swissmedic

Information sheet
Combined studies

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1 Objective and introduction

This information sheet is intended for sponsors of combined studies, contract research organisations (CRO), and investigators. It covers aspects that are unique to combined studies in terms of their submission for authorization to Swissmedic and their conduct. For all aspects 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 with 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 1: The terms defined under 1. apply for each individual aspect of the combined study.
Note 2: 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. *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

ClinO: Clinical Trials Ordinance (SR 810.305)

ClinO-MD:	Ordinance on Clinical Trials with Medical Devices (SR 810.306)
EU:	Euroepan Union
MD:	Medical device
IVD:	In-vitro diagnostic medical device
MP:	Medicinal product
ATMP:	Advanced therapy medicinal product
CRO:	Contract research organisation

1.3 Legal basis and guidances

Combined studies have to be designed so that they simultaneously fulfil regulations and guidelines applicable to the MP / ATMP and the MD / IVD. These 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 / ISO 20916. In case the provisions regarding certain aspects differ between the individual regulations (e.g. definitions, reporting timelines, etc.), the requirements of both regulations have to be fulfilled (for each aspect the according regulations). If one aspect of a combined study reaches its endpoint(s) before the end of the other aspect (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 the terminated aspect do not apply to the ongoing aspect anymore. You can find guidance from the EU with regards to the application and conduct of combined studies information in the following documents:

- MDCG 2021-6 - Rev. 1 (Specifically question 16)
- MDCG 2022-10
- MDCG 2024-4

1.4 Swissmedic information sheets

For all aspects which are identical between combined studies and non-combined clinical trials, please refer to the relevant section(s) of the respective information sheet(s):

- BW600_00_015e_MB: Information regarding clinical investigations with medical devices (MD)
- BW600_00_016e_MB: Information regarding performance studies with 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 notification of safety measures and SUSARs (MP)
- BW315_00_961e_MB: Information regarding mandatory reporting of adverse reactions during a clinical trial with 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 Authorization of combined studies

Studies combining the following study types require authorisation by Swissmedic.

- A category B or C clinical trial of a MP / ATMP: Hereby referred to as the MP / ATMP aspect of the combined study
- A category C clinical investigation of a MD / performance study of an IVD: Hereby referred to as the MD / IVD aspect of the combined study

Contact the cantonal ethics committee if in doubt regarding the categorisation of individual study aspects. For the categorization of ATMP aspects of combined studies, please contact the division ATMP.

2.1 How to apply for the authorization of a combined study

Combined studies must be submitted in parallel to Swissmedic and to the responsible cantonal ethics committee on the same day. To do so, 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 sheets BW600_00_015e_MB / BW600_00_016e_MB.

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 authorization

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 authorize a combined study after approval from the cantonal ethics committee. Once received, Swissmedic will issue a letter of authorisation that contains both the authorisation of the clinical trial of the MP / ATMP (based on the provisions of the Clin-O) and the authorisation 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 for 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. Prepare a second eDok containing the confidential documents.
    b. Fill in the requested information in form BW610_10_028e_FO indicating the delivery ID which you can find on the acceptance of delivery confirmation that you received for the main submission.
    c. Include the form BW610_10_028e_FO in the second eDok.
    In case the confidential documents concern the MP, the respective FO submission form must be included in folder 18.00.

Note that the formal check of your submission will only start once all submissions 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 or its representative.

3 Modifications (Amendments)

Modifications to a combined study can affect the MP / ATMP aspect, the MD / IVD aspect or all study aspects. Note that if a modification concerns the MP / ATMP aspect, changes might also be required in the documentation concerning the MD / IVD aspect, and vice versa. All Modifications need to be submitted as one submission package (eDok) using the eGov Service *eMessage* portal. The submission can include modifications subject to authorization (substantial modifications), notification (non-substantial modifications) or a mixture of both.

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 authorization 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 aspect in clean and track-change mode including the FO submission form.

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 modification(s).

3.1 Special case 1: An amendment affects one or more combined studies and one or more 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 authorization 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 aspect in clean and track-change mode including the FO submission form.

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 authorization 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 aspect in clean and track-change mode including the FO submission form.

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 authorization 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 aspect in clean and track-change mode including the FO submission form.

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, 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.

Vice versa, an existing clinical investigation with a MD / IVD performance study can become a combined study if, for example, a non-licensed MP / ATMP will be added to the clinical investigation / performance study or the authorization 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.

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. Use the eGov Service *eMessage* portal for all submissions (except SUSARs).

4.1 Annual safety report (ASR) / 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_Annual_safety_report. 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 completion, discontinuation or interruption

To submit a notification of the regular end, discontinuation 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 early termination in relation to the MD / IVD, the final report is due within 3 months.

4.3 (Serious) adverse events

Sponsors must ensure that investigators / lab personnel apply seriousness criteria according to the CTR and to the MDR / IVDR to all adverse events. Likewise, the reporting duties of both regulations apply. In the case of companion diagnostics (CDx), it can be difficult to assess the relationship between the IVD (or its test result) and an (S)AE. An (S)AE may occur during the application of a CDx or long after testing. In such cases, Swissmedic will accept events as being categorized as “not related” to the CDx. However, if there are indications of problems with the quality of the testing in the subject concerned which might have influenced the test result, (S)AEs occurring (or have occurred) in that subject should be (re-)evaluated regarding their relationship to the IVD. Problems with testing might be related to sample collection, sample preparation and storage, the IVD itself or its application, test evaluation, etc.

4.4 Safety measures

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

- Notification of discontinuation 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 authorization 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 authorization 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

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