

**Protocol Template for Clinical Research Studies**

*<NB: This template contains instructive text that must be removed when preparing a protocol. Remember to include logos for any collaborating organisations (Sponsor, CRO) on the front page of this document>*

# STUDY TITLE:

*The full study title should mention the study design, population and compound to be studied.*

**Protocol Number:**

**Phase:**

**Study Reference Code:** *The short reference for the study such as protocol number or an acronym for the study. This is optional but may be useful as a quick reference to the study.*

**Eudract Number (*delete if not applicable*):**

**Version Number:**

**Date:**

**Study Sponsor Name & Address:**

**Monitor Name & Address (if other than the sponsor):**

# VERSION CONTROL LOG

*The table below provides an overview of the summary of changes from previous version of this protocol. Where no previous version exists there will be no summary of changes on record.*

|  |  |  |
| --- | --- | --- |
| **Version number** | **Date** | **Summary of changes** |
| 1 |  | N/A |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

# PROTOCOL SIGNATURE SHEET

**This protocol has been approved by:**

|  |  |
| --- | --- |
| **Name & Address:**  <*print – delete this text on completion>* | **Role:**  **Sponsor Representative** |
| **Signature:** | **Date:** |

|  |  |
| --- | --- |
| **Name & Address**  <*print name – delete this text on completion>* | **Role:** |
| **Signature:** | **Date:** |

**Principal Investigator Declaration:**

I have read and understood the requirements and conditions of the study protocol. I am aware of my responsibilities as an Investigator under the guidelines of the Internal Conference on Harmonisation Good Clinical Practice (ICH GCP) standards, the Declaration of Helsinki, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the study team assigned to me who will be involved in the study.

I agree to use the study material, including medication, only as specified in the protocol.

I understand that changes to the protocol must be made in the form of an amendment that must be approved by the Ethics Committee and Regulatory Authorities prior to its implementation.

I understand that non-compliance with the study protocol may lead to early termination of the study.

|  |  |
| --- | --- |
| **Local Investigator’s Name & Address:**  <*print name – delete this text on completion>* | |
| **Signature:** | **Date:** |

Return the original wet signature\* page to the sponsor and retain a copy\* with the study protocol within the Investigator’s Site file.

\* *Reference to wet signature means signature in ink, copy can be a scanned copy or photocopy of the signature page.*

# Contact Details:

*These should include:*

* *Include the name, title, address and telephone number(s) or email address of the sponsor’s medical (or dental if applicable) experts.*
* *Investigators responsible for conducting the trial and the address and telephone number(s) of the trial site(s).*
* *The name, title, address and telephone number(s) or email address of the qualified physician (or dentist if applicable), responsible for all site-related medical decisions (if other than the investigator)*
* *Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.*

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# LIST OF ABBREVIATIONS & DEFINITIONS

|  |  |
| --- | --- |
| **Abbreviation** | **Definition** |
|  |  |
|  |  |
|  |  |

*Instructions for the completion of this template can be found in ICH GCP E6.*

# Background Information

*According to ICH GCP section 6, this section should cover the following:*

* *Name and description of investigational product(s) if applicable.*
* *Summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials related to the study.*
* *A summary of the known and potential risks, if any, and benefits to human subjects.*
* *Description and justification of the route of administration, dosage, dosage regimen and treatment period(s)*
* *A statement that the trial will be conducted in compliance with the protocol, GCP and applicable regulatory requirements.*
* *A description of the study population to be studied.*
* *References to literature and data that are relevant to the trial, that provide background for the trial.*

# Objectives

*This section should include detailed descriptions of the objectives and purpose of the study.*

## Primary Objectives

## Secondary Objectives

# Study Design

*According to ICH-GCP E6 section 6.4 the Study Design should take into account the following:*

* *A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.*
* *A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.*
* *A description of the measures taken to minimize/avoid bias, including:*

*a) Randomization.*

*b) Blinding.*

* *A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).*
* *The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.*
* *A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.*
* *Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.*
* *Maintenance of trial treatment randomization codes and procedures for breaking codes.*
* *The identification of any data to be recorded directly on the CRFs*

*Suggested subheadings are listed below:*

* 1. **Diagrammatic Overview of Study Design**

*<Insert Overview Diagram of Study Design – delete this text on completion>*

## Methodology

## Endpoints

## Target Number of patients

# Expected Duration of Study

# Primary and Secondary Outcome Measures

# Subject Enrolment

*Selection and Withdrawal of Subjects should cover the following:*

* *Subject inclusion criteria.*
* *Subject exclusion criteria.*
* *Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:*

*a) When and how to withdraw subjects from the trial/ investigational product treatment.*

*b) The type and timing of the data to be collected for withdrawn subjects.*

*c) Whether and how subjects are to be replaced.*

*d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.*

*Suggested sub-headings are included below, amend as required.*

## Inclusion Criteria

## Exclusion Criteria

## Control Groups

## Removal of Patients from Therapy or Assessment

# Study Treatments

*This section should cover the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.*

*Medication(s)/treatment(s) permitted (including rescue medication) and nor permitted before and/or during the study must be included.*

*This section must also cover procedures for monitoring subject compliance.*

*Suggested sub-headings are included below, amend as required.*

## Treatment Arms

## Description of Study IMP(s)

## Preparation, Dosage and Administration

## Dose Modification

## Dispensing and IMP accountability

## Method of assignment of subjects to treatment group(s)

## Selection and Timing of dose

## Prior and Concomitant Therapy

# Assessment of Efficacy

*This section should cover:*

* *Specification for efficacy parameters.*
* *Methods and timing for assessing, recording and analysing efficacy parameters.*

# Assessment of Safety

*This section is to cover the following:*

* *Specification of safety parameters.*
* *The methods and timing for assessing, recording, and analysing safety parameters.*
* *Procedures for eliciting reports of and for recording and reporting adverse event and any illnesses that may occur during or in between intervention.*
* *The type and duration of the follow-up of subjects after adverse events.*

# Pregnancy Monitoring (delete if not applicable)

*Where pregnancy is an exclusion criteria, appropriate methods of contraception must be discussed with the participants of child bearing age. Female participants must be screened for pregnancies at regular intervals during the study.*

*Any pregnancies occurring within female trial participants and/or female partners of trial participants must be monitored through to term. Any incidents occurring during the pregnancy must be reported as part of the adverse event reporting process.*

# Study Specific Procedures

*Include study specific procedures (SSPs) related to the conduct of the study. Below is a list of suggested procedures, delete if not applicable to the study.*

## Randomisation

## Blinding Arrangements – breaking of the study blind

## Subject Withdrawal

## Trial Closure

## Continuation of treatment or therapy

# Schedule of Study Visit(s) and Procedure(s)

# Clinical and Laboratory Assessments

*This should include reference ranges.*

# Pharmacovigilance and Safety reporting

# Data Management & Statistics

*This section is to cover the management of data (source data, laboratory results, scans) and statistics covering:*

* *A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).*
* *The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.*
* *The level of significance to be used.*
* *Criteria for the termination of the trial.*
* *Procedure for accounting for missing, unused, and spurious data.*
* *Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).*
* *The selection of subjects to be included in the analyses (e. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).*

## Statistical Analysis

*This section should be prepared in close collaboration with the statistician appointed to the study. See Appendix 1 for additional guidance on Statistical analysis and ICH Guidance E3 that can be downloaded from the following web link:*

[*http://www.ich.org/fileadmin/Public\_Web\_Site/ICH\_Products/Guidelines/Efficacy/E3/Step4/E3\_Guideline.pdf*](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Step4/E3_Guideline.pdf)

* *For this section the emphasis should be on planned analyses, comparisons and statistical tests rather than those actually used.*
* *Where critical measurements are performed more than once, the particular measurements planned as the basis for comparison should be specified.*
* *If more than one analytical approach is possible, the planned approach should be identified. It should also be specified whether the primary analysis is to include adjustment for covariates.*
* *Reasons for planned exclusion of data from analysis should be described (e.g. where data from patients exists but is planned to be excluded from analysis).*
* *Results from subgroups to be examined separately should be identified.*
* *Global scales, severity scores, responses of a certain size and any other categorical responses to be used in analysing responses should be clearly defined.*

*Where appropriate a separate Statistical Analysis Plan (SAP) may be put in place that can be referenced in this section.*

### Data Monitoring & Interim Analysis

*Include details of monitoring of the results of the study, where a Data Monitoring Committee (either appointed within or external to the Sponsor), the composition and procedures should be described in particular procedures to maintain study blinding should be given. Include:*

* *The frequency and nature of planned interim analysis*
* *Specified circumstances for terminating the study*
* *Any statistical adjustments to be employed because of interim analyses should be described.*

### Determination of Sample Size

*This section should cover:*

* *The planned sample size*
* *Justification for the planned sample size (give details of statistical considerations or practical limitations)*
* *Methods for calculating the sample size. Any estimation should be explained as to how these were obtained.*

*For comparative studies intended to show a difference between treatments:*

* *Specify the difference the study is designed to detect.*

*For positive control studies:*

* *The sample size should specify the difference between treatments that would be considered unacceptably large thus the study is designed to be able to exclude.*

## Direct Access to Source Data/Documentation

*It should be specified either in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.*

## Data Handling and Record Keeping

## Quality Control and Quality Assurance

*Indicate plans to ensure the study is conducted to high standards and data produced is credible.*

# Ethics

*Include a description of ethical considerations taken into account relating to the study.*

# Finance and Insurance

*Include details for how the study is being funded and insured, if not already included in a separate agreement. If covered by separate agreements refer to the agreements here.*

# Publication Policy

*Indicate plans for publication if not already addressed in a separate agreement.*

# Archive Plan

*Include plans for the archive of the study once all processes have been completed, if not already covered by a separate agreement. There must be a named archivist appointed, if any arrangements have been made with an offsite archiving company those must be included or referenced in the plans.*

# APPENDIX 1.

**GUIDANCE FOR STATISTICAL/ANALYTICAL ISSUES**

**A. Statistical Considerations**

Details of the statistical analysis performed on each primary efficacy variable should be presented in an appendix. Details reported should include at least the following information:

a) The statistical model underlying the analysis. This should be presented precisely and completely, using references if necessary.

b) A statement of the clinical claim tested in precise statistical terms, e.g., in terms of null and alternative hypotheses.

c) The statistical methods applied to estimate effects, construct confidence intervals etc. Literature references should be included where appropriate.

d) The assumptions underlying the statistical methods. It should be shown, insofar as statistically reasonable, that the data satisfy crucial assumptions, especially when necessary to confirm the validity of an inference. When extensive statistical analyses have been performed by the applicant, it is essential to consider the extent to which the analyses were planned prior to the availability of data and, if they were not, how bias was avoided in choosing the particular analysis used as a basis for conclusions. This is particularly important in the case of any subgroup analyses, because if such analyses are not pre-planned they will ordinarily not provide an adequate basis for definitive conclusions.

(i) In the event data transformation was performed, a rationale for the choice of data transformation along with interpretation of the estimates of treatment effects based on transformed data should be provided.

(ii) A discussion of the appropriateness of the choice of statistical procedure and the validity of statistical conclusions will guide the regulatory authority's statistical reviewer in determining whether reanalysis of data is needed.

e) The test statistic, the sampling distribution of the test statistic under the null hypothesis, the value of the test statistic, significance level (i.e., p-value), and intermediate summary data, in a format that enables the regulatory authority's statistical reviewer to verify the results of the analysis quickly and easily. The p-values should be designated as one- or two-tailed. The rationale for using a one-tailed test should be provided.

For example, the documentation of a two-sample t-test should consist of the value of the t-statistic, the associated degrees of freedom, the p-value, the two sample sizes, mean and variance for each of the samples, and the pooled estimate of variance. The documentation of multi-centre studies analysed by analysis of variance techniques should include, at a minimum, an analysis of variance table with terms for centres, treatments, their interaction, error, and total. For crossover designs, the documentation should include information regarding sequences, patients within sequences, baselines at the start of each period, washouts and length of washouts, dropouts during each period, treatments, periods, treatment by period interaction, error, and total. For each source of variation, aside from the total, the table should contain the degrees of freedom, the sum of squares, the mean square, the appropriate F-test, the p-value, and the expected mean square.

Intermediate summary data should display the demographic data and response data, averaged or otherwise summarised, for each centre-by-treatment combination (or other design characteristic such as sequence) at each observation time.

**B. Format and Specifications for Submission of Data Requested by Regulatory Authority's Statistical Reviewers**

In the report of each controlled clinical study, there should be data listings (tabulations) of patient data utilised by the sponsor for statistical analyses and tables supporting conclusions and major findings. These data listings are necessary for the regulatory authority's statistical review, and the sponsor may be asked to supply these patient data listings in a computer-readable form.

Further details can be found on the following link:

<http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Step4/E3_Guideline.pdf>