Clinical investigation of a new medical app - legal compliance checklist

What is this checklist for?

This checklist is drawn up on the basis of analysis of the relevant provisions of international and European law. Although European law aims at harmonizing the provisions of national legislation across Europe, all analysed provisions of international and European law can be specified or limited by the national laws of the countries where the relevant medical app is developed and tested.

This legal compliance checklist is developed in order to:

1. help developers using the FI-STAR platform to build an app that qualifies as a new medical device, and their legal team to prepare clinical investigation of that device in a way compliant with the existing legal requirements;

2. educate the developers and other parties involved in the clinical investigation about the existence and content of these requirements;

3. point out the importance of seeking local legal counsel's advice on how the relevant international and European law is implemented by the national law.

This checklist is to be used as a guiding and information tool and in close cooperation with local legal counsel. **It is not meant as legal advice.**

The checklist consists of a detailed to-do-list for the pre-trial, trial, and after-trial stages of investigation and incorporates a questionnaire on the national implementing legislation.

Whom is the checklist for?

The checklist is meant for the teams conducting the clinical investigation of a medical app, including medical professionals responsible for the investigation, technical developers and legal advisors.

Is your medical app a medical device?

To determine if your medical app is a medical device and hence if the checklist is of use, check this simple and clear European Commission guidance document on Qualification and Classification of stand alone software with a decision tree and this infographic.

The law at the heart of it

- Council Directive 93/42/EEC on medical devices ('**MDD**')
- 1964 Helsinki Declaration adopted by the 18th World Medical Assembly, amended by the World Medical Assembly (the **'Helsinki Declaration'**)

Important place for national law in your country

National legislation further specifies or makes exemptions from the provisions of the MDD and the Helsinki Declaration. Therefore, it is important that the legal team invplved with the investigation verify how each provision of the MDD and the Helsinki Declaration is implemented in the national law of their country.

THE CHECKLIST

GENERAL PRINCIPLES OF A CLINICAL INVESTIGATION TO BE RESPECTED ON ALL STAGES

- The goals of the research to generate new knowledge should **never take precedence over the rights** and interests of the individual research subjects (Article 8 Helsinki Declaration).
- The **primary duties of the physicians** involved in the medical research are first and foremost to promote and safeguard the health, well-being and rights of patients (Article 4 Helsinki Declaration), and protect life, health, dignity, integrity, right to self-determination, privacy and confidentiality of personal information of research subjects (Article 9 Helsinki Declaration).
- Even though patients give consent to participate in a clinical study, the **responsibility for the protection of the research subjects** should never lie with them, but with the involved physicians or other health care professionals (Article 9 Helsinki Declaration).

STAGE 1: IN PREPARATION OF THE CLINICAL INVESTIGATION

1. **Assess predictable risks** and burdens to the individuals involved in the investigation (e.g. patients and other trial participants).
    a. How do those risks and benefits compare to foreseeable benefits to them and others affected by the condition under investigation (e.g. diabetes)?
    b. Document findings.
    c. Only proceed conducting the study if the benefits outweigh the risks. If the benefits do not outweigh the risks, do not proceed with the study.
2. Draw up **a plan of clinical investigation**:
    a. Make sure it reflects the latest scientific and technical knowledge;
    b. Make sure the plan is defined in a way as to confirm or refute the the app manufacturer's claims for the app (e.g. that an app meant to help doctors read X-rays better actually will do it);
    c. Make sure the plan includes an adequate number of observations (of whether or not, and how your app performs) to guarantee scientific validity of the conclusions.
3. Develop a **clinical investigation procedure** appropriate to the device under examination, including measures **to minimize the risks** to the participants.
4. Identify a **medical practitioner** or another authorized qualified person in an appropriate environment who will have responsibility for the performance of the clinical investigation.
5. Take steps to **ensure appropriate compensation** and treatment for subjects who are harmed as a result of participating in research, e.g. by way of insurance.
6. Investigate what **provisions are made for post-trial access** for all participants who still need an intervention identified as beneficial in the trial (e.g. trial participants may be willing to keep using your app after the trial is over).

7. Have the responsible medical practitioner involved **select subjects** to participate in medical research.

*NB When the responsible medical practitioner combines medical research with medical care, he/she should only **involve his/her patients to the extent that this is justified** by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that there will be no adverse effects to the health of the patients.*

Potential subjects who are incapable of giving informed consent must not be included in a research study when that research study has no likelihood of benefit for them, unless:

- *The study is intended to promote the health of the group represented by the potential subject; and*
- *The research cannot instead be performed with persons capable of providing informed consent; and*
- *Research entails only minimal risks and minimal burden.*

If the research is to involve **vulnerable groups**, e.g. children, ensure that:

- the research addresses the health needs or priorities of this group, and
- cannot be carried out in a non-vulnurable group, and
- this group stands to benefit from the research results.

8. Ensure that the **study is registered** in a publicly accessible database *prior* to subjects recruitment.
9. Commence an **informed consent process**:
    a. Taking account of special information needs of individual potential subjects and **methods** to deliver information, such as the language, **inform the potential subjects** of any relevant aspects of the study, including:
        i. the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researchers, the anticipated benefits and potential risks, discomfort it might entail, post-study provisions;
        ii. the **right to refuse** to participate in the study **or to withdraw** consent at any time without reprisal,
        iii. the option of being informed about the general outcome and results of the study.
        iv. which aspects of their care are related to the research.
    b. Draw up a **consent form** to obtain a written **freely given informed consent.** The information requirements can also be met by drawing up and having the potential subject sign a consent form.

    NB The refusal to participate in a study or a decision to withdraw from the study must never adversely affect the patient-physician relationship.

c. In case a subject is incapable of giving informed consent, seek consent from a legally authorized representative, and the subject's assent if he is capable of giving it. The subject's dissent must be respected.

d. Designate an individual who would seek freely given informed consent.

NB In case a potential subject is in a dependent relationship with the physician or may consent under duress, the consent must be sought by an appropriately qualified individual who is completely independent of a dependent relationship between the potential subject and the physician.

10. Provide the responsible medical practitioner or another authorized qualified person with access to he technical and clinical data regarding the device.

11. Draw up a **research protocol** that must contain:

    a. Clear description and justification of design and performance of each study involving human subjects;
    b. A statement of the ethical considerations involved
    c. Indicate how the principles of the Helsinki Declaration have been addressed;
    d. Information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects,
    e. Information regarding provisions for treating and / or compensating subjects who are harmed as a consequence of participation in the study,
    f. Appropriate arrangements fir post-trial provisions.

    NB The use (or no use) of placebo or no intervention must be considered and justified pursuant to Article 33 Helsinki Declaration.

12. **Submit the research protocol** for consideration and approval to the concerned transparent and independent of the researchers and other undue influences research ethics committee before the study begins. Any amendments to the protocol can only be made after consideration and approval of the committee (Article 23 Helsinki Declaration).

13. Identify the medical **device** intended for clinical investigation;[1]

14. Identify **the class of the medical device** intended for clinical investigation:

    a. Class I,

    b. Class IIa,

    c. Class IIb,

    d. Class III.

In most cases medical apps will be the lowest risk – Class I – medical devices. Annex IX MDD establishes the criteria of classification. In June 2010 the Commission adopted guidelines on classification of medical devices.[2] This infographic may also be of use.

[1] "'**Device intended for clinical investigation'** means any device intended for use by a duly qualified medical practitioner [or any other person who, by virtue of his professional qualifications, is authorized to carry out such investigation] when condicting investigations … in an adequate human clinical environment" Article 1(2)(e) MDD.

15. Identify the **manufacturer** of the device intended for clinical investigation;[3]
16. Appoint or identify an **authorized representative** of the manufacturer;[4]
17. Identify and choose **notified bodies** relevant within their tasks for the device intended for clinical investigation;
18. Identify the relevant **national competent authority or authorities**;[5]
19. Draw up a **statement concerning devices intended for clinical investigations**. The statement must contain:
    a. "Data allowing identification of the device in question,"
    b. "The clinical investigation plan,"
    c. "The investigator's brochure,"
    d. "The confirmation of insurance of subjects,"
    e. "The documents used to obtain informed consent,"
    f. "A statement indicating whether or not the device incorporates a substance or human blood derivative referred to in Section 7.4 Annex I MDD,"
    g. "A statement indicating whether or not the device is manufactured utilizing tissues of animal origin as referred to in Directive 2003/32/EC,"
    h. "The opinion of the ethics committee concerned and details of the aspects covered by its opinion,"

---

[2] European Commission, "Medical devices: Guidance document – Classification of medical devices," Guidelines relating to the application of the Council Directive 93/42/EEC on medical devices, MEDDEV 2. 4/1 Rev. 9

June 2010, available at http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf

[3] The **manufacturer** includes but is not limited to a producer of a medical device. MDD defined the manufacturer as "*the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party*" (Article 1(2)(f) MDD). This definition does not apply to the person who, while not a manufacturer, assembles or adapts devices already on the market to their intended purpose for an individual patient (Article 1(2)(f) MDD, subparagraph 2).

E.g., an institution that outsources the development of a medical app for a smart phone to a third party and brings it out on the market under its name is considered a manufacturer with regard to the app, but not with regard to the smartphone.

[4] An '**authorised representative'** is a natural or legal person established in the EU who "*who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter's obligations under this Directive*" (Article 1(2)(j) MDD).

[5] The **'competent authorities'** are the national authorities of the Member States. They are endowed with supervisory functions regarding the notified bodies.

i. "The name of the medical practitioner or another authorized person and of the institution responsible for the investigations,"

j. "The place, starting date and scheduled duration for the investigations,"

k. "A statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient."

20. **Notify** the intended clinical investigation to the competent authorities in the country where the investigation is to be conducted by means of the **statement concerning devices intended for clinical investigations** (drawn up in accordance with s.2.2 Annex VIII MDD).

For higher risk devices (Class III and implantable and long-term invasive devices of Class IIa and IIb), **THE CLINICAL INVESTIGATION CAN BEGIN IN THE END OF A 60-DAYS PERIOD AFTER NOTIFICATION,** unless competent authorities decided and notified otherwise (Article 15(2) MDD). The competent authorities may authorize the investigation to begin earlier, upon a positive opinion of an ethics committee.

21. Prepare and **keep available** for the national competent authorities **documentation** pursuant to Section 3.2 Annex VIII MDD:

a. A general description of the product and its intended use,

b. Design drawings, methods of manufacture envisaged, in particular as regards sterilization, and diagrams of components, subassemblies, circuits, etc.

c. The descriptions and explanations necessary to understand the abovementioned drawings and diagrams and the operation of the product,

d. The results of the risk analysis and a list of the standards applicable to the device, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements in Annex I MDD if the standards have not been applied,

e. If the device incorporates … a substance or human blood derivative referred to in S. 7.4 Annex I MDD, the data on the tests conducted in this connection which are required to assess the safety, quality, and usefulness of that substance or human blood derivative, taking account of the intended purpose of the device,

f. If the device is manufactured utilising tissues of animal origin, the risk management measures in this connection which have been applied to reduce the risk of infection,

g. The results of the design calculations, and of the inspections and technical tests carried out, etc.

22. Ensure that the manufacturing process produces products which are manufactured in accordance with the documentation pursuant to Section 3.2 Annex VIII MDD, plan and authorize the assessment or audit of the effectiveness of these measures, where necessary.

What national laws in your country implement these provisions? Do they introduce additional requirements or exceptions to the steps prior to the start of a clinical investigation? Give references to the relevant provisions.

How do you (plan to) comply?

STAGE 2: DURING THE CLINICAL INVESTIGATION

1. Perform the clinical investigation in **circumstances similar to the normal** conditions of use of the device (e.g. if an app is meant to be used by a patient at home, make sure this is how the app is tested).
2. Examine all the appropriate features, including those involving the safety and performances of the device, and its effects on patients.
3. Continuously **monitor, assess and document risks** to the patients.
4. Physicians must **assess whether to continue, modify or immediately stop the study** when the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes.
5. Record fully all (if any) serious adverse events and notify immediately to all competent authorities of the Member States where the clinical investigation is being performed.
6. Provide monitoring information on the ongoing study to the research ethics committee, especially the information about any serious adverse effects.

What national laws in your country implement these provisions? Do they introduce additional requirements or exceptions to the steps during a clinical investigation? Give references to the relevant provisions.

How do you (plan to) comply?

STAGE 3: AFTER THE CLINICAL INVESTIGATION

1. **Notify the competent authorities of the end** of the clinical investigation and justify early termination, if it is the case.
2. Draw up **a written report**, signed by the medical practitioner or another authorized person responsible, containing a critical evaluation of all the data collected during the clinical investigation.
3. **Submit a final report to the research ethics committee** containing a summary of the study's finding and conclusions.
4. Researchers have an ethical duty to make **publicly available the results** of their research on human subjects in accordance with guidelines of ethical reporting, in a complete and accurate manner, including negative and inconclusive as well as positive

results. The publication must contain information on sources of funding, institutional affiliations and conflicts of interest.

5. The **statement concerning devices intended for clinical investigations** pursuant to s.2.2 Annex VIII MDD and **documentation** pursuant to Section 3.2 Annex VIII MDD must be kept for a period of at least five years, and in case of implantable devices – at least 15 years.

What national laws in your country implement these provisions? Do they introduce additional requirements or exceptions to the steps after the completion of a clinical investigation? Give references to the relevant provisions.

How do you (plan to) comply?