Course of a clinical trial

(SOP)

I. General introduction

One of the main goals of the UP Centre for Translational Medicine are to help clinicians and basic researchers in the planning, starting, transacting, evaluating and publishing the results of clinical trials. The assistance of UP CTM covers the whole process of the clinical trial including;

before starting the clinical trial:

- assessing the feasibility
- selecting the correct methodology
- selecting the method of data collection
- biostatistical sample size calculation

- obtaining the required official and ethical approvals
- assuring the anonymity and data protection described in the ethical approval
- international registration of the trial
- writing the pre-study protocol

during the clinical trial:

- monitoring the study
- monitoring the sample sizes and activity
- biostatistical follow-up of data
- involving local and foreigner institutes, extending the clinical trial

after the closure of the clinical trial:

- preparing the official and ethical reports
- statistical analysis
- assisting publication

Hungarian legislation and GDPR

UP CTM declares, that clinical trials (non-interventional and interventional) are always performed in the current Hungarian legal environment (Government Decree No. 235/2009, Title 1: Licensing of medical research on humans and Decree No. 23/2002 of the Ministry of Agriculture. Individuals participating in the clinical trials are receiving thorough, verbal information about the possible benefits, harms, process of randomization and use of placebo.

- Patients express their intention to participate by signing the Declaration of consent

- UP CTM provides basic assistance in the collection and submission of regulatory / ethics committee authorization documents.

In addition, UP CTM guarantees compliance with the rules on the handling and protection of patients' personal data in accordance with the General Data Protection Regulation (GDPR), which entered into force on 25 May 2018:

- Participant data can only be accessed by data controllers (doctors, nurses) and data uploaders (administrators).

II. Abbreviations, persons, explanations, contacts

PI	Principal investigator	
SC	Strategical consultant	trials@tm-centre.org
CTC	Clinical trial coordinator	trials@tm-centre.org
IT	IT specialist	it@tm-centre.org
BIOS	Biostatistician	biostatistics@tm-centre.org
HDM	Head of the data management	datamanagement@tm-centre.org
EM	Ethical manager	ethics@tm-centre.org

PI: **Principal investigator:** Professional management of the establishment and maintenance of the study. The „engine" of the trial.
SC: **Strategical consultant:** Participating in the decision making, regarding the structure and support of the study. Supporting the preparation of strategic decisions. Monitoring the starting of the study, facilitating communication.
IT: **IT specialist:** Electronic interface development, testing and coordination of maintenance. Liaison with the IT development team.

BIOS: **Biostatistician:** Coordination of statistical issues related to database creation and analysis (sample size calculation, data systematization, statistical analyzes).
HDM: **Head of the data management:** Organizing training for study colleagues (clinical research administrators, study nurses, and doctors). Local organization of patient involvement. Organizing the control of incoming data, data quality control.
EM: **Ethical manager:** Describing the process of ethical licensing, obtaining, preparing and submitting the documentation required for ethical approval to the relevant authorities. Consultation with the PI during the process.

CTC: **Clinical trial coordinator:** Supporter of the implementation of the clinical trial, participates in all (non-professional) steps of the trial from the first moment of planning to the completion of the administrative tasks after the conclusion of the trial.

III. Timetable of newly starting clinical trials

1. Professional discussion of the raised clinical issue (Preconception and feasibility of the study)

To define and formulate the purpose of the study very precisely, to decide whether an observational / interventional clinical trial is the most appropriate choice to answer the clinical question. If the clinical trial is not the appropriate research tool to answer the question, the issue will be redirected to the registry or meta-analysis coordinator.

PI+CTC+SC

Result: Feasibility of the study

2. Preparation of the protocol

A brief presentation of the protocol on the literary background of the research topic, the objectives of the clinical trial, the expected results and its benefits. In addition, the preparation of a flowchart, showing the process of the clinical trial.

PI+CTC

Result: summary and flow-chart

3. Sample size calculation

The statistician performs the sample size calculation for the patients to be selected and the statistical design in the knowledge of the study variables.

PI+CTC+BIOS

Results: the proposed sample size required to perform the trial

4. Final decision about the starting of the clinical trial

With the involvement of the SC, the decision on the final study type is (i) clinical trial, (ii) registry or (Iii) meta-analysis). Tasks:

• Finalization of the clinical question.

• Determining the number of patients to be involved.

• Determining the time required for the study to succeed.

• Precise definition of inclusion and exclusion criteria.

• Discuss the personal (researchers, administrators) and material (laboratory, freezer, centrifuge, imaging procedures, IT background etc.) conditions of the feasibility of the study.

• Defining the method of data collection.

• Selection of potential participating centers.

• Discussing the financial source.

• Conclusion of a contract between PI and CTM.

PI+CTC+SC+BIOS+VK+KVK+SK+BIOS+HDM

Result: Decisions about the details of the study

5. Writing the pre-study protocol, compiling questionnaires.

The study protocol should describe, which data need to be collected during the test: laboratory parameters, imaging procedures, subjective scales, questionnaire-based questionnaires ...

Discussing the current guidelines of clinical trials (equator network). Filling in the checklist of the proposed guideline, preparing the protocol in English.

PI+CTC

Result: Compiled questionnaires, preparation of the pre-study protocol

6. ITAB (International Trial Advisory Board) discussion

Criticism of the draft study by a group of internationally recognized experts and domestic colleagues participating in the study. Taking into account the suggestions of the judges, finalizing the protocol and concluding the professional discourse. The ITAB is proposed by the PI.

PI+CTC+ITAB members

Results: final consensus

7. Steps that can be performed in parallel

7.1 IT development

Finalization of the CRF / eCRF. Improving data collection. Preparation of the final patient information and patient consent statement. In general, in the case of a single-center, small-element study, it is advisable to collect the data in excel, while in the case of multicenter, large-element studies, it may be justified to create a separate electronic interface.

PI+IT

Result: CRF/eCRF, patient information and patient consent statement

7.2 Preparation of documents in Hungarian, translations.

Translation of all documentation required for the conduction of the clinical trial into English and Hungarian. Compilation of user instructions and useful information required during the examination.

PI+CTC

Result: finalization of the documents

7.3 Preparation of the documentation required for the ethical approval, submission of the permit.

Compilation of the complete documentation package required for authorization. In the case of non-interventional clinical trials, the licensor is the ETT TUKEB, while in the case of interventional clinical trials, the licensor is the national chief physician, but in addition, the opinion of the ETT TUKEB is required.

PI+CTC

Result: final documentation for ethical permission

7.4 International registration

Registration of the study in a known, widely accepted international register (eg ISRCTN).

PI+CTC

Result: international registration

7.5 Pre-study publication

SC assists in the selection of a journal to publish the protocol. Review the requirements of the selected journal (VK + KVK). Preparation of the pre-study publication (VK).

PI+CTC

Result: submission of th epre-study protocol

7.6 Writing user manuals and practical aids.

Preparation of user manuals and aids to assist in the precise conduction of a clinical trial and in the work of participating physicians, nurses, and administrators.

PI+CTC

Result: preparation of user manuals and aids

8. Test-phase of the clinical trial

The study initiation center tests the quality of the protocol, instructions for use, data upload, and evaluation by selecting trial patients. In case of any problems, changes will be introduced. During the test period, the administrative team of the center will also be trained.

PI+CTC+HDM

Result: clinical trial tested in the practice

9. Training for all study participants in each center

Organizing of an information meeting for the colleagues ensuring the course of the investigation, where the delegates of the centers will receive thorough, comprehensive lecture on the precise execution of the investigation steps. Colleagues will also receive the aids needed to perform the study.

PI+HDM

Result: transfer of knowledge required to initiate the trial

10. During the trial

During the initiation and the conduction of the clinical trial, it is important, that everyone adheres to the chronological, ethical, and control steps that ensure proper operation, data protection and full enforcement of copyright! The PI monitors the activity of the involved centers and sends a report on the current patient involvement at specified intervals. The CTC helps the work of PI to maintain activity and share information. During the investigation, HDM is in constant contact with the administrators of the centers. Biostatistians will perform interim analyzes, if they propose any necessary modifications to the further course of the clinical trial. The monitor is responsible for quality assurance of the clinical trial. The CTM Steering Committee provides meetings for delegates of the involved centers on the current status of the clinical trial.

PI+HDM+CTC+BIOS

Result: ethical, professional and statistical follow-up of the trial.

11. Closure of the trial

Sending reports to the appropriate authority / ethics committee. Based on the biostatistical analysis and the results obtained, writing of the manuscript. Selecting a journal.

PI+IT+BIOS+CTC+SC

Result: official closure of the trail and publication.

IV. Publication policy

- Full transparency from all participants in the study is required
- The first and last authors are determined by the researchers, however, the UP CTM - with full transparency - can nominate co-authors taking the number of enrolled patients, and work performed into account.
- The acknowledgment must indicate the providers of financial support from UP CTM involved in the implementation of the project.

V. Responsibilities of the principal investigator

The researcher who initiates a clinical trial assumes full responsibility for the conduction of the trial. It undertakes to keep the examination under continuous professional control, to ensure the activity of the study throughout the trial period, to meet the administrative requirements towards CTM within the deadline (eg adaptation of eCRF / excel, uploading of forms / data to the Internet as soon as possible ...), and when the study is completed, prepares a report on the results of the study.

In addition, the PI should regularly participate in the Multidisciplinary Research Group meetings (on Skype or in person), where it is possible to discuss the results achieved so far, any problems that may arise. PI is obliged to elect a UP CTM employee as a member of the steering committee in agreement with SC.

In addition to the researchers initiating the clinical trial, the UP CTM must also represent the interests of the data uploaders. UP CTM is entitled to decide on a new principal investigator in place of the PI, who does not perform the undertaken professional task, in consultation with the data uploading centers!

Assessing changes: changes may be needed, either in the protocol or in the questionnaire, etc. CTC needs to be notified about any changes that occur. The SC can help decide in this situation whether an ethical notification of the change is warranted.