swissmedic

Information sheet
Combined studies

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List of contents

1 Objective and introduction

This information sheet is intended for sponsors of combined studies, contract research organisations (CRO), and investigators. It covers topics that are unique to combined studies in terms of their submission for approval to Swissmedic and their conduct. For all topics which are identical between combined studies and non-combined clinical trials, please consult the relevant sections of the respective information sheets for medicinal products (MP) / advanced therapy medicinal products (ATMP) and / or medical devices (MD) / in-vitro diagnostic medical devices (IVD). In Switzerland, the cantonal ethics committee is in charge of the delimitation of research projects and answers questions concerning applicable legislation (see www.swissethics.ch for a list of cantonal ethics committees). The requirements of the ethics committees with regards to the submission and conduct of combined studies are not addressed in this information sheet.

A combined study can be, for example:

- An ATMP, which is not licensed in Switzerland, will be delivered through a non-CE marked drug pump.
- A non-CE-marked IVD will be used to measure levels of a specific biomarker on the basis of which patients are selected for treatment with a MP that is not licensed in Switzerland.
- A non-CE marked hydrocephalus shunt device will be implanted and patients will receive a post-implantation antiemetic medication, which is used off-label.

1.1 Terms and definitions

1. *Clinical trial:*
   a. *Clinical trial on MP / ATMP*: See Art. 2 letter a ClinO
   b. Clinical trial of MD: See Art. 2 ClinO-MD
      i. Clinical investigation: See Art. 2 letter a^{bis} ClinO-MD
      ii. Performance study: See Art. 2 letter a^{ter} ClinO-MD

2. *Combined study*:
   The term 'combined study' has not yet been formally defined in a Swiss or European regulation. For the purpose of this information sheet, combined studies can be understood as studies that involve:
   - A clinical trial of an MP / ATMP in parallel with an interventional performance study of an IVD
   - A clinical trial of an MP / ATMP in parallel with a clinical investigation of a MD

Note: Clinical trials of products that are a combination should not to be confused with combined studies. See annex A7 of BW600_00_015e_MB for more information on products that are a combination.

3. *Aspects of a combined study:*
   Study documents, such as the Clinical Investigation Plan (CIP) / Clinical Performance Study Plan (CPSP), or information in a submission may have content that is relevant to the clinical trial of the MP / ATMP. In this information sheet, such content is referred to as an MP / ATMP aspect of the combined study. Likewise, content of a document or submission relevant to the interventional performance study or clinical investigation of a MD is referred to as a device aspect. Note that some content may be relevant to both and is therefore an MP / ATMP aspect as well as a device aspect.
   Make sure that you clearly state which aspects are concerned when making submissions on combined studies. Always complete the corresponding checkboxes in the Swissmedic forms.

4. *Conforming MD / IVD:*
   A CE-marked MD / IVD used in a clinical investigation / performance study, used according to the CE-marked instructions for use and not prohibited in Switzerland. Note that an MD / IVD manufactured and used in-house can be conforming too. For additional information, please consult our decision trees (*decision tree for clinical investigations, decision tree for IVD performance studies).*

1.2 Abbreviations

ATMP:	Advanced therapy medicinal product
CDx:	IVD that is a companion diagnostic
ClinO:	Clinical Trials Ordinance (SR 810.305)
ClinO-MD:	Ordinance on Clinical Trials of Medical Devices (SR 810.306)
CRO:	Contract research organisation
CTR:	Clinical Trial Regulation (Regulation (EU) 536/2014)
EU:	Euroepan Union
IVD:	In-vitro diagnostic medical device
IVDR:	In Vitro Diagnostics Regulation (Regulation (EU) 2017/746)
MD:	Medical device
MDR:	Medical Device Regulation (Regulation (EU) 2017/745)
MP:	Medicinal product

1.3 Legal basis and guidances

Combined studies have to be designed so that they simultaneously fulfil regulations and guidelines applicable to the clinical trial of the MP / ATMP and the clinical trial of the MD / IVD. Applicable regulations include the ClinO and ClinO-MD, and in extension the regulations (EU) 536/2014 and (EU) 2017/745 or (EU) 2017/746, as well as ICH GCP and ISO 14155 or ISO 20916. If the provisions in the applicable regulations differ (e.g. definitions, reporting timelines), the requirements of both regulations have to be fulfilled (for each aspect of the according regulations). If one of the two trials of a combined study reaches its endpoints and therefore ends before the other (e.g. the performance study lasts for 2 years, whereas the medicinal product study lasts for a total of 10 years), the regulatory requirements for ongoing trials end for that trial.
You will find European guidance with regard to the submission of applications and to the conduct of combined studies in the following documents (please check the European Commission website for new publications):

- MDCG 2021-6 - Rev. 1, specifically question 16
- MDCG 2022-10
- MDCG 2024-4

1.4 Swissmedic information sheets

Please read the information provided by Swissmedic on the requirements for MP / ATMP clinical trials and for interventional performance studies / clinical investigations of medical devices:

- BW600_00_015e_MB: Information regarding clinical investigations of medical devices (MD)
- BW600_00_016e_MB: Information regarding performance studies of IVD medical devices (IVD)
- BW101_10_004e_AA: Guideline Clinical Trial Application Dossier (MP)
- BW101_10_003e_AA: Guideline Amendments Clinical Trials (MP)
- BW101_20_002e_MB: Information on reporting safety measures and SUSARs (MP)

- BW315_00_961e_MB: Information regarding mandatory reporting of adverse reactions during a clinical trial of TrP/GT/GMO (ATMP)

You can find further information on our website for both clinical trials on medicinal products and medical devices (except information on submission procedures for combined studies, which are explained in this information sheet).

2 Approval of combined studies

Studies that combine the following clinical trials require approval by Swissmedic as a combined study:
- A category B or C clinical trial of a MP / ATMP and
- A category C clinical investigation of a MD / performance study of an IVD

Contact the cantonal ethics committee if in doubt regarding the categorisation of the individual clinical trial. For the categorization of clinical trials of ATMP, please contact the division ATMP of Swissmedic.

2.1 How to apply for the approval of a combined study

Combined studies must be submitted in parallel to Swissmedic and to the responsible cantonal ethics committee on the same day. Submit one submission package (eDok) using the eGov Service *eMessage* portal. You can find information on how to prepare and submit an eDok in annex A6 of the information sheet BW600_00_015e_MB or BW600_00_016e_MB.

Submissions can be made and questions of Swissmedic can be addressed by the sponsor or any person / entity appointed by the sponsor. If no authorisation has previously been filed for this person / entity, place the power of attorney in folder 15.00 of your eDok.

The eDok should be populated as follows:
- Folders 00.00 – 17.00: Place the documentation for the MD / IVD aspect including the form BW610_10_026e_FO (MD aspect) or BW610_10_027e_FO (IVD aspect). In case the combined study has more than one protocol, place them in sub-folder 04.00. Place cover letter(s) and any decision(s) of ethics committee(s) or foreign competent authority decision(s) in folders 01.00, 02.00 and 03.00 respectively, irrespective of whether they concern the MD / IVD or the MP / ATMP aspects.
- Folder 18.00: Place the documentation for the MP / ATMP aspect including the FO submission form.

2.2 Review and approval

The content of your application will be reviewed by the respective experts at Swissmedic responsible for the MD / IVD or MP / ATMP aspects of the combined study. During and / or after the content review, Swissmedic can ask for additional information or ask questions. If a positive decision is

possible on the basis of the documents submitted, Swissmedic will inform you and wait for the decision of the cantonal ethics committee. Due to the provisions of the ClinO-MD, Swissmedic can only approve a combined study after approval from the cantonal ethics committee. Once received, Swissmedic will issue a letter of approval that contains both the approval of the clinical trial of the MP / ATMP (based on the provisions of the Clin-O) and the approval of the clinical trial of the MD / IVD (based on the provisions of the ClinO-MD).

2.3 Submission in case of more than one sponsor

In exceptional cases, combined studies can have more than one sponsor. In this case, please list all involved sponsors on the application form BW610_10_026e_FO / BW610_10_027e_FO. Swissmedic will send all correspondence to the sponsor (or its representative) listed first on the application form.

2.4 Submission in case of confidentiality restrictions

If the person / entity making the main submission to Swissmedic does not have access to certain documents needed for the submission for reasons of confidentiality, they can be submitted separately in a second submission. In this case, please follow the steps below:

1. Describe the situation in the cover letter of your main submission and list the affected documents. State how many additional submissions are foreseen together with the anticipated submission date.
2. Select the appropriate tick box indicating that the submission is affected by confidentiality restrictions in the form BW610_10_026e_FO / BW610_10_027e_FO.
3. Upload the main eDok and wait for the acceptance of delivery confirmation.
4. Instruct the person / entity who will submit confidential documents to perform the following steps:
    a. Fill in the form BW610_10_028e_FO using the delivery ID which you can find on the acceptance of delivery confirmation that you received for the main submission.
    b. Prepare an eDok as described in *Submission of authorization applications and notifications*, place the form BW610_10_028e_FO and all confidential documents in the eDok.
    c. In case the confidential documents concern the MP/ ATMP aspect, the respective FO submission form must be included in folder 18.00.
    d. Submit the eDok as described in *Submission of authorization applications and notifications*.

Note that the formal check of your submission will only start once all parts of the submission have been received by Swissmedic and the documentation is complete. If deficiencies or questions arise that concern the documents affected by confidentiality restrictions, Swissmedic will directly contact the person / entity listed on the form BW610_10_028e_FO as the holder of the confidential documents. All other communication will be sent to the sponsor listed first on the application form or to its representative.

3 Modifications (Amendments)

Modifications to a combined study can affect MP / ATMP aspects, MD / IVD aspects or both aspects. Note that if a modification concerns MP / ATMP aspects, changes might also be required in the documentation concerning the MD / IVD aspects, and vice versa. All modifications need to be submitted as one submission package (eDok) using the eGov Service *eMessage* portal.
For information on how to prepare an eDok and submit it via the portal, please see *Submission of authorization applications and notifications*.
The submission can include modifications subject to approval (substantial modifications), notification (non-substantial modifications) or a mixture of both.
Submissions can be made and questions of Swissmedic can be addressed by the sponsor or any person / entity appointed by the sponsor. If no authorisation has previously been filed for this person / entity, place the power of attorney in folder 15.00 of your eDok.

The eDok should be populated as follows:

- Folders 00.00 – 17.00: Place any new and / or modified documentation for the MD / IVD aspect in clean and track-change mode including the form BW610_20_025e_FO. On the form, indicate whether the modification(s) is / are subject to approval or notification, or both. For each modification, tick the study aspect(s) concerned. All modified protocols should be placed in sub-folder 04.00. Describe the modifications forseen and the reasons for them in your cover letter.
- Folder 18.00: Place any new and / or modified documentation for the MP / ATMP aspects including the FO submission form. Please consult the information sheet BW101_10_003e_AA for information regarding submission format.

You can find the automatic acknowledgement of receipt, which is sufficient for non-substantial modifications, in the *eMessage* Portal. For substantial modifications, you need to wait for the decision letter from Swissmedic before you can implement the modifications.

3.1 Special case 1: An amendment concerning the MP / ATMP affects several combined studies, or combined studies and additional clinical trials

The same investigational MP / ATMP might be used in more than one study. Consequently, modifications or updates to the MP / ATMP documentation (e.g. IMPD updates) can affect (a) multiple combined studies, or (b) one or more combined studies and one or more clinical trials. If the planned modifications, as well as the involved sponsor and Swiss representative are identical across these studies, you can choose between the following options for submission:

If (a) is the case, submit one eDok using the eGov Service *eMessage* portal.
The eDok should be populated as follows:

- Folders 00.00 – 17.00: Place the form BW610_20_025e_FO and list in section 2 all reference numbers of the combined studies (1000xxxx) affected by the amendment. On the form, indicate whether the modification(s) is / are subject to approval or notification, or both. Place the modified documentation for the MD / IVD aspect in track-change mode in the respective sub-folders of the

eDok. All modified protocols should be placed in sub-folder 04.00. Describe the situation in your cover letter.
- Folder 18.00: Place the modified documentation for the MP / ATMP aspects, including the FO submission form. Please consult the information sheet BW101_10_003e_AA for information regarding submission format.

If (b) is the case, you have two options:
One submission: Submit one eDok using the eGov Service *eMessage* portal.
The eDok should be populated as follows:
- Folders 00.00 – 17.00: Place the form BW610_20_025e_FO and list in section 2 all reference numbers of the combined studies (1000xxxx) and clinical trials (70xxx) affected by the amendment. On the form, indicate whether the modification(s) is / are subject to approval or notification, or both. Place the modified documentation for the MD / IVD aspect in track-change mode in the respective sub-folders of the eDok. All modified protocols should be placed in sub-folder 04.00. Describe the situation in your cover letter.
- Folder 18.00: Place the modified documentation for the MP / ATMP aspects, including the FO submission form. Please consult the information sheet BW101_10_003e_AA for information regarding submission format.

Two submissions: Submit one eDok for the combined study using the eGov Service *eMessage* portal, and one eDok for the clinical trial(s) for MP / ATMP trials according to the submission process as described for MPs / ATMPs.
The eDok for the combined studies should be populated as follows:
- Folders 00.00 – 17.00: Place the form BW610_20_025e_FO and in section 3 tick the appropriate tickbox indicating that you have submitted an identical amendment for (a) clinical trial(s) of a medicinal product. On the form, indicate whether the modification(s) is / are subject to approval or notification, or both. All modified protocols should be placed in sub-folder 04.00. Describe the situation in your cover letter.
- Folder 18.00: Place the modified documentation for the MP / ATMP aspects including the FO submission form. Please consult the information sheet BW101_10_003e_AA for information regarding the submission format.

Swissmedic will only charge you once for the review of the documents. Note that the above options only apply if the sponsor and its representative are identical across all amendments / submissions. If this is not the case, each amendment has to be submitted individually and will be invoiced separately.

3.2 Special case 2: Re-categorisation of a clinical trial, a clinical investigation or a performance study as a combined study

An existing clinical trial of a MP / ATMP can become a combined study if, for example, a MD / IVD used in the clinical trial loses its conformity or a non-conforming MD / IVD is added to the clinical trial. In this case, submit one submission package (eDok) using the eGov Service *eMessage* portal.

The eDok should be populated as follows:

- Folders 00.00 – 17.00: Place the documentation for the new MD / IVD aspect including the form BW610_10_026e_FO (MD aspect) or BW610_10_027e_FO (IVD aspect). In your cover letter, mention that the trial was previously approved by Swissmedic as a clinical trial of a MP/ATMP, the Swissmedic identification number, and the exact reason for the change to a combined trial.
- Folder 18.00: Place the updated documentation for the MP / ATMP aspect including the FO submission form (amendment). Make sure the MD / IVD and its regulatory status are correctly described in the documents, and that reporting duties for clinical investigations / performance studies are correctly integrated. Please consult the information sheet BW101_10_003e_AA for information regarding the submission format.

Vice versa, an existing clinical investigation of a MD / IVD performance study can become a combined study if, for example, a non-licensed MP / ATMP is added to the clinical investigation / performance study or the approval status of an MP / ATMP used in a clinical investigation / performance study changes. In this case, submit one submission package (eDok) using the eGov Service *eMessage* portal.

The eDok should be populated as follows:

- Folders 00.00 – 17.00: Place the documentation for the updated MD / IVD aspect including the form BW610_20_025e_FO (amendment). In your cover letter, mention the MP / ATMP and the exact reason for the change to a combined trial. Make sure the MP / ATMP and its regulatory status are correctly described in the documents, and that reporting duties for clinical trials of MPs / ATMPs are correctly integrated.
- Folder 18.00: Place the new documentation for the MP / ATMP aspect including the FO submission form. Please consult the information sheet BW101_10_003e_AA for information regarding the submission format.

Note that the change to a combined study means that you have to submit new documentation regarding any products added to or modified in the study and update previously approved documents. You will always have to update the study protocol(s). Additionally, changes are often required to the CRF(s), the patient information, the IB, the IFU, etc. Please contact the responsible ethics committee in order to receive instructions on how to submit to them.

4 Reporting duties during combined studies

The reporting duties for clinical trials of MPs / ATMPs (according to ClinO) and those for clinical investigations of MDs / performance studies of IVDs (according to ClinO-MD) both apply to combined studies, including timelines and definitions of safety events. Note that different follow-up lengths can be foreseen for each of the trials in a combined study (see also section 1.3). As a consequence, some reporting duties may end prior to the completion of the entire combined study.

Use the eDok submission format and the eGov Service *eMessage* portal for all submissions (except for SUSARs (see section 4.4.) and MDCG tables, see section 3.4). For information on how to prepare an eDok and submit it via the portal, please see appendix A6 of the information sheets BW600_00_015e_MB / BW600_00_016e_MB.

Submissions can be made and questions of Swissmedic can be addressed by the sponsor or any person / entity appointed by the sponsor. If no authorisation has previously been filed for this person / entity, place the power of attorney in folder 15.00 of your eDok submission.

4.1 Annual report / Development safety update report (DSUR)

It is possible to submit one report that includes information regarding both the MP / ATMP and the MD / IVD to Swissmedic, or separate reports for each aspect of the combined study. For the submission of all ASR / DSUR, use the form BW610_20_025e_FO and indicate which aspect(s) of the combined study are concerned by the report: MP, ATMP, MD / IVD or multiple. All reports should be placed in the folder 17.3.0. If the report includes information regarding the MP / ATMP, please also include the FO submission form and place it in folder 18.00.

4.2 Study end, premature termination or interruption

To submit a notification of the regular end, premature termination or interruption for reasons not related to safety, use the form BW610_20_025e_FO and indicate which aspect(s) of the combined study are concerned by the notification: IMP, ATMP, MD / IVD or multiple. If the notification concerns the MP / ATMP, please also include the FO submission form and place it in folder 18.00. A final report must be submitted within one year of the end of the trial (or aspect thereof). In case of a temporary halt or premature termination in relation to the MD / IVD, the final report is due within 3 months.

4.3 (Serious) adverse events and device deficiencies

Sponsors must ensure that investigators / lab personnel apply seriousness criteria according to the CTR and to the MDR / IVDR to all adverse events. The reporting duties of both regulations apply, use both the reporting procedures defined by Swissmedic for clinical trials of medicinal products and those for clinical trials of medical devices.

Special considerations for CDx

- Adverse events:
  - If the purpose of a CDx is to identify patients with a propensity for a particular adverse drug reaction (e.g. malignant hyperthermia caused by an MD), the occurrence of that SAE in subjects must be assessed at least as "possibly related" to the CDx. Make sure such expected risks are described in the performance study protocol. The description should include the type, severity, and frequency of the SAE (a) in the general population, (b) in exposed patients who are not tested, and (c) expectations in the study arms.
  - In the case of other CDx, it can be difficult to assess the relationship between the IVD (or its test result) and an (S)AE that is an adverse drug reaction. In such cases, Swissmedic will accept events as being categorized as “not related” to the CDx.

- Device deficiencies including malfunction and use errors or the quality of the samples (collection, preparation or storage:

- Report device deficiencies with SAE potential to Swissmedic on the appropriate form
- Identify the affected samples and consider re-testing, if possible
- Update the relatedness attribution to the CDx of SAEs that are adverse drug reactions in the affected subjects
- Submit updated SAE reports to Swissmedic if an SAE is re-classified from 'not related' to 'probably', possibly' or 'causally related' to the CDx, the comparator or study procedures, in accordance with section 7.2.3 of the information sheet BW600_00_016e_MB.
- If subjects in Swiss centers can be affected, Swissmedic expects information / updates on the following topics (see also section 4.4. below):
  - interruption of recruitment, reasons for not interrupting recruitment
  - planned corrective and preventive actions
  - information sent to investigators
  - repeat testing, reasons why testing is not repeated
  - number of subjects in Switzerland for whom the quality of the results may have influenced patient management decisions (e.g. the patient would not have been eligible for inclusion in the combined trial) and / or may influence future decisions
  - follow-up of these subjects, including outcomes and actions taken in these subjects

4.4 Safety measures

The following safety measures must be submitted to Swissmedic using the form BW610_20_026e_FO:

- Notification of premature termination or interruption / temporary halt of a combined study (or aspect thereof) for safety reasons
- Notification of safety and protective measures
- Notification of urgent safety measures (USM)

In the form, indicate which aspect(s) of the combined study are concerned by the safety measure(s): IMP, ATMP, MD / IVD or multiple, and populate the eDok according to the instructions in section 3.

For submission of suspected unexpected serious adverse reactions (SUSARs), fill in the CIOMS form and follow the instructions on the Information sheet BW101_20_002e_MB. Note that you need to use the Swissmedic reference number for SUSAR submissions indicated on the letter of approval for the combined study.

For submission of a notification for an event related to ATMPs, fill in the form BW315_00_960e_FO and follow the instructions on the Information sheet BW315_00_961e_MB. Note that you need to use the Swissmedic reference number for SUSAR submissions indicated on the letter of approval for the combined study.

5 Contacts in case of questions

- Questions concerning the Swissmedic *eMessage* portal: eSubmission@swissmedic.ch

- Questions concerning an ongoing procedure or an approved combined study: Contact the person mentioned on Swissmedic correspondence or clinicaltrials.devices@swissmedic.ch

Change history

Version	Change	sig
2.1	Updated list of contents and typos.	sci
2.0	- Addition of new content in section 1.1 (aspects of combined studies), section 1.2 (additional abbreviations), sections 2.1 and 3 (submissions by different persons), section 4 (the MD / ATMP trial and MD / IVD trial in a combined study can have different durations, submission of safety information), section 4.3 (special considerations for CDx concerning safety reporting and the notification of safety measures). - Improved wording in sections 1.3, 1.4, 2.4 and 3.1. Updated terminology throughout the document as a revision of the Swiss ordinances on human research has resulted in some changes (authorisation/approval, clinical trial with/clinical trial of, etc.).	sci/lme
1.0	Erstversion	hem