Minimal Guidelines for the Monitoring of Early Clinical Trials (Phase I–II) in Europe Under CRC/EORTC/NCI Joint Agreement

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An agreement was reached between the Cancer Research Campaign Phase I/II Clinical Trials Subcommittee (CRC), the European Organization for Research and Treatment of Cancer, New Drug Development Office (EORTC/NDDO) and the National Cancer Institute Liaison Office (NCI Liaison Office) on minimal guidelines for monitoring early clinical trials in Europe. This agreement concerns compounds under joint development and has the approval of the Joint CRC/EORTC/NCI Steering Committee. These guidelines are in agreement with the Commission of the European Communities Guidelines of Good Clinical Practice for the trials on medicinal products in the European Community. In addition, the guidelines fulfill the US regulatory requirements which should facilitate the filing of Investigational New Drug Applications (IND) with the USA Food and Drug Administration. The intention is to increase cooperation among the parties and minimise the administrative burden. Minimal guidelines include the description of protocol content and handling, data collection procedures, reporting of adverse reactions, drug inventory and procedures for monitoring.

MINIMAL GUIDELINES

The protocol

(a) Investigators wishing to design a new protocol should adhere to the rules of protocol content set up by their group [1–6]. Minimal standard content rules are listed in Table 1. Recognised criteria of assessment such as the Common Toxicity Criteria [7] should be adopted. (b) The protocol should be approved by the Protocol Review Committee of the lead organisation and by the national/local Institutional Review Board (IRB). The composition of the IRB must be in accordance with local regulations. (c) Human subjects must be protected according to the Declaration of Helsinki. The informed consent may be written or oral according to local regulations. These regulations must be specified in the protocol. (d) Protocol amendments must go through the same review process as the entire protocol. (e) It is recommended to organise a central protocol library in each institution that will provide information about the protocol, protocol amendments, date of activation and closure of the protocols.

Data collection

Standard case report forms (CRF) that are approved by the lead organisations must be used. Minimal content is listed in Table 2.

Table 1.

Protocol minimal content
- Master protocols are usually used within each group as guidelines for preparation of the protocols. These guidelines should at least include

Protocol face sheet containing
- Date of the document
- Local protocol number
- Title of the study
- Protocol chairman (name and full address)
- Name of the institution(s)
- For EORTC and CRC supplied drugs, a listing of each drug and EORTC/CRC number
- For NCI-supplied IND drugs, a listing of each drug and NSC number

Essential elements of a protocol
- Every protocol must include the following elements
  - Objectives
  - Background and rationale
  - Study design (e.g. number of patients per dose level, specification of pretreatment allowed per dose level, etc)
  - Patient eligibility criteria
  - Treatment plan
  - Pharmaceutical information
  - Procedures for patient entry on study
  - Criteria for response and toxicity assessment
  - Monitoring of patients
  - Dose modification for toxicity
  - Off study criteria
  - Statistical considerations
  - Records to be kept
  - Adverse drug reactions procedures
  - Participation
  - Ethical considerations/informed consent
  - Monitoring of the study
  - Appendixes including
    - Performance status scale
    - Surface area computing scale
    - Toxicity criteria

Reporting of adverse reactions (ADR)

Rules for reporting of ADR which are specific to each country should be specified in the protocol. Investigators participating in clinical trials should adhere to these specific rules. The minimal items to be included in the ADR forms are listed in Table 3.

Drug inventory

Adequate inventory should be kept by the responsible investigator/pharmacist in each institution involved in the clinical trial. A protocol oriented drug accountability system is recommended. Records of the drug accountability should be maintained and made available for site visits. This inventory should include, at least, items listed in Table 4. Drug accountability should be performed by the drug sponsor and/or the lead organisation. For compounds that have no industrial sponsor, drug accountability will be performed by the lead organisation.

THE MONITORING

Monitoring of the centres will be performed to verify that trials may be carried out within the institution according to pre-established scientific, medical, and ethical criteria. In addition,

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Table 2.

Case report forms minimal content
- Grading and scales specified in the protocol should be used.
- Laboratory units should be specified if other than the units mentioned on the forms

General information to be included on each form
- Protocol number, patient identification, institution name
- Date and signature of the investigator

Study registration form
- Patient characteristics including date of birth, age, sex, body weight, height, surface area, performance status, date of diagnosis, initial diagnosis, stage of disease, histology, date of inclusion in the study
- Eligibility checklist

Patient history form
- Previous treatments specifying for:
- surgery: dates, procedures, findings and extent of residual disease
- Radiotherapy: radiation type, dates of first and last doses, sites irradiated, schedule used, total dose administered, response
- Chemotherapy/hormonotherapy/immunotherapy: agent and schedule used, dates of first and last doses, total dose, response

Patient physical examination (initial and follow-up forms)
- Description of any abnormality and its relevant history by site (head, neck, breasts, heart, lungs, abdomen, genitalia, integument, skeleton, neurologic, endocrine)
- Performance status, weight, temperature, pulse, respiratory rate, blood pressure at the frequency required by the protocol

Extent of disease (initial measurements and follow-up measurements)
- Localisation and description of the lesion, irradiation of the lesion, measurability, evaluability or non-evaluability, how the measurement is determined, measurements of the lesion(s), dates of the measurements, evaluation of response by lesion

Study drug administration form
- For each drug administered: drug name, date of administration, start time, course number, dose level, actual dose administered, dose units, route of administration, duration of administration and duration units

Adverse event form
- Toxicity type, grade, date of onset and date resolved, day nadir/apex, estimated relationship to the drug, action required, therapy required for patient relief, outcome of the adverse event, whether the compound was reintroduced

Course assessment form
- Date start of the course, course number, evaluability of the course, overall response assessment

Concomitant medication form
- Any concomitant measure/medication received detailing: agent, total daily dose, schedule, reason for use, start and end dates

Physicians notes form
- Form devoted to physician comments

Off study summary
- Date off study, reason off study, best response to treatment, date onset, date relapse survival information including date, vital status (alive in follow-up, lost to follow-up, death)
- Cause of death, autopsy related information if available

Laboratory data
- Mandatory data are date of analysis, laboratory test name, laboratory value and laboratory unit. Specific laboratory values and frequency required by the protocol should appear on the form

Initial and follow-up investigations
- Mandatory data are date of investigation, investigation name (e.g. ECG, chest X-rays) and results. Specific investigations required by the protocol should appear on the form

Table 3.

Adverse reaction form (ADR)
The form should include at least
- Name of the person completing the form
- Institution
- Date

Demographics information
Patient information including
- Patient identification (ID)
- Age
- Sex
- Date of initial diagnosis
- Malignancy
- Performance status at the start of the study
- Sites of metastatic disease
- Current non-malignant disease and current non-protocol medications

Drug information including
- Drug name
- Source of the drug
- Type of reaction
- Toxicity criteria used
- Toxicity grade reported
- Date of reaction
- Protocol number
- Dose level
- Date of first course administration
- Date of last drug administration
- Number of courses

Documentation of the reaction
- Description of the ADR including grade, date onset, date resolved, laboratory findings, physical findings, complications, outcome, investigators assessment of the relationship to the drug, action taken, therapy required.

Additional comments
Date and signature of the reporter

Table 4.

Drug inventory minimal content
- Name of the institution
- Protocol number
- Drug name, dose form, strength
- Protocol title
- Responsible investigator
- Date delivered
- Patient identification
- Dose delivered
- Manufacturer and lot number
- Recorder's initials

Table 5. Site visit form required content

General information on the visit
- Institution visited including name and address
- Principal investigator name
- Date of visit
- Initial or follow-up site visit
- Composition of visiting team
- Composition of the team visited
- Procedure used to inform the center of the visit

General information on the visited centre
- Flow chart of institution organisation including departments, laboratories, special units
- Summary of institution funding situation
- Overall patient accrual/year, major tumour types
- Protocol accrual/year
- Principal investigator responsibilities and curriculum vitae

Facilities
- In patient units
  - Documentation of the presence of a Phase I/II Unit
  - General organisation of the unit including: number of beds, medical doctors, research nurses, data managers.
  - If no specific unit exists, description of procedures
- Out patient unit
  - Description of procedures
- Laboratory facilities (routine and research laboratories)
  - Visit of facilities
  - Description of main material available
  - Quality control procedures used
- Institutional meetings
  - Description of organised meetings (e.g. general, ward, phase I)

Protocol handling
- Description of standard protocol handling including:
- —who writes protocols, who is responsible for handling
- —protocol approval procedures including protocol review committees (scientific, ethical), composition of the committees, legal requirements in the country
- —Institutional Review Board (IRB) or equivalent, composition, role in protocol review (scientific, ethical)

Toxicity reporting
- Description of local legal requirements, procedures used for collecting and reporting minor and major expected and unexpected toxicities
- Documentation of forms used

Informed consent
- Description of local legal requirements
- Description of the process used for oral/written consent
- Essential elements of the consent form

Data management
- Protocol office
  - Presence/absence of a central office
  - Role of central office, responsibilities
  - Information procedures about activation of new protocols/protocol changes in the institution
- Data handling
  - Who handles the data (specifically for phase I, II, III)
  - Which type of flow sheets are used
  - Computer facilities
  - Quality control procedures

Pharmacy inspection
- Visit of facilities
- Staff composition/responsibilities
- Drug dispensing procedures including:
- —documentation of facilities for storage and their adequacy
- —procedure used to restrict access to pharmacy and investigational supplies and protection against unauthorised prescription/use
- —drug inventory and accountability: existence and availability of records, filing systems
- —maintenance of protocol specific supplies
- —procedures for notification of study closure and return of unused supplies

Phase I/II program
- Documentation of previous, ongoing and planned phase I/II trials, patient accrual
- Description of treatment organisation including responsible persons for drug administration, follow-up organisation
- Pharmacokinetic studies: description of procedures

individual studies will follow the current European and local recommendations for the performance of clinical trials with new anticancer agents [1–6, 8].

General site visit

The purpose of the general site visit is to review the overall quality of study conduct, compliance with local regulations and data handling procedures. The following instructions will be considered: (a) investigators interested in initiating a clinical trial with a drug jointly developed must have their facilities evaluated. (b) The site visit team will include at least one representative from each group (CRC, EORTC/NDDO, NCI). (c) Investigators and centres will be notified in advance of the date of the visit, its intent and the composition of the team. (d) Site visits should be planned before the initiation of phase I trials and every 2 years thereafter (or more often, according to the specific group rules). (e) Minimal content of the site visit form is listed in Table 5. (f) A written report detailing the status of the centre and eventually the proposals will be prepared by the team.

Table 6. Data to be audited

Data	No. of patients (%)
Patient's ID number and initials	100
Informed consent	100
Responding patients	100
Toxic deaths, major ADR	100
Remaining data	10%*

* This percentage might be increased for trials including fewer than 10 patients, or whenever considered necessary by the audit team.

Table 7. Data audit form minimal content

General information
- Institution visited including name and address
- Principal investigator name
- Date of visit
- Composition of visiting team
- Composition of the team visited
- Procedure used to inform the centre of the visit
- Protocol(s) audited

Protocol handling
- List of patient included in the study
- List of patient charts required for audit
- Compliance with protocol phase I/II procedures for:
  - —escalation and de-escalation of dosage
  - —drug administration
  - —drug accountability
  - —toxicity reporting

Source verification

For selected charts one separate audit form should be used to document source verification, it should include:
- Documentation of informed consent
- Eligibility criteria verification
- Drug administration according to planned schedule
- Response evaluation according to protocol requirements
- Initial and follow-up evaluation according to protocol requirements including history and physical examination, laboratory data, additional investigations.

Data audits

Data audits will be performed to document the reliability of the data and to ensure proper reporting. The following instructions will be considered: (a) the audit team will be composed of representatives of the group depending upon its specific interests (CRC/NCI, EORTC, NDDO/NCI). (b) Investigators must be notified in advance about the date of the visit, its intent and the composition of the team. (c) Data audits should be done as early as possible after the initiation of Phase I trials and at the end of the trials (or more often according to the specific group rules). Data to be audited are listed in Table 6. (d) Minimal content of the audit form is listed in Table 7. (e) A written report detailing the status of the audit and eventual proposals will be prepared by the auditing team.

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