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Clinical Evaluation of Mobile Medical Apps

A Process Orientated Guide

Abstract: Computer applications in medicine are very important. However, there are differences in quality of such software, which periodically led to discussions about safety, regulation, and registration of software applications. Today, the admission procedure of medical products is highly regulated, and this applies also for mobile medical apps. The clinical evaluation is one important aspect of the admission procedure, especially due to the latest regulatory changes of the guideline MedDev 2.7/1 revision 4. The requirements have increased, and uncertainty grows in medical app development companies. The aim of this paper was the development of a process orientated guide, that gives an overview of the needed steps of a clinical evaluation of mobile medical apps and that could help to give a rough estimation about the necessary effort. The guide was developed, based on the relevant literature and legal texts. The clinical evaluation can be conducted in five substeps: “Planning and Scoping”, “Literature Research”, “Literature Assessment”, “Clinical Data Analysis” and “Reporting”. Prospectively, this guide will be evaluated by developers and adjusted, as soon as Medical Device Regulation is legally binding.

Keywords: Mobile apps, Developers’ guide, mHealth.

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1 Introduction

1.1 Development of regulatory affairs in computer applications

The way of establishing software applications in medicine has been long and difficult. In 1989, Hafner et al. already stated that using computer applications in medicine may be less harmful than not using them [1]. Today, we take computers and software in medicine for granted and their usage became an integral part of modern medicine. Nevertheless, there are differences in quality of such software. Consequently, there have always been incidents that triggered discussions about safety, regulation, and registration of software application in medicine. For example, Lancet published in 1996 a small software error that led to reduced detection rates of Down’s syndromes during pregnancies [2]. The most experience in regulating software in medicine hail from the USA, where the Food and Drug Administration regulated medical device related software in 1976 for the first time [3, 4]. Over time, the basic idea of regulations has changed. In 1997 Wyatt [5] stated that certification of medical computer systems requires information about the system’s structure, performance, and impact on users as well as the environment they work in. He concluded that clinical evaluation of software in medicine must switch from clinical users (requirements) to the system itself (structure and function) and back to the user (clinical trials).

1.2 Current legislation for medical devices

In 2007, the Council of the European Union has published the amending directive 2007/47/EC [6], that underlines the explicit applicability of the European regulations for medical devices to software. Thereupon, the discussion about the regulation of stand-alone software and mobile medical apps (MMA) raised. This is not surprising, because according to industry estimates [7], more than 1.7 billion smartphone and tablet users will have downloaded MMAs at the end of 2018. These users include health care professionals, consumers, and patients.

In 2013, the FDA published the guidance document “Mobile Medical Applications: Guidance for Food and Drug Administration Staff”, a new point of reference for the regulation of MMAs also for European manufacturers. The FDA had to update this guidance within two years to be consistent with the guidance document “Medical Devices
Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices” [8].

But the development of the regulations continues: In 2017, the medical device regulation (MDR) was published [9]. One of the relevant updates is the classification of stand-alone software, such as MMAs. So far, a lot of stand-alone software could be classified as class I product. The new classification rule 11 of the MDR Annex VIII states, that software “…intended to provide information which is used to take decisions with diagnosis or therapeutic purposes…” must be at least class IIa. If there might be a serious deterioration of a person’s state of health, it must even be class IIb [9]. Based on the definition of a medical device (Article 2, MDR), it can be postulated, that most medical stand-alone software will be classified as class IIa or higher. This leads to an enormous additional effort for the software manufactures and a prolonged development time.

1.3 Clinical evaluation of mobile medical apps

An additional aspect of the regulation of an MMA and the long way to make a product available on the market is the clinical evaluation. Its purpose is to prove the conformity with relevant general safety and performance requirements under normal conditions of the intended use of the medical product. Furthermore, undesirable side-effects should be detected, an evaluation of the acceptability of the benefit-risk-ratio should be based on clinical data providing sufficient clinical evidence [9].

In June 2016, the European Commission published the latest revision of the “Clinical Evaluation: A Guide for Manufacturers And Notified Bodies Under Directives 93/42/EEC And 90/385/EEC”, the so called MEDEV 2.7/1 revision 4 [10]. Due to publication of the MDR, the next update (revision 5) is in progress and can be expected soon.

The aim of this paper is the exposition of a simple guide for the clinical evaluation of MMAs, based on the MEDEV 2.7/1 revision 4. Manufacturers of medical products and software developers should be given an overview of the needed steps of a clinical evaluation of MMAs and a rough estimation about the necessary effort.

2 Material and Method

Based on a literature research, all relevant European standards and guidelines were sighted. Usability and risk management aspects were worked out to develop an integrative process workflow. Comparisons with other examples (such as the FDA model) were made. The following literature was used, and relevant information was extracted and condensed:

- Directive (EU) 2007/47/EC
- Directive (EU) 93/42/EEC
- Regulation (EU) 2017/745
- EN ISO 14971:2012
- DIN EN 62366-1:2017
- Applying Human Factors and Usability Engineering to Medical Devices.

3 Results

The clinical evaluation procedure can be compromised to five stages (see Fig. 1). Each stage contains different work packages and requirements.

![Figure 1. Five stages of a conform clinical evaluation.](image-url)

**Evaluation Plan/ Scoping:** The MMA must be defined as accurately as possible. Information of the risk analysis regarding clinical risks should be referred. Data sources and types should be determined. An overview of the current applicable standards and guidelines that represent the state-of-the-art in the corresponding medical field. The evaluator team must be determined, which is not trivial, due to high and explicit requirements that will hardly be met by one person. The evaluator team should consist of researchers, medical writers, and medical affairs experts who are familiar with the product technology and the medical application. Members should have a university degree and at least five years professional experience.

**Literature Research:** Clinical Data can be subdivided into:

- Preclinical Data
- Clinical Trials
• Scientific Literature
• Public Product Specifications

All these data must be considered in the clinical evaluation, if available.

Preclinical data are usually generated from external accredited laboratories during verification, validation, or standard testing. Clinical trials are complex and expensive, but necessary, if there are insufficient clinical data available. The aim of a clinical trial is a statistically significant result that gives evidence for a clinical function or benefit. Scientific literature must be scrutinized, search strategy should be accurate and objective and based on a search protocol (included terms, excluded terms, boolean search etc.). The following databases should be included:

- www.livivio.de
- www.ieeexplore.ieee.org
- www.clinicaltrials.gov
- www.embase.com
- www.cochranelibrary.com

Furthermore, adverse event databases should also be checked – BfArM (Germany), MAUDE (USA), Swissmedic (Swiss), and MHRA (GB) – for incidents of similar MMAs. Public product specifications are usually available on the homepage of the legal manufacturer.

**Literature Assessment (individual analysis):** Useful criteria for the assessment should be determined initially to simplify the subsequent work. Based on the full text of publications (not on summaries), the assessment should be performed in a structured and comprehensible way. Quality of data considerations should include the study design, the peer-review procedure, the Journal Impact Factor, and the Level of Evidence. Furthermore, metadata should be recorded, such as inclusion and exclusion criteria, number of patients, age, aim of the study, methods, results and input on performance and safety, amongst others. The contribution of each data set must be weighted, based on the experience and knowledge of the evaluator – usually, randomized controlled trials receive the highest weighting.

**Clinical Data Analysis (accumulated analysis):** The aim is a sound and comprehensive analysis, that demonstrate compliance of the collected data with each of the Essential Requirements regarding the clinical safety and performance. The evaluator should determine if additional clinical investigations are necessary or not and if a post market clinical follow-up (PMCF) is needed.

**Clinical Evaluation Report:** The aim is an executive summary, containing sufficient information to be understood by an independent party. The structure should reflect all the four previous stages. In addition, information about the evaluator team and corresponding declarations of interests should be added (further information can be found in appendix 11 of the MedDev 2.7/1 rev.4).

The manufacturer must determine and explain the repetition rate of the clinical evaluation based on post market surveillance and PMCF where appropriate. These updates are usually conducted each year for high-risk products and otherwise every two to five years.

### 4 Discussion

The requirements for a clinical evaluation of an MMA are high and complex. It is difficult for small development companies to handle all these requirements appropriately, and in many cases a certain monetary amount must be budgeted for consulting companies. Nevertheless, this process orientated guide should help to anticipate the needed steps and to calculate the workload. In this way, certain steps can be integrated in early working phases to avoid the rude awakening at the end of the project.

Prospectively, this guide should be tested and evaluated by various developers regarding understanding, usability, and practicability. In 2020 at the latest, when MedDev 2.7/1rev. 5 is published and MDR will become law, this guide must be adapted.

In recent years, most clinical data came from literature of equivalent products and little data came from clinical trials [11]. The proof of equivalence is getting more complicated with the new MDR, thus the number of clinical trials and PMCFs will increase significantly. These circumstances could put further pressure on small companies and unfortunately reduce the innovative capacity.

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References


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