

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 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 (EC) with regards to the submission and conduct of combined studies are not addressed in this information sheet.

Examples of research that require a Swissmedic approval procedure for combined studies:

- An ATMP is not licensed in Switzerland and will be delivered with 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 the patients will receive a post-implantation antiemetic medication used off-label.

			
Submission of one study documentation * **	Synchronised review: One RFI from Swissmedic with MD and MP aspects *	One response from sponsor covering RFIs of Swissmedic and EC * **	One decision with MD and MP aspects *
Sponsor sends the same trial documents to Swissmedic and the EC	Synchronisation between the involved units at Swissmedic, all questions are raised together	Sponsor sends the same answers and document changes to Swissmedic and the EC	Decision of all units of Swissmedic are provided together
	EC sends its RFI separately	If not all aspects are answered, Swissmedic and the EC will inform the sponsor separately so he can complete the file	EC sends its decision separately
<p>* Swissmedic runs a single point of contact (SPoC) for all administrative/ procedural matters (unit MDCI)</p> <p>** parallel submission to Swissmedic and EC (same documents on the same day)</p>			

1.1 Abbreviations, legal basis and guidances

1.1.1 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 Trials Regulation (Regulation (EU) 536/2014)
DSUR:	Development Safety Update Report
EC:	Ethics Committee
EU:	European Union

IVD:	In-vitro diagnostic medical device
IVDR:	In Vitro Diagnostics Regulation (Regulation (EU) 2017/746)
MD:	Medical device
MDCI:	Unit Medical Devices Clinical Investigations
MDR:	Medical Device Regulation (Regulation (EU) 2017/745)
MP:	Medicinal product
RFI:	Request for further information
SPoC:	Single Point of Contact

1.1.2 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, see also section 4.2.2 below.

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](#)

1.2 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](#)).

1.3 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_MB](#): Guideline Clinical Trial Application Dossier (MP)
- [BW101_10_003e_MB](#): 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.

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.

For your submission to Swissmedic, submit one submission package (eDok) to the single point of contact of Swissmedic (SPoC, unit MDCI) using the portal [eGov Service eMessage](#): Choose the delivery type “BW610_10_021e_FO” for combined studies including a medical device, and delivery type “BW610_10_024e_FO” for combined studies including an IVD. You can find information on how to prepare and submit an eDok in ‘[Submission of authorization applications and notifications](#)’.

Please note that incomplete submissions are not accepted, e.g. when necessary pre-clinical tests on the analytical performance for an IVD are not yet available, or when the investigator’s brochure for a non CE-marked medical device is still missing. For options to begin clinical activities earlier, please refer to the section below on the sequential initiation of a project.

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 decisions of ethics committees or foreign competent authority decisions 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](#)’, in the correct subfolder of folder 18.

Make sure you send all CRFs used during the combined study to both authorities (including those used at testing labs).

Do not add, delete or rename any folders in the standardised folder structure. In particular, ensure that you do not drag and drop any of your folders into the folder structure. Please consult the information sheet [BW101 10 003e MB](#) for information regarding the submission format.

2.2 How to submit applications for sequential initiation of a project

Some study designs foresee the sequential investigation of different products. For example, a clinical trial of a non-conforming MP is first initiated with conforming assays. Later, an interventional

performance study with a companion diagnostic that is not CE-marked is intended to be added. In this case, you have two options:

- If the complete documentation for all aspects is available (MD / IVD aspect and MP / ATMP aspect), request approval for a combined study.
- If only one part of the documentation is ready (MD / IVD aspect or MP / ATMP aspect), submit an approval application for the part that is ready. When the second part is available, make a submission according to section 3.2 of this document and there is a switch to procedures for combined studies.

In the example above, if the documentation for the investigational companion diagnostic is not yet available, submit documentation according to the requirements and the procedures for clinical trials of MPs and explain the situation in your cover letter. After approval, you can begin your project as a clinical trial of an MP.

When your first application has been approved and the documentation for the IVD aspect is ready, follow the instructions in section 3.2 and describe the situation in your cover letter.

Note that it is not possible to submit an application for a combined study containing only parts of the documentation (i.e., either the MP / ATMP documentation only, or the MD / IVD documentation only).

2.3 Review and approval of a combined study

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, see Figure 1. During and / or after the content review, Swissmedic can ask for additional information or ask questions (request for further information, RFI). Due to the provisions of the ClinO-MD, Swissmedic can only approve a combined study after approval from the cantonal ethics committee. 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. Once the decision has been 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).

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 an additional 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. Modifications affecting the MD / IVD aspects and the MP / ATMP aspects can be submitted as one submission package (one eDok). Swissmedic will approve modifications submitted as one submission package in the same letter at the same time.

In case one of the modifications needs to be implemented ahead of others (e.g., implementation of a safety update to the MP / ATMP aspect ahead of implementation of modifications to the MD / IVD aspects), you have two options:

- Option 1 (preferred): Submit separate applications for the urgent and non-urgent modifications, or
- Option 2: Submit one application and inform us in the cover letter which aspect needs to be implemented ahead of others, including a rationale.

Remark: In combined studies, the assessment of whether a substantial modification affects the MD / IVD aspect should not be limited to changes concerning the product and its characteristics (e.g. a modification to the device, its CE-marking, or information on newly identified device-related risks). Instead, any modification affecting elements of the combined study described in submissions to Swissmedic should be considered. This may include changes to informed consent documents, changes to or addition of study sites, eligibility criteria, follow-up assessments, endpoints, or other elements relevant to the MD / IVD aspect. If you are unsure whether your substantial modification

affects the MD / IVD aspect, please contact the Swissmedic contact indicated on previous Swissmedic correspondence or write to clinicaltrials.devices@swissmedic.ch.

For information on how to prepare an eDok and submit it via the the portal [eGov Service eMessage](#), please see '[Submission of 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: Always include the form [BW610 20 025e FO](#) in folder 00.00. 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 foreseen and the reasons for them in your cover letter. Provide any new and / or modified documentation for the MD / IVD aspect in track-change mode.
- Folder 18.00: Place any new and / or modified documentation for the MP / ATMP aspects (including the '[FO submission form](#)') in the correct subfolders of folder 18.

Immediately after a submission, you will find two automatic acknowledgements in *eMessage* (for successful upload and for technical validation). Check whether the technical validation was successful, as the message serves as proof of your submission. 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 portal [eGov Service eMessage](#).

The eDok should be populated as follows:

- Folders 00.00 – 17.00: Always include the form [BW610 20 025e FO](#) in folder 00.00 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](#), in the correct subfolder of folder 18. Please consult the information sheet [BW101 10 003e MB](#) for information regarding the submission format.

If (b) is the case, you have two options:

One submission: Submit one eDok using the portal [eGov Service eMessage](#).

The eDok should be populated as follows:

- Folders 00.00 – 17.00: Always place the form [BW610 20 025e FO](#) in folder 00.00 and list in section 2 all reference numbers of the combined studies (1000xxxx) and of any non-combined 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](#), in the correct subfolder of folder 18. Please consult the information sheet [BW101 10 003e MB](#) for information regarding the submission format.

Several submissions: Submit one eDok for each combined study using the portal [eGov Service eMessage](#). Via the eGov Service *eSubmission* you can submit one eDok for all non-combined clinical trial(s) with MP / ATMP affected by the change (according to Swissmedic's submission process for clinical trials of MPs / ATMPs).

The eDoks 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](#), in the correct subfolder of folder 18. Please consult the information sheet [BW101 10 003e MB](#) 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: Clinical trial, clinical investigation, or performance study becomes a combined study

An existing clinical trial of a MP / ATMP needs to be amended and procedures need to be switched to those for combined studies 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 portal [eGov Service eMessage](#).

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](#) (if the device is an MD) or [BW610 10 027e FO](#) (if the device is an IVD). 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.
- Folder 18.00: Place the updated documentation for the MP / ATMP aspect, including the '[FO submission form](#)' (amendment), in the correct subfolder of folder 18. 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 MB](#) 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 portal [eGov Service eMessage](#).

The eDok should be populated as follows:

- Folders 00.00 – 17.00: Always include the form [BW610 20 025e FO](#) in folder 00.00. Place the documentation for the updated MD / IVD aspect in the corresponding folders. 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](#), in the correct subfolder of folder 18. Please consult the information sheet [BW101 10 003e MB](#) 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 portal [eGov Service eMessage](#) 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 '[Submission of authorization applications and notifications](#)'.

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 separate reports to Swissmedic for each aspect of the combined study (MP / ATMP and MD / IVD), or to submit a single report. If you intend to submit a single report and you have a template designed for only one aspect of the combined study, make sure you include all the necessary information for the other aspect as well.

For the submission of all annual reports / DSUR, always include the form [BW610 20 025e FO](#) in folder 00.00 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 completion, termination or interruption

4.2.1 Completion, termination or interruption of all aspects of the combined study

To submit a notification of the regular completion, premature termination or interruption for reasons not related to safety, always include the form [BW610 20 025e FO](#) in folder 00.00. Also, place form '[FO submission form](#)' in folder 18.00 of your eDok.. A final report must be submitted within one year of the completion 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.

4.2.2 Completion, termination or interruption of one aspect only of the combined study

If one aspect of a combined study ends prior to the other aspect, only the remaining aspect will continue as either a clinical trial of a MP / ATMP or a clinical investigation of a MD / IVD performance study. No new letter of approval will be issued.

If one aspect of the combined study has been terminated in Switzerland, the study will remain a combined study until all reporting duties of the sponsor have been fulfilled.

To submit a notification of the regular completion, premature termination or interruption for reasons not related to safety that affects either the MD / IVD aspect or the MP / ATMP aspect, always include the form [BW610 20 025e FO](#) in folder 00.00 and indicate which aspect of the combined study are concerned by the notification. If the notification concerns the MP / ATMP, please also include the '[FO submission form](#)' and place it in folder 18.00. Note that if the MD / IVD aspect ends before the MP /

ATMP aspect, any future submissions need to be made using only the form '[FO submission form](#)'. Instructions can be found on our [website](#).

A final report must be submitted within one year of the completion 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 MP), 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 relatedness 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 or reasons for not interrupting recruitment
 - planned corrective and preventive actions
 - information sent to investigators
 - repeat testing or 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, always include the form [BW610_20_026e_FO](#) in folder 00.00:

- 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): MP / 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 (70xxx).

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 (70xxx).

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
4.0	In section 3, remark added on amendments affecting the MD/IVD aspect of a combined study.	sci
3.0	In section 1, new figure for quick overview of procedures in Switzerland, reorganisation of the subchapters and improved wording. In sections 2.1, 2.2, 3. 3.1 and 3.2, more information added, especially on the sequential initiation of projects and on modifications affecting several combined studies. New section 4.2.2. added concerning the completion, termination or interruption of one aspect only of a combined study.	sci
2.2	Updated texts in section 3 on the submission of modifications, sections 4.1 on templates for annual reports, 4.2 adjusted wording. Updated dokument links and abbreviations.	sci
2.1	Updated list of contents and typos.	sci
2.0	<ul style="list-style-type: none"> - 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 MP / 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