Multicentre studies:
Concept for a simplified procedure according to the Human Research Act (HRA)

- Applications for clinical trials subject to the Ordinance on Clinical Trials (ClinO) can be submitted either by the coordinating investigator or by the sponsor, while those for research projects subject to the Human Research Ordinance (HRO) can be submitted by the project manager. The applicant is the primary contact for the ethics committees (ECs).
- When submitting applications to the participating ECs, please also enclose the confirmation of receipt issued by the Lead Ethics Committee (LeadEC), as well as the LeadECs confirmation that the application documents are formally correct and have been included on the agenda.
- Please quote the LeadEC and (local) CEC no. in ALL correspondence.
- The simplified procedure is used for centres that join the study at a later date (substantial amendment).
- If a Clinical Research Organisation (CRO) assumes the role of sponsor or applicant, this fact should be clearly declared, stating a single contact person. Any subsequent references to the sponsor should be interpreted as including the CRO.
- The billing address should be communicated to all participating ECs in the first covering letter.
- Swiss ECs will only accept documents that use the current Swissethics templates (www.swissethics.ch).
- The applicant is responsible for ensuring that the participating ECs and local investigators receive and use the documents approved by the LeadEC.

Objective

Multicentre studies that are being conducted in several cantons / trial centres should not have to be reviewed in full by every CEC. Under Art 47 para. 2-4 of the HRA, the local participating ethics committees are responsible for deciding, in a presidial procedure, whether a LeadEC determined by the coordinating investigator should review the application in full according to the regular procedure. This ruling is designed to reduce the workload of the local committees, reduce the administration for applicants and make it possible to start trials sooner. The ultimate aim is to make Switzerland an attractive place to conduct research.

This concept will probably be binding on all stakeholders as of 1 January 2014. Special situations are discussed under ‘Special circumstances’.
Definitions

1. Coordinating investigator: The person with responsibility in Switzerland for coordinating the investigators responsible for the individual trial sites.

2. Applicant: The sponsor can submit the application instead of the coordinating investigator. In this case, the sponsor takes on the obligations of the investigator, as well as the notification and reporting obligation towards the competent ethics committee (=LeadEC). However, the application documents must be co-signed by the competent, local investigator (Art. 27 ClinO). This applicant is also the ECs’ primary point of contact for correspondence.

3. Lead Committee (LeadEC) is the EC in Switzerland that is responsible for the coordinating investigator. The LeadEC is responsible for approving the multicentre research project in Switzerland and forwarding its decisions to the sponsor, coordinating investigator and participating ECs. The LeadEC also sends its decisions to Swissmedic/FOPH if the clinical trial falls into categories B or C.

4. Participating ethics committees are all other Swiss ECs involved in the study. They do no more than issue an assessment relating to the local information and send this to the LeadEC.

5. Locally specific documents are documents that are adapted to the needs of a particular local trial centre, e.g. information for participants with contact address, informed consent form with address, and other documents with local contact addresses issued to participants, contracts, CVs and GCP certificate for the investigator concerned, list of trial personnel, local advertisements, insurance policies if appropriate, etc., or documents that are required only for a particular trial centre.

6. 'The documents are formally correct' means that the application can be included on the LeadEC’s agenda. This means that the documents required by the corresponding checklist are complete and comply with the templates. The statement of the scientific secretariat is a constituent part of the draft decision for the attention of the committee.

7. The stipulated time limits are expressed in calendar days (not working days)
Preconditions for participation

1. Sponsors, investigators and Swiss ECs that are participating in a multicentre study are legally obliged (Art. 47 HRA) to take part in the multicentre procedure.

2. All participating parties shall operate in accordance with the current laws and regulations (e.g. ICH-GCP, ISO-EN 14155, Human Research Act (HRA) and associated ordinances (HRO, ClinO, OrgO-HRA, etc.).

3. Correspondence:
   The applicant initially submits the documents specified in Annex 3 ClinO and Annex 2 HRO to the LeadEC, then, after a formal initial review and at the request of the LeadEC, to the participating ECs. The applicant is also responsible for sending resubmissions (e.g. revised documents, amendments, annual safety update reports).

4. The LeadEC forwards its decisions to the sponsor, the coordinating investigator, the participating ECs and the national authorities (Swissmedic/FOPH) if the clinical trial falls into category B or C.

5. The participating ECs report their assessments to the LeadEC.

6. Type of correspondence:
   - Applicant: Depending on the individual ethics committee, applications for clinical and non-clinical trials are submitted to the ECs either a) electronically via the FOPH portal (www.kofarm.ch) and with one printed copy (see www.swissethics.ch) or b) by post with one copy on a CD/USB stick and, depending on the individual ethics committee, x paper copies. In the long term, the aim is to have all applications submitted electronically.
   - LeadEC: The LeadEC communicates all its decisions to the applicant electronically and, where required (depending on cantonal procedural law), also on paper. Correspondence with the other participating parties (participating ECs, sponsor/coordinating investigator, national authorities) is sent in electronic form only.
   - Participating ECs: The participating ECs send correspondence to the LeadEC in electronic form and, depending on the individual EC, possibly also in paper form (according to the requirements of cantonal procedural law).

Concept:

The concept applies to all multicentre studies conducted at various Swiss trial centres according to a uniform protocol.

1. The applicant sends the LeadEC the signed and dated application documents (copy or original) in accordance with Annex 3 or 2 of the corresponding HRA ordinance. If the clinical trial falls into category B and C, the applicant can also simultaneously submit the documents to Swissmedic or the FOPH in accordance with Annex 4 ClinO.

2. The scientific secretariat of the LeadEC checks the documents for formal accuracy within 7 days and sends a list of any deficiencies to the applicant. Once the documents are formally correct, the LeadEC notifies the applicant and other participating parties (and, for category B and C studies, Swissmedic/FOPH as well).
3. The applicant sends documents that have been adapted to local circumstances (and, depending on the document, also signed and dated by the local investigator as an original or copy) to the participating ECs.

4. The participating ECs review the locally specific conditions within 15 days in a presidial procedure and notify the LeadEC of their assessment.

5. The LeadEC makes its decision within 45 days using the appropriate procedure under Art. 5-7 OrgO-HRA, and notifies the applicant and other stakeholders of its decision (and also Swissmedic/FOPH for category B and C studies).

6. The applicant sends the revised/new documents needed to fulfil conditions to the LeadEC and – if conditions relating to local circumstances have been imposed – participating ECs for re-reviewing.

7. The participating ECs review the revised documents according to their assessment using the presidial procedure and report the result of their repeat assessment to the LeadEC as soon as possible, but within 15 days at the latest. The LeadEC reviews fulfilment of its conditions – also using the presidial procedure – as soon as possible, but within 15 days at the latest, and issues its approval. It sends the approval to the applicant and other participating parties (also to Swissmedic/FOPH for category B and C studies). If local conditions imposed by a participating EC risk delaying the approval process, the LeadEC can issue an approval that excludes the trial centre in question. The LeadEC sends its approval of the application and the list of participating, approved trial centres to both the applicant and other stakeholders.

8. The applicant make the approved documents available to all trial centres in accordance with Annex 3, point 4 ClinO and Annex 2, point 8 HRO, and is responsible for ensuring that the local, approved trial centres use the documents approved by the LeadEC.
Coordinating investigator or sponsor submits application to the LeadEC.

Formal initial review of the application documents by scientific secretariat of the LeadEC within 7 days.

Is the application formally complete?

Yes

Formal initial review of the application documents by scientific secretariat of the LeadEC within 7 days.

Deficiency list by e-mail

No

Coordination investigator or sponsor submits application to the local ECs

Local ECs review the application from a local perspective within 15 days

Local ECs report their assessment to the LeadEC.

The LeadEC decides whether or not the application is OK within 45 days.

Can the study be approved?

Yes

The LeadEC notifies the coordinating investigator, sponsor and local ECs of its positive decision.

*Positive* decision

No

The LeadEC informs the coordinating investigator, sponsor and local ECs about completeness.

Scientific secretariat of the LeadEC sends deficiency list to investigator or sponsor

Deficiency list by e-mail

Signed and dated application documents in electronic and paper format

Locally adapted application documents in electronic and paper format

Assessment by e-mail

Info e-mail on completeness

Procedure for submitting multicentre studies

Multicentre studies concept according to HRA

Swiss Ethics Committees on research involving humans

2.4.2014

Procedure for submitting multicentre studies / By Unistore, Christophe Truchet
Special circumstances:

1. **Scheduled participating trial centres are not ready at the same time**

   If a local trial centre is not ready by the time the scientific secretariat of the LeadEC has completed its initial review of the application, the applicant can resubmit this trial centre as a substantial amendment after the application has been approved by the LeadEC (Art. 29 ClinO; Art. 18 HRO).

2. **Participating EC does not agree with the LeadEC’s decision**

   Under Art. 47, para. 3 HRA, the participating local EC only reviews the technical and operational preconditions. Its comments on these preconditions are binding on the LeadEC. This means, for example, that if the local EC at site A considers that the technical preconditions for the investigator or other persons participating in the trial, as defined in Art. 6 ClinO, are not fulfilled, the LeadEC has to refuse approval for trial site A. The same applies to operational preconditions (particularly infrastructure).

   The ethics committees responsible for the other trial sites can also submit their comments on other aspects of the application to the Lead Committee. However, the LeadEC is free to decide whether or not to take account of such assessments in its approval (Dispatch on the HRA, p. 8135).

   As mentioned above, it is only bound to respect the participating EC’s comments insofar as these concern technical or operational preconditions.

3. **More than one linguistic region involved**

   Where a study is being conducted in more than one linguistic regions, particular attention should be paid to translations. The participating EC is responsible for assessing the translation of documents, but not their content.

   If the participating EC criticises the translation when it is first submitted, the LeadEC has to take this criticism into account when making its decision. The participating EC then receives the revised documents (e.g. Patient Information/Patient Consent) for re-reviewing before they are approved. If this EC still regards the new version as unacceptable, the trial centre in question is excluded from the current approval.

4. **Procedure for applications that were approved by one or more ECs in accordance with the Swissethics concept prior to 2014 and to which new trial centres are to be added and/or amendments made**

   The procedure is based on the current concept under the HRA. If this LeadEC no longer exists – i.e. if it has joined a cooperative group of ECs – this cooperative group of ECs then becomes the LeadEC.

5. **Procedure for multicentre studies that were submitted to ECs prior to 2014 in parallel – i.e. independently – and therefore not in accordance with the Swissethics concept, and to which new trial centres are to be added and/or amendments made**:

   Applications submitted independently to several ECs prior to 2014 and not processed using the multicentre procedure set out in the Swissethics concept will continue to be processed as independent applications, since the documents may differ both in terms of content and form.

   If an EC has previously approved a multicentre study using the presidial or simplified procedure and agreed with the decision of the EC that initially reviewed the application, it can adopt this procedure for subsequent amendments.
6. Applications involving division of labour between various trial centres

Applications involving a uniform protocol but a division of tasks between trial centres are processed according to the current concept. If, for example, a biobank is set up at a participating trial centre that is not identical with the location of the coordinating investigator, the participating EC reviews the operational and technical preconditions for the biobank, and the LeadEC assesses the application as a whole.

7. Studies based at one trial centre and conducted throughout Switzerland (e.g. Internet surveys, questionnaire mailings, telephone interviews)

These projects are not treated as multicentre studies. The application must be submitted to the EC responsible for where the trial centre is located, i.e. where the study is planned and conducted and where the data is analysed.

8. Studies based at one trial centre and conducted throughout Switzerland that involve research activities at various locations (examinations by a GP/regional hospital outside the EC’s jurisdiction, collection and dispatch of blood, urine or saliva samples at the patient’s home by the patient him/herself or a specialist from the trial centre)

These projects are treated as single-centre or multicentre applications under the HRA, depending in each case on the extent of the local trial centres’ involvement and the possible risks that may arise in connection with the study at the various trial centres outside the jurisdiction of the LeadEC. Advance clarification with the LeadEC is recommended. As regards single-centre approval procedures, it is recommended that the ECs concerned be notified about the study and given additional documents for information purposes if they so request.

Procedure for multicentre studies AFTER approval

General

In general, the rules are the same as for initial submissions. The LeadEC assumes responsibility for all study-related matters and takes the decisions. The participating ECs only assess locally specific events and document contents.

New trial centres and amendments

If additional trial centres and/or amendments are subsequently added, the documents should be submitted to the LeadEC. The subsequent procedure follows the concept described above.

As regards amendments, please note that – as for single-centre studies – the ECs use a different definition of substantial amendments (Art. 29 ClinO, Art. 18 HRO) than the national authorities (Swissmedic, FOPH; e.g. Art. 34 ClinO), since they are responsible for different aspects.
Safety reporting procedure

As a general remark, it should be noted that the safety reporting procedure varies according to the addressee (sponsor, ECs, national authority), risk category, study type (drug study, medical device study, data and sample research etc.) and independently of the LeadEC concept.

The additional procedure for the ECs is described below only for multicentre studies (Art. 40-43, 63 ClinO; Art. 21 HVF):

The local investigator reports serious adverse events to the sponsor within the specified time limit. The sponsor notifies the participating EC of events that it is obliged to report within the specified time limit.

If the coordinating investigator is the applicant, the sponsor also notifies him of serious adverse events. The coordinating investigator is then obliged to report the events to the LeadEC.

Research projects conducted as non-clinical trials under Art. 21 HRO must be temporarily halted throughout Switzerland if an SAE occurs. The participating EC reviews the SAE to establish whether the operational and technical preconditions are still fulfilled and whether local or general measures are necessary, then informs the LeadEC and the submitting party accordingly. The LeadEC decides within 30 days whether the study should be continued or whether action to safeguard the interests of the continuing participants is required at all trial centres or only at the local trial centre. If a the problem is specific to the local trial centre, the study can be cleared for continuation at the other trial centres (partial decision).

The applicant should submit annual safety update reports to all ECs, along with non-substantial local amendments (e.g. staff changes, list of personnel).

Study discontinuation / interruption and end of study

The procedure is described in the ordinances and is self-explanatory (Art. 38 ClinO; Art. 22, 36, 40, 43 HRO).

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