FEEDBACK FROM

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SWISSMEDIC'S EXPERIENCE WITH THE REGULATORY CHANGES FOR CLINICAL INVESTIGATIONS WITH MEDICAL DEVICES IMPLEMENTED IN 2021

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Swissmedic, the Swiss Agency for Therapeutic Products, evaluates and approves clinical trials of medical devices in humans if the devices are not CE-marked or are used off-label. These activities are conducted by the Medical Devices Clinical Investigations division, which also ensures continuous surveillance while the clinical trials are in progress. In 2021, the European Medical Device Regulation introduced new requirements for clinical investigations with medical devices. In parallel, the new Swiss Ordinance on Clinical Trials with Medical Devices came into force, applying the European requirements in Switzerland. This legislation introduced major changes to medical device requirements and authorisation procedures. In this article, Swissmedic summarises its stakeholder-oriented response to these legislative changes. In addition, it refers to new information sheets, templates, and decisions trees that are available.

PREPARING FOR THE ONSET OF NEW REQUIREMENTS FOR MEDICAL DEVICES

The European Medical Device Regulation (**MDR**), which included new product requirements, was first published in 2017. Due to the COVID-19 pandemic, its planned entry into force in 2020 was postponed for one year. However, well before the regulation came into force on 26 May 2021, manufacturers started aligning the development of new products to the new requirements. Across Europe, various manufacturers submitted MDR-based product documentation to competent authorities for the approval of clinical investigations. Even though the authorities in some European countries rejected such documentation if submitted before 26 May 2021, Swissmedic accepted MDR-based documents because it considered the MDR to cover all product requirements of the previous regulation. In order to assist hospitals and small- and medium-sized manufacturers, Swissmedic published templates on its website for documents required by the MDR, notably for the voluminous template on compliance with standards and the general safety and performance requirements of the MDR. Collaborative preparations for MDR requirements were made at the European level. Swissmedic made its initial template available to the working group in charge of European documents; the template was also integrated into guidance document MDCG 2021-08 and made available to all sponsors in the European region.

IMPLEMENTING CHANGES TO THE AUTHORISATION PROCEDURE FOR MEDICAL DEVICES

Under the old regulatory framework, both parallel and sequential submissions to Swissmedic and to the responsible ethics committee were possible. Consequently, there was no possibility for reviewing institutions to coordinate efficiently with each other. Since the implementation of the new regulatory framework in 2021, procedures have been streamlined and cooperation between institutions has been strengthened in Switzerland. Parallel submission is now mandatory for all applications for risk category C clinical trials with medical devices, often referred to as pre-market clinical investigations. Cantonal ethics committees are responsible for delimiting research projects, so they should be contacted prior to parallel submission if there is any doubt about categorisation or other delimitation aspects.

In Switzerland, the right to be heard allows for communication between applicants and reviewing institutions, including the adaptation of study documents by the sponsor during the authorisation procedure. This has proven to be important for carrying out procedures efficiently. In addition, a simplified review procedure was introduced in 2021 and can be requested for certain investigations of non-invasive class I and class IIa devices. Swissmedic has published corresponding explanations in information sheets on clinical investigations with medical devices and performance studies with in vitro diagnostic medical devices (**IVDs**).

On 26 May 2022, principles that have applied to medical devices since 2021 also came into force for authorisation procedures for performance studies of IVDs. All authorisation procedures for pre-market clinical investigations of medical devices and interventional IVD studies now include parallel submission, an extensive right to be heard, and a simplified review of certain minimum risk research projects.

RESPONDING TO THE 2021 CHANGES

Since Swissmedic accepted MDR-based documentation early on, the transition to MDR requirements in 2021 went smoothly, and surprisingly few questions arose. In the vast majority of cases, Swissmedic was able to respond to stakeholders' questions within one week. In 2022, Swissmedic approved 37 first-time applications for clinical trials and 100 changes requiring approval. Overall, Swissmedic checked a total of 143 notifiable changes, 106 annual safety reports, and 41 other safety reports from ongoing trials in Switzerland.

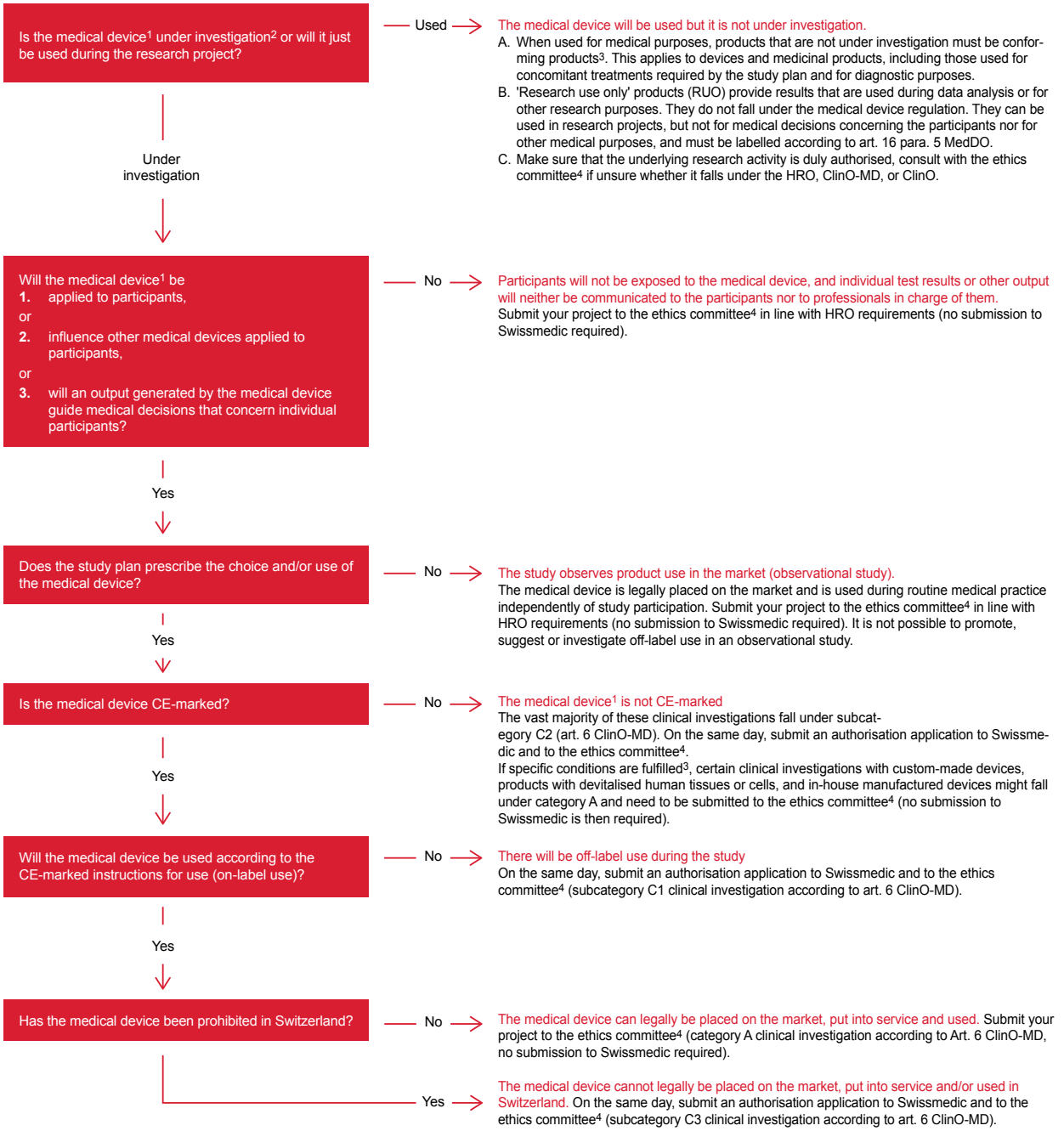
Despite a relatively smooth transition, sponsors kept sending questions to ethics committees and Swissmedic on the delimitation of research projects and asking whether specific projects would need Swissmedic's approval. Insecurities were possibly fostered by changes introduced with the Swiss Ordinance on Clinical Trials with Medical Devices (**ClinO-MD**). Notably, the ClinO-MD incorporates new EU definitions, which replace earlier terminology used in Switzerland that was based on the World Health Organization (**WHO**).

In 2021 and 2022, questions that arose were mostly related to the following issues:

- the distinction between interventional and non-interventional research
- products that can be placed on the market and used without a conformity mark
- research use only (**RUO**) products not intended to have a future medical use
- the location of laboratories for performance studies.

Some of these questions proved to be tricky due to the number of Swiss and European legal texts that needed to be consulted. Therefore, in 2022 Swissmedic, swissethics, and the Federal Office of Public Health developed decision trees for applicants that are simple to use (see **Figure 1** and **Figure 2**). These decision trees, additional information on specific delimitation issues, and updates are now available online in Swissmedic's information sheets, which will be further refined based on feedback from sponsors.

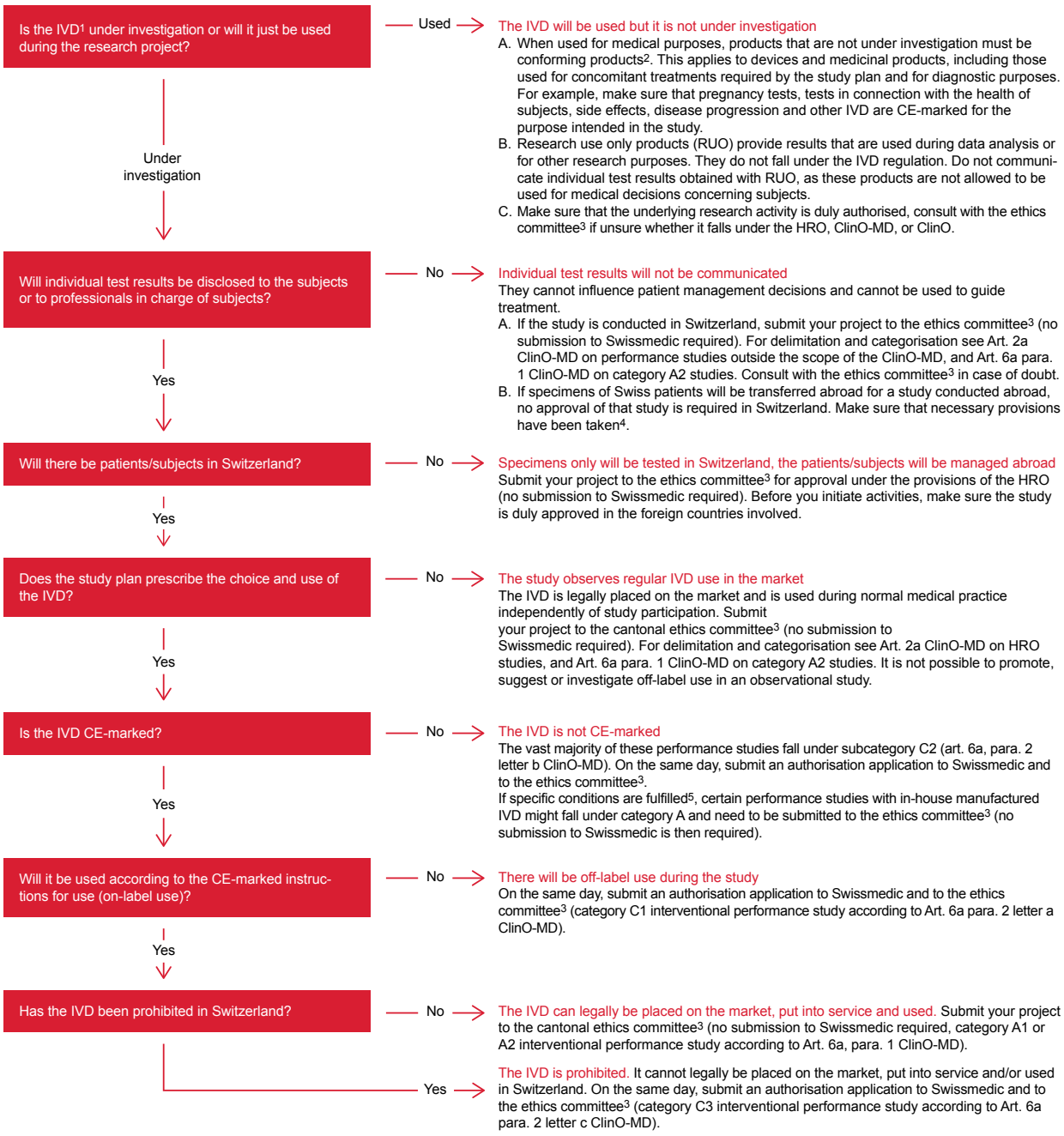
Figure 1: Decision tree for authorisation applications related to clinical investigations with medical devices



[1] The medical device can be a stand-alone product, or a product that is used as part of a system, including software (e.g. an app or an MRI sequence). Refer to art. 1 to 3 MedDO for definitions and exceptions. Consult the information sheet BW630_30_007e_MB (Medical Device Software) and the European guidance document MDCG 2019-11 in order to determine whether a software is a medical device.
[2] Investigation for assessment of the safety or performance of the device.
[3] See Annex A7 of this information sheet for guidance on clinical investigations with custom made devices, with therapeutic products that contain devitalised human tissues or cells, or with certain medical devices manufactured and used in the same healthcare institution.
[4] The application for the clinical trial is submitted to the ethics committee responsible for the investigator. In a multicentric clinical trial the application is submitted to the lead ethics committee responsible for the coordinating investigator. The coordinating investigator is the individual with responsibility in Switzerland for coordinating the investigators responsible for the various trial sites in Switzerland. The list of ethics commissions that details the cantons for which they are responsible can be found here: www.swissethics.ch/en/ethikkommissionen.

Source: Swissmedic's Information Sheet: Clinical Investigations with Medical Devices (version 4.2, dated 11.04.2023, pp. 6–7)

Figure 2: Decision tree for authorisation applications related to performance studies with IVD



[1] The IVD can be used alone, or used as part of a system, including software (e.g. an app). Refer to the IVDO for definitions and exceptions. Consult information sheet BW630_30_007e_MB (Medical Device Software) and the European guidance document MDCG 2019-11 in order to determine whether a software is an IVD.
[2] See annex A7 of this information sheet for guidance on interventional performance studies with IVD manufactured and used in the same healthcare institution.
[3] The application for the clinical trial is submitted to the ethics committee responsible for the investigator. In a multicentric clinical trial the application is submitted to the lead ethics committee responsible for the coordinating investigator. The coordinating investigator is the individual with responsibility in Switzerland for coordinating the investigators responsible for the various trial sites in Switzerland. The list of ethics commissions that details the cantons for which they are responsible can be found here: www.swissethics.ch/en/ethikkommissionen.
[4] You can find templates for material transfer agreements on the website of the Swiss Biobanking Platform. On the website of swissethics you can find a template for a general consent for specimens taken in the clinical routine, and a template for a study specific informed consent form for specimens taken specifically for the study (www.swissethics.ch > Templates > Patient information and Declaration of consent). Please contact the cantonal ethics committee in case of doubt.
[5] See annex A7 of the information sheet for guidance on interventional performance studies with IVD manufactured and used in the same healthcare institution.

Source: Swissmedic's Information Sheet: Performance Studies with IVD (version 3.3, dated 11.04.2023, pp. 5–6)