



Protocol template in accordance with CTR Annex I

The following protocol template take into consideration all requirements set in the EU Clinical Trials Regulation (CTR), Annex I.

How to use the template:

All sections and subsequent requirements should be included in the protocol. Hence, to ensure compliance with the CTR no sections/bullets from this template must be deleted but instead justification must be provided if the posed requirement is not valid/relevant for the trial in question.

It is strongly recommended to carefully read the [guidance given on the DKMA website](#) and for non-commercial sponsor to consult with the [GCP-units and their guidance's](#).

It may be helpful to consult the [International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use \(ICH\) M11 template](#) for more detailed guidance for the set-up of the trial protocol. Please be aware that the ICH M11 template is not considering all requirements by the CTR and hence, is not a stand-alone template for clinical trials in EU.

Format requirements:

- The first part (1) of the template is the requirements of the front page(s) and it is important to always have a date and a numeric version control (to be updated when amended).
- The protocol shall, when possible, be written in an easily accessible and searchable format, rather than scanned images.

Format requirements when submitting substantial modifications:

- The protocol must be submitted in both track-changes and clean versions It should be clear from the updated protocol which changes are considered substantial and applied for together with an explanation of each change.



- The new version of the document shall be identified by the date and an updated version number.

1. Front page(s)

General information about the trial and the persons responsible for the trial, including:

- a) Protocol title, date and code/name or short title, all appendices and amendments must be numbered and dated. Furthermore, the EU CT number.
- b) Name and address of the sponsor and any person, company, institution or organisation to whom the sponsor has delegated tasks.
- c) Name and title of the person/persons authorised to sign the protocol and the protocol amendments on behalf of the sponsor.
- d) Name, title, address and telephone number of the sponsor's medical/dental advisors for the trial
- e) Name and title of the investigator responsible for the trial (in the case of a multi-site trial please state the name and title of the investigator responsible for the trial at all centers/sites), including the coordinating investigator and the addresses and telephone numbers of all the relevant trial center(s)/sites.
- f) Names and addresses of laboratories and other hospital departments, technical departments and/or institutions involved in the trial.
- g) A declaration stating that the trial will be carried out in accordance with the protocol and current statutory requirements/legislation.
- h) A description of the time schedule, including dates for the start of the trial, the trial period and completion.
- i) a statement that the clinical trial shall be conducted in compliance with the protocol, with this Regulation and with the principles of good clinical practice;



2. Background information

- a) a comprehensive list of all investigational medicinal products and all auxiliary medicinal products;
- b) a summary of findings from nonclinical studies and clinical trials that potentially have clinical significance and from clinical trials that are relevant to the trial
- c) A summary of known and potential risks and possible benefits for the trial subjects including an evaluation of the anticipated benefits and risks.
- d) A description and justification of the dose, method and frequency of administration and treatment periods
- e) A description of the study population

For emergency trial subjects, the scientific grounds for expecting that their participation has the potential to produce a direct clinically relevant benefit shall be documented.

- f) in case patients were involved in the design of the trial, a description of how.
- g) References to literature and data that are relevant and form the basis for the trial/ that provide background. Furthermore, a discussion of the purpose and relevance of the clinical trial to allow Member State assessment in accordance with:
 - the anticipated therapeutic and public health benefits taking account of all of the following: – the characteristics of and knowledge about the investigational medicinal products; – the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, the explanation and justification
 - the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the clinical trial and methodology, including sample size and randomisation, comparator and endpoints
 - the risks and inconveniences for the subject, taking account of all of the following: the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal



products; — the characteristics of the intervention compared to normal clinical practice; — the safety measures, including provisions for risk minimization measures, monitoring, safety reporting, and the safety plan; — the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated.

3. Trial plan and trial design

- a) Clear indication of the primary and any secondary endpoints of the trial.
- b) A description and a discussion of the type/design of the trial (e.g. double blind, placebo controlled, parallel group comparative) – ideally illustrated by a flow chart
- c) A description of arrangements for the reduction or elimination of bias, including: - randomisation; a description of the randomisation method – including procedures and practical arrangements -blinding; a description of the blinding (single blind, double blind, double dummy etc.) and practical procedures for safeguarding the blinding
- d) A description of the trial treatment, justification for dose, posology, frequency, packaging and labelling of the study medicine/investigational medicinal product including any placebo and reference products and auxiliary medicinal product.
- e) A statement of whether the investigational medicinal products and auxiliary medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and a justification for the use of non-authorised auxiliary medicinal products in the clinical trial;
- f) A description of the groups and sub-groups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs (ex: age, gender, participation of healthy volunteers, patients with rare and ultra-rare diseases);
- g) A description of the expected duration of the individual trial subject's participation in the trial and an indication of the trial periods (e.g. run-in, wash-out and follow-up) and the duration of these



- h) a clear and unambiguous definition of the end of the clinical trial in question (in most cases this will be the date of the last visit of the last subject; any exceptions to this shall be justified in the protocol)
- i) A description of the rules for stopping/discontinuing the trial or interrupting treatment of individual subjects and/or parts of the trial
- j) a description of the accountability procedures for the supply and administration of medicinal products (investigational medicinal products and placebo) to subjects including the maintenance of blinding, if applicable. Information on where the randomisation code is stored and procedures in case the code is breached and procedures for breaking codes.
- k) An indication of the data considered to be source data and which is recorded directly on the Case Report Forms (CRFs) – e.g., data not previously written down or electronically registered.

4. Selection of trial subjects and criteria for inclusion in and exclusion from the trial

- a) A description of the inclusion criteria.
- b) A description of the exclusion criteria
- c) A description of criteria and procedures for leaving the trial (i.e. withdrawal of the study medicine/cessation of participation in the trial), stating:
 - when and how the trial subjects are to discontinue the study medicine/leave the trial
 - which data is to be collected from trial subjects from whom the study medicine is to be withdrawn or from trial subjects who have left the trial, as well as when such data should be collected -to what extent and how trial subjects leaving the trial are to be replaced by new subjects - follow-up procedures for trial subjects who have stopped using the study medicine/left the trial – NB! including drop-outs.
- d) a justification for including subjects who are incapable of giving informed consent or other special populations, such as minors



- e) if a specific gender or age group is excluded from or underrepresented in the trials, an explanation of the reasons and justification for these exclusion criteria;/ • a justification for the gender and age allocation of trial subjects

5. Treatment of trial subjects

- a) A description of the treatment, including product name(s) of all products, dose, posology, frequency and treatment period(s), including follow-up periods.
- b) If a clinical trial is conducted with an active substance available in the European Union under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 5) only and not specify the trade name of each product.
- c) Rules for concomitant treatment/medication before and/or during the trial (including "rescue medicine") including medicinal products, which are permitted or not permitted, before or during the trial;
- d) Arrangements for promoting and controlling close adherence to the treatment (compliance monitoring). Furthermore • a description of the arrangements, for tracing, storing, destroying and returning the investigational medicinal product and unauthorised auxiliary medicinal product
- e) Issues regarding labelling and the unblinding of investigational medicinal products shall be addressed in the protocol, where necessary.
- f) a description of procedures for monitoring subject compliance, if applicable
- g) Statement of any subsequent treatment for the trial subjects when they leave/terminate the trial where such additional care is necessary because of the subjects' participation in the trial and where it differs from that normally expected for the medical condition in question.



6. Evaluation of effect

- a) Specification and justification of the effect parameters
- b) Methods for time points for measurement, registration and analysis of efficacy parameters.

7. Safety evaluation

- a) Specification and justification of safety parameters
- b) Methods and times for measuring, recording and analysing the safety parameters
- c) Procedures for registration and reporting of adverse events/adverse reactions (see section 12 concerning events/adverse reactions), including how long these records should continue after the trial subject has stopped using the study medicine. Also, procedures on how these individual reports are to be forwarded on completion of the trial – Final report
- d) With regard to the notification of adverse events, the protocol shall identify the categories of:
 - adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor; and
 - serious adverse events which do not require immediate reporting by the investigator to the sponsor

The protocol shall describe procedures for:

- eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor,
- reporting by the investigator to the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting;
- reporting of suspected unexpected serious adverse reactions by the sponsor to the EudraVigilance database; and
- follow-up of subjects after adverse reactions including the type and duration of follow-up



- In case the sponsor intends to submit a single safety report on all investigational medicinal products used in the trial in accordance with Article 39(1a), the protocol shall indicate the reasons therefor.
- e) Arrangements for avoiding and treating complications
- f) Statement of how and how long the trial subject should be monitored in case of adverse events/adverse reactions. Furthermore, a summary of monitoring arrangements.

8. Statistics

- a) Description of the statistical methods employed – including time(s) for scheduled interim analyses. More specific: a specification of the efficacy and safety parameters as well as the methods and timing for assessing, recording, and analysing of these parameters;
- b) Justification of the scheduled number of patients – including considerations/calculations of the size of the trial and its clinical relevance. (In multi-centre trials, the number of trial subjects planned to be included per trial must also be indicated).
- c) The significance level to be applied
- d) Criteria for termination of the trial
- e) Procedures for dealing with missing data, unused data and false data. False data may be e.g. interpolated data, and it is not necessarily false and for reporting any deviation from the original statistical plan;
- f) Procedures for reporting deviations from the original statistical plan
- g) Statement of the trial subjects, whose data will be included in the statistical analysis (e.g. all randomised subjects, all subjects receiving medication, all eligible subjects and all subjects who can be evaluated).

9. Charter of DSMB/DMC

- a) The protocol shall be accompanied by the Charter of the Data Safety Monitoring Committee, if applicable (Separate upload to CTIS). Any DSMB/DMC should be mentioned in the protocol.



10. Direct access to source data/documents, including the investigator's authorisation to direct access to source data/documents (including patient files) in connection with monitoring, auditing and/or inspection by a scientific ethics committee, the Danish Medicines Agency or by health authorities in other countries.

- a) a description of arrangements for monitoring the conduct of the clinical trial
- b) a statement from the sponsor (either in the protocol or in a separate document) confirming that the investigators and institutions involved in the clinical trial shall permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents.

11. Quality control and quality assurance, including confirmation that ordinary procedures for quality control and assurance are complied with, cf. sections 3 and 4 of the Danish executive order on GCP (Appendix 3) / Confirmation that standard procedures for quality control and quality assurance will be complied with, cf. ICH GCP guidelines (see Glossary sections 1.46 and 1.47).

- a) a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects;

12. Ethical questions

- a) Specific ethical considerations in relation to the trial
- b) Description of how the trial subjects (patients, healthy volunteers, patients for whom the treatment of their illness is not the aim of the trial) are to be informed and how their consent will be obtained. Possible reasons for not obtaining informed consent from the trial subjects themselves/ especially when subjects are incapable of giving informed consent
- c) a description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from trial subjects, where applicable, unless contained in a separate document;



13. Handling and archiving data. Guidelines for handling, processing and archiving all of the collected data for each trial subject participating in the trial, plus other data relevant to the trial.

- a) a description of the arrangements to comply with the applicable rules on the protection of personal data; in particular organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed
- b) a description of measures that will be implemented to ensure confidentiality of records and personal data of subjects concerned in clinical trials

14. Financing and insurance. Specification of the financing and insurance status of the trial

15. Guidelines for publication:

- a) Description of where the results are intended to be published/announced - Please see the current guidelines for researchers and scientific ethical committees. Furthermore, a statement that result will be submitted to CTIS within one year of the end of trial. If not duly substantiated reasons for submission of the summary of the results of the clinical trials after more than one year;

16. Summary and appendices. The trial protocol must contain a summary and relevant appendices (e.g. instructions for personnel, description of special methods of approach).

- a) The protocol shall be accompanied by a synopsis of the protocol. Please consult EudraLex Volume 10 Q&A for content of the synopsis (separate upload to CTIS).

17. Literature references. A list of the literature referred to in the protocol must be attached.

Change log for template:

08 March 2023 – Fixed issues with numbering of sections in the template.