Summary Report

2nd Swissmedic Roundtable Innovation (RTI)
Digital Endpoints

Monday, 22 November 2021
15.00 – 16.30

1.	**Welcome and Introductions** Introduction followed by a round of introduction of the participants
2.	**Swissmedic perspective on Digital Endpoints** Please refer to presentations from Swissmedic ● Software may be a medical device, with requirements when used in (combined) clinical trials ● Swissmedic does not offer a qualification procedure (advice/opinion) ● Swissmedic suggests a step wise and case by case approach ● Access consortium might be a medium-term possibility, as collaboration on clinical trials design and/or sponsor advice within Access consortium is considered ● Swissmedic sees the need for stringent quality control, data and privacy protection as well as clarification of data ownership
3.	**Industry perspective on Digital Endpoints** Please refer to the presentation from Industry Advantage of digital endpoints ● Digital endpoints can help resolve unmet measurement needs, provide a more granular view into disease, measure outcomes in the real-world setting of patients and offer the possibility to use the same digital measure in clinical practice ● Data are transferred and processed in almost real-time ● Team and sites have access to up-to date data at any time ● Timely monitoring of adherence and data quality Qualification procedure ● From industry perspective, current qualification procedures at EMA and FDA are: time-consuming and resource intense processes, more fit for purpose pathways are needed ● Industry would value a joint scientific advice procedure with Access health authorities to discuss digital endpoint ● A case study was presented where the Medical Device qualification of the digital health tool used to collect the endpoint data has been discussed with regulators in EU and US (i.e. DKMA, BfArM, EMA, FDA). They all concur that if the digital health tool is not used with a medical purpose in the clinical trial (i.e. there is no medical purpose for the individual patient), it does not qualify as a medical device under the Medical Device Regulation. It is to be noted, that this has to be evaluated on a case by case basis. Importantly, the quality of the data collected via the digital health tool has to be ensured through computer system validation processes, as is standard in clinical trials.

Data privacy / Data protection

- According to Swissethics, data privacy is key. Requirements on the use of data need to be established
- Referring to case study 2, from patient perspective it is important that patients would not need to consent to each of the apps, if apps are grouped on a platform

4. Open discussion

Collaboration with Access partners

- Industry representatives were pleased to see the Access strategic plan
- First discussions on possibility of joint scientific advice between Access partners have taken place
- Swissmedic reached out to Access partners ahead of the Roundtable Innovation. While so far no information on regulatory requirements from Access partners is published, all agencies showed interest to continue discussions on digital endpoints
- Industry representatives would be supportive of Access partners to develop a regulatory framework for digital endpoints and to recognize the endpoints qualified or accepted by other Agencies, such as EMA and FDA

Device agnostic

- It was discussed whether in future digital endpoints that are agnostic of the device could be considered. It is important to note that the current qualification procedures do not qualify the digital health tool that collects the measure: they qualify the clinical outcome assessment or biomarker and list the requirements for the adequate collection digital health tools.
- The interoperability of platforms is essential in the future

Missing data

- Industry would need advice on how to best handle missing data (e.g. data might be missing because patients might feel particularly unwell and might forget to collect data) and data collected when patients do not comply with the instructions of the test (e.g. through pre-specified quality flags to identify if the test was not conducted correctly such as when patients leave the phone on the table when they should carry it while they walk)
- Swissmedic states that there is no big difference in missing data on digital compared to conventional endpoints. Acceptability is depending on the amount and on the distribution between treatment arms (missing completely at random/at random/not at random) as well as on the statistical methods (e.g. imputations) applied to mitigate their impact.
- Swissmedic is aware of the challenge to get good quality data from patients with neurodegenerative disorders and patients with cognitive impairment
- Algorithms for neurodegenerative disorders: very hard for a machine to differentiate between voluntary and involuntary movements.
- Excluding (missing) data from the analysis is considered as deviation from the ITT principle and would have to be justified thoroughly. Pre-specified quality flags could be used to flag data, and the methods should be discussed with the Agency in more detail. Using artificial intelligence for identifying erroneous measurements would add even more uncertainty.

Harmonisation of requirements through the International Council of Harmonisation of technical requirements (ICH)

- Swissmedic suggests to submit a new topic proposal
- Currently not clear, if such a topic could be accepted in the upcoming new topic cycle as more stringent criteria for acceptance are applied due to the pandemic
- Industry refers to long processes until a guideline is implemented and the need for more immediate guidance from regulators on evidence requirement, as presented in the slide-deck
- It was noted that the revision of ICH E6 will include considerations for non-traditional interventional clinical trials (Annex-2) such as "*digital tools and direct data capture, including as the use of data collected outside of trial settings is being explored*" (ICH E6 GCP – Update on Progress, Public Web Conference Report, May 18 & 19, 2021).

5. Closing remarks and next steps

Swissethics perspective

- Focus on the patients
- Digital Health Tools / software should not be a burden for patients and data privacy should be ensured
- Neither the Ethic Committees nor swissethics offer a qualification procedure (advice/opinion) to the researchers

Investigators perspective

- It is important to close the gap between professional assessment and PRO (=patient reported outcomes), a chance and motivator for all stakeholders involved
- Agencies should take over and publish regulatory requirements, e.g. regulatory agencies could ask for interoperability
- The underlying technology should be looked at, not the device itself
- Emphasizes the importance of the topic and reminds participants that no data is even worse

Federal Office of Public Health (FOPH)

- Regulation for digital endpoints is in place (Human Research Act), as regulation is technology neutral
- The human research act is currently being revised. However, due to the pandemic, the revision has been postponed to a later point in time

Patient perspective

- Emphasizes the opportunities of digital endpoints for patients and the importance of including the patients perspective from the beginning, i.e. when planning the design of a clinical trial

Industry perspective

- Industry highlighted the importance of the dialogue between all stakeholders and having a fit for purpose pathway to interact with Agencies to discuss digital endpoints

- Industry acknowledges the importance of having such topics included in the masterplan “Biomedizinische Forschung und Technologie”
- Supports collaboration with Access partners, specifically for scientific advice and having discussions such as this Roundtable Innovation with all Access partners at the same time

Swissmedic perspective

- Validation of new digital endpoints is challenging and complex, Swissmedic does not offer a qualification procedure
- Software as a medical device: Medical Device Regulation and requirements for use in (combined) clinical trials are to be considered. Depending on the medical purpose of the digital health technology, certain software may fall under Medical Device Regulation. In other research cases, the digital health technology may not require medical device certification. The medical purpose would need to be assessed on a case by case basis.
- Early engagement via Scientific Advice suggested (but will require multi-disciplinary approach)
- Case by case approach is suggested
- Supports the Access consortium as a platform for discussion on regulatory requirements