REPUBLIC OF TÜRKİYE
MINISTRY of HEALTH

TÜRKİYE MEDICINES AND
MEDİCAL DEVICES AGENCY

Guideline on Identifying Triggers for Routine Inspections and/or Inspections "Based on Defined Grounds" and Scope of Such Inspections

1. Introduction:

There is a clear need to verify the GCP compliance of clinical trials included in applications to the centralised procedure, either as part of new applications, as extensions to existing authorisations for approved products, or as clinical information provided as part of post marketing obligations..

The Turkish Medicines and Medical Devices Agency (TITCK) issues marketing authorizations for medicinal products for human use that are deemed appropriate following administrative, technical, and scientific assessment and evaluation carried out in compliance with marketing authorization legislation. The Agency receives assurance from GCP inspections of clinical trials included in the marketing authorization application file regarding the validity and quality of the data submitted.

In theory, more investigation may be necessary for all clinical trials listed in the marketing authorization application file. However, this is not practical and is not always necessary. GCP inspection is a labor and resource intensive operation. As a result, an inspection should be sought whenever triggers are found and the alternative technique is unable to offer the required level of assurance, or whenever problems are still present after the assessment procedure has been completed. To monitor GCP compliance and to offer ongoing assurance, some applications could be chosen for routine inspections. In order to ensure that all scenarios are addressed, applications, clinical trials, and centers should be chosen based on a variety of criteria.

At various stages of applications and evaluations, triggers can be discovered. These may be gleaned from the application file before the beginning of the evaluation (preliminary review) and could potentially be used as predefined factors for a “routine” inspection request, or they may be derived from the evaluation process itself that led to a request for an inspection based on defined grounds.

The effects of the various triggers are varied and should be assessed while taking into account the whole application file. In case there are numerous triggers, it may be beneficial to contact Inspectors and internal stakeholders to elucidate whether and how they can be taken into account during a GCP inspection. However, it should be emphasized that this guideline only offers an overview for inspectors and does not provide a full list of triggers, allowing for routine or inspection "based on defined ground" requests to be made of clinical trial and marketing authorization application files.

2. Purpose:

This guideline is intended to provide an overview of potential triggers as part of a routine inspection program that can be used for the selection of marketing authorization applications concerning medicinal products for human use and clinical trials and that can be discovered at different stages of the evaluation and that can help the evaluator to make an informed decision regarding inspections "based on defined grounds" and that can be used to initiate an inspection.

3. Scope:

This guideline applies to clinical trials included in marketing authorization applications as well as ongoing clinical trials. Since bioequivalence studies are the focus of a different guideline, this guideline does not address specific triggers related to those studies.

4. Basis:

Article 22 of the Implementing Regulation on Clinical Trials of Medicinal And Biological Products (Amended: OG-25/6/2014-29041), published in the Official Gazette dated 13 April 2013 and numbered 28617, served as the basis for the preparation of this guideline.

5. ABBREVIATIONS

The meanings of abbreviations included in this guideline are as follows:

EU	European Union,
US FDA	The US Food and Drug Agency,
BA/BE	Bioavailability/Bioequivalence,
EMA	European Medicines Agency,
Phase 1	Phase 1 clinical trials
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
GCP	Good Clinical Practice
Agency	: Turkish Medicines and Medical Devices Agency,
CRF	Case Report Form,
CRO	Contract Research Organization,

6. Routine Inspections:

Routine GCP inspections are ones that are carried out without any particular triggers or worries to check on GCP compliance. Considering that not all applications can be examined, routine inspections must include a random component. The following aspects should be taken into consideration when choosing marketing authorization application files, studies, and locations for routine inspections in order to guarantee that a variety of situations are taken into account and that limited inspection resources are used effectively and efficiently:

a) <u>Selecting the marketing authorisation application file</u>:
- Quality of the file:
  - Missing documents (e.g. GCP declaration, audit certificates, lack of monitoring process documents),
  - Inconsistencies,

- Issues with the applicant's previously submitted application files.

- Type of product (e.g. recombinant product, monoclonal antibody, cell therapy, gene therapy, new chemicals, blood product, orphan medicinal product, etc.),
- Applicant/Sponsor/CRO (whoever has the authority to conduct important portions of the study):
  - Organizational size (big, medium, and small);
  - The applicant's initial application,
  - Sponsorship type (commercial/academic),
  - Inspection history (never inspected/been a long time since last inspection/adverse inspection findings)
  - The study (ies) is not sponsored by the applicant,
  - Business-related factors (bankruptcy, change of ownership, merger, other organizational changes)
- The extent of clinical data (single pivot study, a small number of patients, high contribution from a small number of researchers, retrospective data collection, case studies, bibliographic, standard clinical package, BA/BE study).
- Therapeutic area/indication (e.g. complex study protocol, design, etc.).
- Type of endpoint (flexible/rigid).
- Target population (pediatric, disabled, life-threatening diseases, emergencies, all types)
- Other
  - Countries where the research was conducted,
  - The application includes earlier studies (e.g. outdated ICH GCP guidelines or relevant legislation),
  - Availability of negative inspection outcome from agencies in other countries (such as the EU member states, EMA or US FDA).

b) Selection of study: studies for this type of inspection are often pivotal. The following aspects should be taken into consideration when there are more than one pivotal studies:
- Extent of the study (number of centers and volunteers)
- The complexity of the work organization (involvement of many CROs/suppliers, subcontractors, countries),
- Complex study design.

c) Choosing centers:
- Patient/voluntary intake rate (high/medium/low),
- Centers not previously inspected by EU member states, EMA and/or US FDA,
- Inspection history,
- Country where the study was carried out,
- Selection of the inspection centers from various geographic areas,
- Centers for which questions about the validity, representativeness, or reliability of reported trial data were raised in the trial outcome report.

Inspection should be requested when the triggers listed above are identified during the evaluation of a marketing application and when alternative methods other than inspection fail to provide the necessary assurance or when unresolved issues remain at the end of the evaluation process.

The inspection request is made by the Department of Medicines Marketing Authorization and/or the Department of Herbal and Support Products. In line with the inspection request made by the aforementioned Departments, it is decided by the Vice Presidency Of Inspectorate whether an inspection is required or not.

7. Inspections based on defined grounds

These are triggered inspections, which are requested by assessors because there is a concern about deviation from GCP in relation to the overall trial conduct or to the conduct at a particular site.

Considering that some of these issues might be noticed by the reviewers during the thorough pre-review of the application file without having any direct bearing on the study data, some of the criteria listed in section 2 that are used to choose routine inspections, have some overlap (e.g., inspection history, single pivotal study, etc.). Other triggers may be identified at the time of evaluation after additional analysis of the marketing authorization application file, and therefore the triggers presented in this section have been organized by taking into consideration some of the topics of the ICH E3 Guidelines (Structure and Content of Clinical Study Reports).

Although triggers may have been identified, there may not always be a need for an inspection and alternative methods of investigation may be more appropriate, such as reporting concerns to the Vice Presidency Of Inspectorate before requesting an inspection, or asking the applicant for information regarding matters to be clarified. It is decided by the Vice Presidency Of Inspectorate whether an inspection is required or not.

7.1. Ethics:

- Lack of information regarding the ethics committee's review of all or some clinical trial documents (such as the protocol, processes for collecting volunteer information and consent, and volunteer recruitment methods),
- The study's ethical aspects (such as the inclusion of few volunteers, the high percentage of illiterate participants in the study population, the demand for witnesses, etc.) and the lack of explanation of any issues encountered if any,
- Obvious issues in either the voluntary consent process or the information given to the study volunteers.

7.2. Researchers and the study's organizational structure:

- Complex administrative structure (e.g. many CROs/suppliers, subcontractors, etc.)
- Previous unfavorable inspection findings of one or more related parties,
- Interested parties' qualifications to handle the workload necessary for the study (e.g. If there's a need for using central facilities to identify endpoints or based on details from the CV of the lead researcher; the number of patients in a given center is too high etc.).

7.3. Protocol:

- Study design considerations (e.g. complex study design, use of placebo and/or comparison, insufficient justification regarding the compared product selection etc.)
- Significant modifications made to the protocol during the study (e.g., modifications to the primary endpoint or statistical methods or inclusion/exclusion criteria / multiple protocol modifications,
- Considerations regarding treatment:
  - Inspected product, its characteristics and treatments are unclear:
    - Inconsistencies between the study protocol and the study report in regards to dosage forms, packaging, labeling, storage conditions, dose, treatment schedule and duration,
    - Specific stability sensitivities of the inspected product, along with poor storage and transport conditions.
    - Preparation by the pharmacist and/or clinical staff prior the application,
    - Modifications made to the product during the study,
    - Complex titration or dose calculation.

- Assignment of volunteers to treatment groups:
  - Extraordinary,
  - Imbalance between treatment groups,
  - Inadequate understanding of randomization techniques.

- Blindness:
  - Lack of blinding methods and/or absence of such procedures
  - Inadequate measures to protect blindness (e.g. Occurs as a result of distinct inspected products due to manufacturing methods, laboratory data, adverse reactions, lack of efficacy, or non-blinded research participants, a member of the data monitoring committee, an interim analysis, etc.);
  - Concerns regarding concomitant treatments (e.g. use of concomitant prohibited medicines, concerns about interactions with concomitant medicines/direct effects on study endpoints etc.),
  - Concerns regarding treatment compliance (e.g. complexity of treatment regimens, side effects, differences between centres etc.),
  - Quality assurance considerations (information indicating significant issues concerning the conduct of the study, GCP compliance)

7.4. Volunteers participating in the study:

a) The inclination of volunteers:
  - Unusual/inexplainable discrepancies in the number of patients.
    - Differences between planned sample size and volunteers screened or randomized or followed:
    - In each treatment area
    - In each study phase,

- In the type and frequency of the disease and the characteristics of the center.

- Unusual/inexplicable differences between study centers:
  - Unusually high number of volunteers, drop out rate and/or follow-up period,
  - Centers being inactive for a long time following a large scale and rapid recruitment of volunteers,
  - Centers that joined the research later to increase volunteer recruitment,
  - Differences in dropout rates of subjects obtained by comparing the ratio of volunteers excluded from follow-up during the study and the ratio of volunteers screened at baseline in various centers to randomized volunteers.
- Differences between countries: unusually high recruitment and dropout rate.
- Characteristics and/or distribution of volunteers differing from demographics and other patient characteristics usually observed regarding the disease or location.

b) Deviations from the protocol: None/too many/not disclosed (e.g deviations from inclusion criteria, study visit windows, prohibited medicines)

7.5. Efficacy and safety evaluation criteria and data:

a) Efficacy and security variables:
- Inconsistencies between the protocol and clinical trial report's definitions of study variables that are unclear or inexplicable.
- Measurement of efficacy or safety variables:
  - New method or new analytical procedure,
  - Need for special equipment,
  - Need for special training for personnel,
  - The appropriateness of the measurement techniques,
  - Lack of or inadequate recording of non-standard efficacy or safety measures
  - Lack of [sufficient] provisions in the procedure for assessing the efficacy and/or safety (eg. with regard to clinical specimens, there are no provisions regarding sampling, identification of tubes, test conditions, etc.)
- Changes in facilities where critical measurements are taken
- Evaluation of clinical results: The following aspects of the data flow process should be taken into account if someone other than the researcher is in charge of the evaluation (such as the sponsor, external reviewers, or an external committee):
  - Adequate instructions/training provided to researchers for collecting and reporting efficacy parameters.
  - Identification and independence of external observers/committees.
  - Procedures for reviewing, evaluating, and documenting results and training, including maintaining blinding.

b) Statistical methods:

- Modifications made to statistical methods/endpoints during/after the study, particularly to the statistical analyzes not included in the program and/or modifications made before unblinding.
- After the data had been unblinded, a choice may have been made to exclude patient data from the analysis for no apparent reason, for concerns raised by those reasons, especially when the results were suitable for the test product, or to leave the data out of the study altogether.

c) Inaccuracy/inconsistency regarding the clinical data obtained:
- Conflicting results that differ from the findings of other studies or the literature.
- Data presenting unusual trends or anomalous variability or little deviation (e.g. low or high variability of efficacy parameters which are expected to have much higher or lower natural variability; unexpectedly low levels of (serious) adverse event reports or concomitant treatments, etc.)
- Data that, when compared to the findings of other researchers or studies, show an anomalous bias in favor of the test product.
- Inconsistent, inaccurate or incomplete data collecting and reporting:
    - Poor CRF design (e.g. protocol changes not reflected in CRF).
    - Absence of pertinent data lists.
    - Discrepancies between patient data lists and the information presented in the clinical trial report's main body.
    - Too many missing values.
    - Dropouts who don't live up to the relevant committee member's standards concerning the active ingredient or measurement type.

8. Ongoing Clinical Trials:

8.1. Routine Inspection:

The Clinical Studies Department and the Vice Presidency Of Inspectorate conduct an overall assessment at the end of the year, taking into account the concerns regarding ongoing clinical trials indicated in Articles 6 and 7. Considering the audit resources, the clinical trials to be inspected in the following year are determined and included in the inspection program.

8.2. Triggered Inspection:

Inspections carried out as a result of the discovery of a breach of the relevant legislation provisions concerning good clinical practices or the existence of a concern regarding a deviation from GCP, or the notification/notice received by the Agency.

9. Miscellaneous and Final Provisions

9.1. Enforcement

This guideline goes into effect on the day of approval.

9.2. Execution:

The provisions of this Guide are executed by the President.

ANNEX - 1

An overview of the selection criteria commonly implemented during the pre-screening stage of standard GCP inspections, as per Article 7.

<table>
<tr><td rowspan="16">Selection of Marketing Authorization Application</td><td rowspan="6">Product type</td><td>Recombinant/Monoconal antibody</td></tr>
<tr><td>Cell therapy/Gene therapy</td></tr>
<tr><td>New chemicals</td></tr>
<tr><td>Blood product</td></tr>
<tr><td>Orphan medicinal product</td></tr>
<tr><td>Other</td></tr>
<tr><td rowspan="4">Applicant/Sponsor/CRO</td><td>Size (Large, medium, small)</td></tr>
<tr><td>The applicant's initial application,</td></tr>
<tr><td>Sponsor type</td></tr>
<tr><td>Inspection history</td></tr>
<tr><td rowspan="3">Summary of clinical data</td><td>Single pivot study</td></tr>
<tr><td>A small number of volunteers</td></tr>
<tr><td>High contribution from a small number of researchers</td></tr>
<tr><td colspan="2">Therapeutic area/indication</td></tr>
<tr><td rowspan="5">Target population</td><td>Pediatric</td></tr>
<tr><td>Subject open to influence</td></tr>
<tr><td>Patients with critical illnesses</td></tr>
<tr><td>Emergency</td></tr>
<tr><td>All types</td></tr>
<tr><td>Other</td><td>Availability of negative inspection outcome from third-country authorities</td></tr>
<tr><td rowspan="2">Selection of pivotal studies</td><td colspan="2">Extent of the study (number of centers and patients)</td></tr>
<tr><td colspan="2">Complexity of study design</td></tr>
<tr><td rowspan="4">Choosing centers</td><td colspan="2">Patient intake rate (high, medium slow)</td></tr>
<tr><td colspan="2">No previous inspection history/no inspection history</td></tr>
<tr><td colspan="2">Settlement (third countries/emerging economies)</td></tr>
<tr><td colspan="2">Centers about which the clinical trial report expressed concerns.</td></tr>
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