritten data entries should be clear, readable, and indelible. Records of each activity should be made at the time the activity takes place. In addition, such records should be made in such a manner as to allow the monitoring of all important research-related activities. In case of changes on a data entry; such change should not prevent the original information from being read and must be signed and dated by the person making the change.

4.5. Medical Laboratory:

The facilities where laboratory services are procured for both the screening of the volunteers planned to be included in the study and the clinical tests to be carried out within the scope of the study can be either within the hospital where the center is located, or outsourced services can be provided towards such purposes. Laboratories in which biological samples will be analyzed must meet the following conditions as a minimum:

- Should be authorized by our Ministry (for domestic facilities),
- Should ensure the calibration of the equipment used, as well as the application of the quality control procedures and the performance of their regular maintenance,
- Should employ procedures for the safe transfer of samples from the clinical area to the laboratory and documenting the storage/transfer conditions during such transfer,
- Should ensure the availability of a stock control procedure to track the expiration dates of reagents and consumables,
- Should employ quality assurance and quality control systems, including an internal audit program,
- Should ensure that necessary precautions are taken regarding the protection of personal data of volunteers,
- Should employ a system for archiving source documents, including computer raw data.

The clinical laboratory should participate in external accreditation (ISO 15189) or a comparison program among laboratories to support the reliability of its results and document the adequacy of the facility.

In the event the clinical laboratory is included in a comparison program among laboratories, the results obtained for each parameter studied in the laboratory should also be followed and documented by the quality assurance department of the phase 1 center.

Clinical laboratories may be inspected as part of a phase 1 center inspection or study-based inspection. For more information on clinical laboratory inspections; “Guidelines for Conducting Good Clinical Practice Inspections for Laboratories Participating in Clinical Medicines Trials” may be used as a reference.

A procedure should be established for the transfer of samples to the clinical laboratory. Furthermore, since it is not appropriate to disclose the identifying information of the volunteers participating in the study to parties other than the competent authority/persons in accordance with the relevant legislation, necessary precautions should be taken during the process of sending the samples of the volunteers to the clinical laboratory for analysis, invoicing and communicating the results. Procedures should be established for sample

management, including collection and processing of samples, evaluation of delayed and missed samples, labeling, tracking, storage, and shipping. Labeling, receipt, storage of samples and documentation of all these processes should ensure sample integrity and traceability. In addition, all related actions and processes should be traceable, from blood collection to delivery to the clinical laboratory and obtaining laboratory results.

A dated and certified list of normal ranges for all relevant parameters studied in the clinical laboratory and the laboratory's accreditation certificate, if any, should be documented and any changes to them should be followed. A quality system should be implemented in the clinical laboratory, rejection/acceptance criteria for samples and approval/change authorizations for results should be defined. Laboratory results and all related raw data should be preserved by the clinical laboratory for the period defined in the relevant legislation. Data integrity requirements apply to all work-related tests; raw data must be adequately protected from modification or deletion.

5. Personnel:

In accordance with the relevant legislation, phase 1 clinical trials should be conducted by an appropriate team with adequate training and experience in good clinical practices and a pharmacologist, a medical physician with expertise, or a doctorate.

The center should have a dated and approved organizational chart showing the key positions and staff assigned to these positions. The organizational chart should be updated as required, and the older versions should be archived. Job descriptions and responsibilities should be defined for all personnel working at the center. Job descriptions must be dated and signed by the relevant personnel. For all personnel employed in the center; the information and documents related to personnel such as curriculum vitae, education/training records, job description, job acceptance/confidentiality agreement, etc. should be followed, updated when necessary, and archived. Furthermore, a form should be created showing the signatures and initials of all personnel in the research team.

The minimum number and qualifications of personnel for dosing days should be specified, and the measures to be taken whenever key personnel is not available at the center during the study day should be defined. All personnel responsible for the care and management of volunteers should receive emergency and/or advanced life support training (see 4.2.2), and such training should be repeated on a regular basis.

All new personnel, including part-time and temporary personnel, should receive orientation training on general issues such as confidentiality, safety, health, use of procedures and center policies, as well as the relevant legislation. The procedure should also define the content and frequency of periodic training, the filing of training documents, the minimum qualifications of the trainer in in-house training, assessment/evaluation and definition of the minimum success level, and methods of monitoring and recording training. Periodic training for personnel are listed (but not limited to) below:

- Personnel and physicians responsible for the care of volunteers should receive regular training on resuscitation.
- Drills should be performed on scenarios involving possible medical emergencies (cardiac arrest, anaphylaxis, cytokine release syndrome, etc.). In case of introducing any changes, the personnel should be informed and trained when changes are made to procedures.
- Periodic training should be organized regarding Good Clinical Practices and legislation.

6. Volunteers:

In regards to phase 1 clinical trials to be conducted with healthy volunteers, relevant processes for the recruiting and management of volunteers should be defined. In this context, a database of volunteers should be established and this database should include, if possible, a photograph of the volunteer. Volunteers should be given a photo ID card to be used during their stay at the center. For the purpose of documenting the volunteers participating in the study, copies of the study ID card and identity card (or driver's license, etc.) given to the volunteers should be archived in the trial master file after the trial process is completed.

Any aspects of how to prevent volunteers from participating in multiple studies (such as needle marks on the forearm and low blood count results etc.) should be defined in the procedure. The methods followed for the verification of the volunteer's medical history, such as chronic disease/concomitant therapy, etc., should also be described in the procedure. Furthermore, warnings regarding participation in more than one study at the same time/concomitant treatment/use of medicines should be clearly included in the informed consent form.

To prevent cigarettes, food/drink, and other materials not permitted by the study protocol from being brought into the work area, volunteers should be searched, and infrastructure and procedures should be put in place to identify relevant materials with mutual signatures and return them at the end of the trial process. The number of beds in the wards and the number of personal lockers allocated to the volunteers should be compatible. The processes regarding the payments to be made to the volunteers and the methods of obtaining informed consent and creating a pool of volunteers should be defined in the procedure.

Issues concerning the volunteer database, access rights to volunteer data, and the protection of volunteer data confidentiality should be explained in the relevant procedures, and a phone number of the person to be contacted in case of emergency, as well as the relationship status of such person, should be recorded when registering the volunteers in the database.

7. Quality Management:

Quality assurance and quality control systems should be in place at the center to ensure that studies are conducted, documented, and reported in accordance with the study protocol, GCP, GMP, and legal requirements. Detailed procedures in accordance with national/international regulations should be established in order to ensure standardization in the study and the operations conducted, covering all phases of the study and all operations carried out at the center.

The quality assurance unit should report to the center's senior manager, while the quality assurance personnel should be independent of the studies performed. The organizational chart and the activities carried out at the center should be arranged in this context.

As a minimum, quality assurance personnel should have received training on quality assurance systems such as Good Clinical Practices (GCP), quality management system, and internal inspections.

The quality assurance unit should perform the following as a minimum:

- Ensuring that quality management systems are followed, reviewed and updated,
- Ensuring that the procedures are made available to the personnel and followed,
- Checking all data obtained from the study for reliability and traceability,

- Planning and conducting internal inspections at regular and determined intervals and following any necessary corrective actions in this context,
- Conducting surveys to evaluate outsourced services and service providers within the scope of the study and monitoring any necessary corrective actions,
- Reporting inspection findings to center management and lead researcher
- The quality management system should include root cause analysis, monitoring of trends, and all aspects of data integrity and implementation of appropriate corrective and preventive actions (CAPA).

Regarding procedure and document management; current versions of procedures should be available in the relevant study areas, old versions should be archived, and reviewed periodically, any changes should be communicated to personnel, and relevant training should be provided.

The root causes should be investigated regarding the findings determined as a result of the internal inspections. The center management should be regularly informed about the activities carried out by the quality assurance unit, as well as their results and the necessary measures to be taken.

8. Risk Assessment and Risk Management:

The risks that may arise from the investigational product and/or the study design and methodology in Phase 1 clinical trials should be minimized.

These risks should be thoroughly evaluated prior to any clinical trial, particularly during the transition from preclinical studies to initial exposure studies in humans, where uncertainties regarding the tolerability and safety of the investigational product are greatest. The risk assessment process should include an assessment of risks related to the investigational product, clinical procedures, volunteer safety and rights, and reliability of study results. In this context, processes related to risk assessment and management in the phase 1 clinical trial center should be defined in the procedure. Furthermore, aspects such as how to document the risk assessment, review the risk assessment (e.g. continuous monitoring and updating as necessary), and who is responsible for monitoring and documentation of risk management compliance should also be defined in the procedure.

All aspects of phase 1 clinical trial, including data from preclinical studies, should be reviewed, evaluated, and appropriately reviewed within the scope of risk assessment and risk management, by persons with appropriate technical, scientific, and clinical expertise established by the center, starting from the proposal stage and throughout the study period, and appropriate risk reduction activities should be recommended and followed up.

The points that can be evaluated in the risk assessment process are stated (but not limited to) below:

- All aspects pertaining to the investigational product such as class, novelty, species-specificity, mechanism of action, potency, dose/concentration relationship for efficacy and toxicity, administration, and method of administration of the investigational product,
- Study design,
- Whether the data provided is sufficient to calculate the initial dose or any dose escalation and whether these data have been produced within the framework of a quality system
- Initial dose calculations, dose escalation recommendations, stopping criteria,
- Maximum exposure and dose,
- Transition from a single dose to multiple doses,
- Evaluation of participants and initiatives,
- Data/documents used in the risk assessment process, their version and status (draft/final),

- Availability of any specific antidote or emergency treatment,
- Adequacy of the center and personnel in respect to potential medical emergencies,
- Scenarios for a specific emergency,

Additional personnel and resources (e.g. specific training, expertise, facilities, etc. for conducting the trials). After evaluating all aspects of the research, the identified risks and the measures to be taken to mitigate such risks should be documented.

8.1. Risks Arising from Investigational Product:

It is stated in the ESG (Expert Scientific Group on Phase I Clinical Trials) report that it is not possible to make a comprehensive list of all possible risk factors related to investigational products and targets due to scientific uncertainties arising from the nature of innovative medicines. Therefore, the assessment of risks or hazards that may arise from the investigational product should be fact-based and scientifically sound. Furthermore, the ESG report provides examples of some agents that require special attention due to the high risk of harming volunteers during initial exposure studies and factors. These are;

- any agent of which effects may cause serious physiological disturbances to vital body systems,
- Agonistic or stimulatory effects,
- new agents or new mechanisms of action for which there is no previous experience,
- species-specificity which makes preclinical risk assessment challenging or impossible to perform,
- The potency of the agent (for instance; compared to a natural ligand),
- Multifunctional agents (e.g. bivalent antibodies, FcR binding sites),
- Cell-associated targets (cell surface targets that activate signaling pathways),
- Targets that 'by-pass' normal control mechanisms,
- Immune system targets,
- Targets in-vivo systems with great biological amplification potential.

A risk assessment conducted on any investigational product in first-exposure studies in humans needs to consider other factors in addition to the factors listed above, some of which may prove to be more significant in the future. Examples to the aforementioned may be given as below;

- Agents with a target not found in animal models,
- Combination products; for instance, retroviral vectors in gene therapy (the new combination may pose a new risk, even if components have been used previously in humans),
- 'biosimilars' that differ significantly from the innovative product (e.g. post-translational modifications),
- New adjuvant vaccines; especially those that direct the antigen to signaling molecules on the surface of the immunocyte or that are designed to stimulate the production of pro inflammatory cytokines from lymphocytes or antigen-presenting cells,
- Significant changes in the administration route, posology, or formulation of an agent.

When the sponsor receives new safety/toxicological data on the investigational product, the lead researcher should be notified immediately, and clear and detailed responsibilities should be stated in the contract that the parties will sign.

8.1.1. Agents Other than the Investigational Product:

In clinical trials, comparator or rescue medications are also used apart from the research product. The risks posed by each of these to the volunteer, as well as the risks in combination with the investigational product, should be considered.

8.1.2. Risk Management for Investigational Product:

Risk management for the investigational product covers determining the appropriate starting dose, escalation, and administration of doses.

8.1.2.1. Starting Dose:

Calculation of the starting dose in the first exposure study to be conducted on humans is a central factor influencing the safety of trial volunteers. There are two different methods recommended for determining the starting dose:

- NOAEL (No Observed Adverse Effect Level)
- MABEL (Minimal Anticipated Biological Effect Level)

In case different safe starting dose values are obtained by different methods, the lowest value should be taken as the starting dose.

8.1.2.2. Dose Escalation:

As a general rule; the dose/toxicity or dose/effect relationship observed in preclinical trials should guide the two dose levels in dose escalations, whichever is steeper.

Dose escalation should only be made after careful consideration of all data obtained from previous doses. Dose adjustments can be made only after reviewing all relevant data (e.g., safety data, PK data if available) and discussing it with the sponsor (dose increase or decrease or unchanged).

The relevant procedure should clearly state that the study will not be continued until the Institution and Ethics Committee approval is obtained regarding the violation of the limits foreseen for dose escalation or regarding a significant change in the protocol. Furthermore, the trial-stopping rules must be clearly defined in the protocol.

Data reviewed and decisions made regarding dose adjustments (dose increase or decrease or unchanged) should be clearly documented. The decision for dose escalation should be approved by the sponsor and the lead researcher, and such decisions and approvals should be clearly documented prior to dosing the volunteers.

8.1.2.3. Dose Administration:

The number of volunteers dosed, the time between dosing, cohorts of volunteers, and follow-up period between dosing will vary depending on the investigational product, the route of administration of the investigational product, and the type of trial conducted.

In the event the investigational product is a high risk, the first dose in any cohort should be administered in such a way that only one participant receives the active investigational product (not randomized to placebo). The volunteer dosed in this way should be closely observed for at least 24 hours by the nurse, the lead researcher and, if necessary, by an experienced intensive care specialist or anesthesiology and reanimation specialist, and this process should be documented.

Furthermore, unless there is a clear scientific rationale and/or risk-proportionate justification

for rapid injection of an investigational product to be administered via IV, it should be given by slow infusion instead. The protocol should include details on the rate and duration of infusion.

8.2. Risks Arising from Clinical Procedures:

The clinical procedures to be applied within the scope of the trials should be evaluated with consideration of standard practices and procedures. For instance, in case an invasive procedure such as a biopsy is normal practice for standard treatment/care, its inclusion in the trial protocol poses no additional risk to the participants. On the other hand, it will pose an additional risk if it is applied only as per clinical trial protocol and is not part of standard care/treatment.

For the management of risks arising from clinical procedures, the following aspects need to be considered:

- The qualification, experience and training of the personnel in terms of the clinical procedure to be applied,
- Requirement of special facilities or equipment for conducting the procedure,
- Need for additional monitoring actions to identify problems and take action towards protecting volunteers,

8.3. Risks Arising from Failure to Obtain Appropriate Informed Consent:

In accordance with the relevant legislation; in the event that the ethical committee considers that the benefit to be obtained is greater than the possible risks arising from the research, the research can be commenced after the approval of the ethics committee and the approval of the Agency, provided that duly informed consent is obtained. The trial is carried out only if these conditions are maintained. Prior to starting the trial, the person or legal representative who wants to volunteer to participate in the research should be sufficiently and clearly informed by the principal investigator or a researcher from the research team about the purpose of the research, its methodology, expected benefits, foreseeable risks, challenges, unfavorable aspects in terms of the health and personal characteristics of the person and the conditions in which the research will be carried out and continued, and that they have the right to withdraw at any time from the trial process.

The process of obtaining informed consent in trials to be carried out on child participants, those with a certain degree of mental disorder, and those in intensive care and/or unconscious patients should be carefully considered and should comply with the provisions of the relevant legislation.

Individuals volunteering for the study should be provided with sufficient time to read the informed consent form, discuss with family and friends, and ask questions to the center personnel, if necessary.

8.4. Risks Arising from Failure to Protect Personal Data:

Personal data (T.R. Identity Number, full address, telephone number, date of birth, medical history etc.) are collected from volunteers or volunteer candidates for the volunteer databases created by the center or within the scope of the trial process.

Collection, management, and transmission of personal data should be carried out in accordance with the relevant legislation. Access to personal data should only be provided to the authorized person(s) and necessary precautions should be taken in this respect. In addition, the participant has the right to request that their personal data be removed from the center's database.

8.5. Risks Arising from the Reliability of Trial Results:

Data collected during the trial process must be complete, consistent, and accurate. The data should possess the following characteristics:

- Attributable - It should be stated by whom and when it was carried out,
- Readable - Data must be readable throughout its life cycle,
- Concurrent - The activity should be documented when it is carried out,
- Original - There must be raw/source data or certified true copy,
- Accurate - Data must be accurate, real, complete, valid and reliable,
- Complete - All data collected to obtain the necessary information, including any testing, retesting, or reanalysis, should be documented,
- Consistent - Data must be generated in a reproducible manner,
- Robust - Data should be recorded in appropriate and approved systems where it can be stored for the period defined in the relevant legislation,
- Available - Data should be accessible for review and inspection during the period defined in the relevant legislation.

However, risks arising from trial design, such as inclusion criteria, randomization, treatment, masking, outcome measures, and follow-up process, as well as risks arising from data collection methods and trial center features may affect the reliability of study results.

Foreseeable risks should be identified within the scope of the relevant study, including but not limited to those listed above, and appropriate risk mitigation activities should be carried out. Appropriate quality control procedures should be applied in accordance with the amount of data to be collected and the speed of such data collection.

Annex-1. Relevant Sources

1. ABPI, 2012, Guidelines for Phase I Clinical Trials
2. MHRA Phase I Accreditation Guidance (Final 28-Oct-15)
3. MRC/DH/MHRA Joint Project, 2011, Risk Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products
4. Early Stage Clinical Trial Taskforce, 2006, Joint ABPI/BIA Report
5. TSO, 2006, Expert Scientific Group on Phase I Clinical Trials
6. WHO TRS No: 996 Annex 9
7. US Food and Drug Administration, 2005, Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers
8. International Conference on Harmonisation, Guidance on Non Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for pharmaceuticals, M3(R2).
9. International Conference on Harmonisation, Note For Guidance On Toxicokinetics: The Assessment Of Systemic Exposure In Toxicity Studies, S3A
10. International Conference on Harmonisation Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals, S6(R1).

Annex-2. List of Sample Procedures

The procedures listed below are shared for aiding in establishing a general framework, and nonetheless, phase 1 centers are required to establish their own procedures to cover all activities conducted at the center in accordance with the workflow processes. In this context, some of the processes listed below can be combined, some processes can be handled separately or new processes can be added.

Procedures Related to Clinical Processes:

1. Acceptance of the trials and signing of the clinical trial contract with the sponsor,
2. Preparation of the study protocol and protocol changes (in case the study protocol is prepared by the center)
3. Preparation of trial brochure (for trials without sponsor),
4. Procedure for obtaining approval for the trial from the Ethics Committee and TITCK (for trials without a sponsor)
5. Volunteer database (including its validation),
6. Volunteer management (management, selection and evaluation of volunteers)
7. Preparation of the informed consent form (for trials without a sponsor),
8. Obtaining consent from volunteers,
9. Admission of volunteers to the center and hospitalization procedures,
10. Trial management group working procedures/principles, duties and responsibilities,
11. Evaluation and mitigation of risks in phase 1 clinical trials,
12. Dose selection and dose escalation for phase 1 clinical trials,
13. Rules for administering and stopping doses,
14. Providing protocol training to the clinical trial team, sharing the duties and responsibilities of the research team, and distributing responsibilities,
15. Execution of the Phase 1 Clinical Trial,
16. Execution of other clinical trials (if deemed necessary),
17. Medicine room management and medicine room requirements,
18. Acceptance, storage, distribution, accounting, return or disposal of the investigational product,
19. Preparation, serving to volunteers, and monitoring of standard foods,
20. Administering and removing IV branules to volunteers,
21. Administration of research product to volunteers,
22. Recording, evaluation, and reporting of adverse events/reactions occurring during the trial,
23. Procedures for discharging volunteers from the center,
24. Procedures for making payment to volunteers,
25. Recreation area and monitoring of these areas throughout the volunteers' stay at the center,
26. Management of suppliers,
27. Selection and appointment of specialist/consultant physicians to carry out the activities related to the clinical trial,
28. Preparation of the trial result report (for trials without a sponsor),
29. Use and maintenance of the intensive care unit and emergency cart,
30. Management and maintenance of the clinical center,
31. Sorting and storage of samples,
32. Usage, maintenance and calibration procedure for the equipment used in the center,

33. Maintenance of temperature and humidity recorders, recording of temperature and humidity values,
34. Ensuring line cleaning before and after distribution of the investigational product,
35. Handling medical emergencies, providing basic and advanced emergency life support, and transfer to intensive care,
36. Code breaking/unblinding, training of relevant personnel and code-breaking rehearsal,
37. Case report form, data collection and filling in case report forms,
38. Preparation and review of the case report form (for studies without a sponsor),
39. Preparation of the trial master file (TMF) (for trials without sponsor)
40. Recording and reporting of protocol deviations/violations,
41. Monitoring of the trial by the sponsor,
42. Procedures for volunteers entering and exiting the center,
43. Use and maintenance of the emergency call system,
44. Collection of blood samples from volunteers,
45. Numbering of samples collected from volunteers,
46. Measurement of vital signs and physical examination,
47. Transfer of serum/plasma samples to the clinical laboratory,
48. Anomalous laboratory results,

Procedures Related to Quality System:

1. Procedure writing procedure,
2. Preparation, publication, distribution, collection, and archiving/disposal of quality documents,
7. Quality management,
4. Supervision of changes,
5. Corrective/preventive actions,
6. Internal and external inspections,
7. Notification of non-compliances and violations,
8. Inspection of places where services are provided,
9. Trial result report inspection,
10. Regulatory authority inspections and sponsor's audits,

General Procedures:

1. Control and disposal of medical wastes,
2. Personnel training,
3. Medical records and source data,
4. The procedure for archiving and retrieval of documents,
5. Handling extraordinary situations (flood, earthquake, etc.),
6. Maintenance and control of fire alarm systems,
7. Pest control,
8. Validation of computerized systems (if any)
9. Electronic signature and system access control (if any),
10. Backup, restore and archiving of electronic data,
11. Controlled access to relevant areas of the center,
12. Installation, labeling, use, and maintenance of equipment used in the center,