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Insights from the European Medicines Agency on digital health technology derived endpoints

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This study evaluates the use of digital health technologies (DHTs) for endpoint measurement in clinical trials, as documented in the Qualification Opinions, Qualification Advice, and Scientific Advice procedures issued by the European Medicines Agency (EMA) between 2013 and 2022. Accelerometers are the most proposed DHTs, followed by glucose monitors and smartphones. Accelerometers are often proposed for nervous system diseases to support mobility measures and objective testing. Most DHTs were proposed for efficacy endpoints. The feedback provided by EMA emphasizes the importance of validation, precision, and a clearly defined context of use. The EMA's recent action plan further supports advancing DHT methodologies in clinical trials.

Keywords: Digital health technologies; Digital biomarkers; Remote monitoring technologies; Decentralized trial elements; European Medicines Agency

Introduction

With the advancement of technology, digital tools are increasingly used in drug development, including clinical trials. Digital health technologies (DHTs), such as mobile apps, wearable devices, and implantable sensors, offer significant advantages in remote data collection by reducing participant burden and promoting trial adherence. They allow for dense data collection, aiding the real-time identification of safety issues and the assessment of novel endpoints.[(p1),(p2),(p3)] Several studies have shown the feasibility of DHT use and a correlation with patient-reported outcomes in various conditions, highlighting the potential of DHTs in clinical trials.[(p4),(p5),(p6),(p7)] In addition, studies have suggested that digital endpoints can detect clinically meaningful changes with greater accuracy and frequency than traditional measures, making them reliable and relevant tools for both clinical trials and real-world monitoring. For instance, wearable and smartphone-based technologies have been shown to outperform conventional assessments, such as the 6-minute walk test and MDS-UPDRS (Movement Disorder Society Unified Parkinson's Disease Rating Scale), by capturing subtle motor and cognitive changes in conditions such as Duchenne muscular dystrophy (DMD) and Parkinson's disease (PD).[(p8),(p9)]

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Nevertheless, regulatory experience with the use of these tools to measure treatment effects in the context of registrational studies is minimal.[p8],[p10],[p11] Therefore, their validity for providing clinically relevant and convincing evidence related to the primary objective of the study, as stipulated in International Conference on Harmonisation Guidance (ICH E9), has not been established.[p12] The European Medicines Agency (EMA) offers several pathways for sponsors to receive feedback on DHTs that are intended to measure novel endpoints. In the context of a specific product development, sponsors can seek advice through the scientific advice (SA) procedure, whereas the qualification of novel methodologies for drug development procedure can be followed if the DHT has been developed independent of a specific product.[p13],[p14] Depending on the data provided, the EMA may issue a publicly available qualification opinion (QO) or a confidential qualification advice (QA), with the option of publishing a censored version as a letter of support.

A previous study reviewed the QAs, QOs, and SAs related to DHT-derived endpoints issued between 2013 and 2019, revealing an increase in DHT-related procedures from 3 procedures in 2013 to 19 procedures in 2019.[p10] The COVID-19 pandemic, which began in 2020, reinforced this heightened interest in digital tools for facilitating the remote conduct of ongoing and COVID-19-related clinical trials.[p15] In light of this shift, we aimed to investigate whether an increasing trend towards DHT-related advices has persisted, considering the pandemic as a potential accelerator. This study expands upon the earlier findings by reviewing QAs, QOs, and SAs concerning DHTs issued from 2020 to 2022. All SAs, QAs, and QOs issued from 1 January 2013 to 31 December 2022 were retrieved from internal EMA databases, including both initial and follow-up advices. Relevant entries were identified using a text search algorithm with predefined keywords (see Supplementary materials: Methods). Data extracted from these included the type of DHT and the therapeutic area. In addition, an inductive thematic analysis was conducted for SA and QA questions posed by applicants between 2020 and 2022.

DHTs in QO, QA and SA procedures

A total of 81 SAs, 14 QAs and 2 QOs were included in our study (Figure 1). There was an increase in the number of SAs related to DHTs from 3 in 2013 to 16 in 2019, followed by a decline in subsequent years to 6 in 2022. By contrast, QAs and QOs related to DHTs were scarce before 2019 with 1 QA in 2015, 1 QA in 2017 and 2 QOs in 2018, but there was a notable increase in QAs in the following years, with the highest number in 2022 (n = 4). This increase in QAs suggests growing interest in the use of DHTs for drug development, although only two QOs concerning DHTs for endpoint measurement were issued in the studied 10-year time period. The EMA published two letters of support for promising

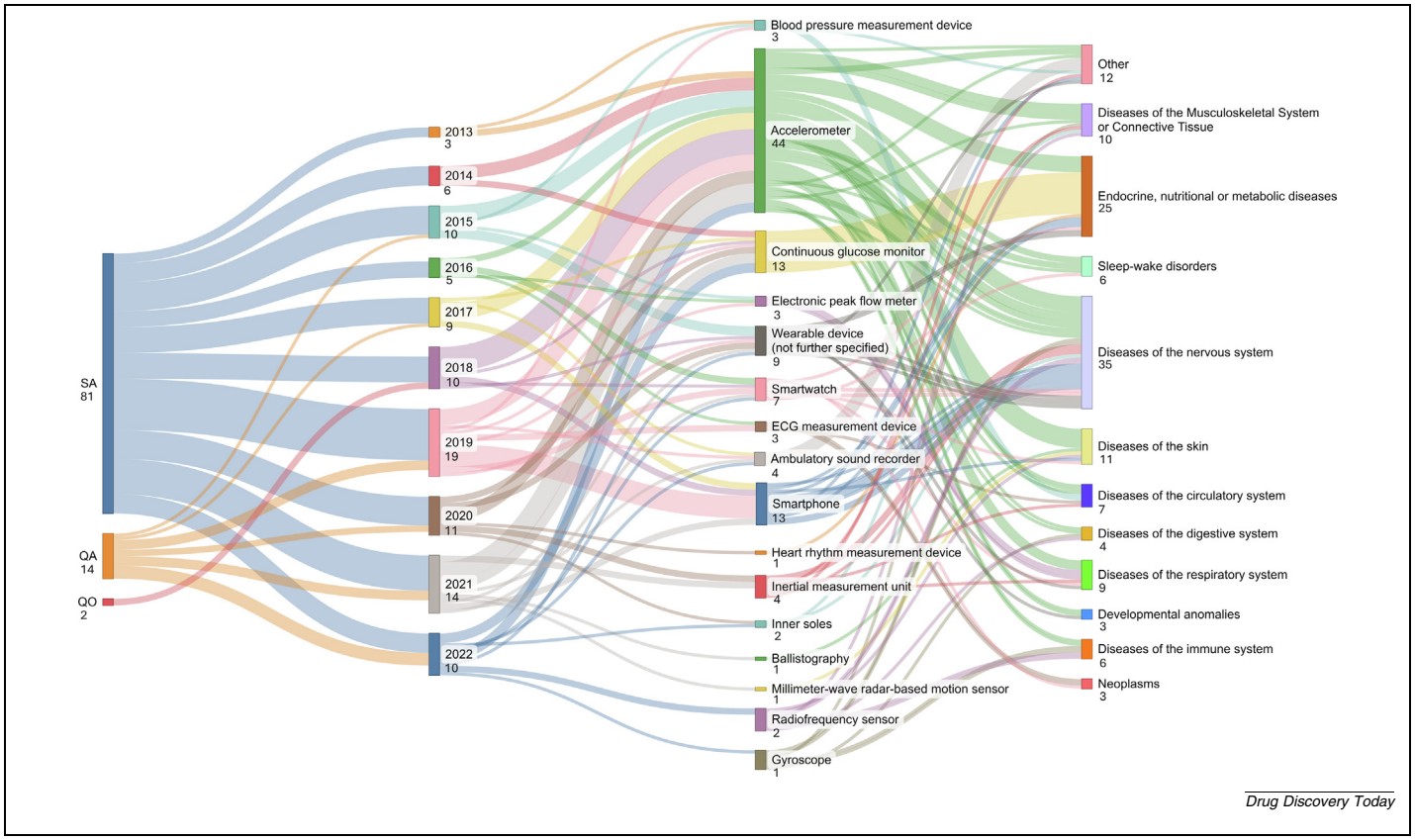

FIGURE 1

Sankey diagram illustrating the flow of advice types, publication years, proposed devices, and associated disease areas. Between 2013 and 2022, the number of scientific advice (SA) procedures related to digital health technologies (DHTs) increased until 2019, after which these numbers declined. The qualification advice (QA) procedures showed an increase over the years. Accelerometers were the most frequently proposed DHTs (n = 44), followed by continuous glucose monitoring devices (n = 13) and smartphones (n = 13). In nine cases, the device was referred to as wearable technology without further specification by the applicant. DHTs were most commonly proposed for diseases of the nervous system (n = 35).

methodologies for the Innovative Health Initiative (IHI) project Mobilise-D in 2020 and 2021, focusing on mobility biomarkers in diseases such as PD, multiple sclerosis (MS), chronic obstructive pulmonary disease (COPD) and proximal femoral fracture (see Supplementary Table 1).

Most commonly proposed DHTs and their applications across disease areas

Accelerometers were the most frequently proposed DHT (n = 44), followed by continuous glucose monitoring (CGM) devices (n = 13) and smartphones (n = 13). Different types of devices that contain accelerometers were combined into one group, which included DHTs intended to measure activity, mobility, sleep parameters, scratching and fatigue, while continuous glucose monitors were proposed for glucose measures. Notably, following the EMA's endorsement of stride velocity 95th centile (SV95C) measured by a valid and suitable wearable device as a secondary endpoint in DMD trials in 2019, inertial measurement units (IMUs) have been proposed in QAs. This is the first digital endpoint measured by a wearable device to have received EMA endorsement through a QO. As of June 2023, SV95C has further been qualified as a primary endpoint (see Supplementary Table 1). Although the primary goal of EMA qualification is to assess and validate an approach or endpoint rather than a specific device, the QO also outlines the technical specifications of devices that are suitable for measuring SV95C.

DHTs were most commonly proposed for diseases of the nervous system (n = 35), such as PD (n = 9), Huntington's disease (HD) (n = 6), MS (n = 5) and Alzheimer's disease (n = 1). Within these disease areas, DHTs were mainly used for different mobility measures, but also for cognitive measures. This can be attributed to the lack of objective measures in this field, where current standards mainly rely on subjective assessments of patient well-being. Therefore, there is a need to develop objective tests and outcome measures.[p16] Such DHTs can be developed, for instance, through pre-competitive consortia, such as those facilitated by IHI projects. An analysis by Bakker *et al.*[p17] of the EMA's biomarker qualification process from 2008 to 2020 showed that an increasing number of applications were submitted by consortia. In addition to DHTs for diseases of the nervous system, DHTs were frequently proposed for endocrine, nutritional or metabolic diseases (n = 25), such as diabetes mellitus (n = 11) and mucopolysaccharidosis (n = 5). The use of CGM devices in diabetes is expected, as this practice is encouraged by the EMA. Their draft guideline on diabetes treatments recommends that these DHTs should be incorporated into clinical trials for diabetes.[p18] Furthermore, CGM results have previously been approved for inclusion in the summary of product characteristics for insulin therapies.[p19] Notably, DHTs were also proposed for endpoint measurement in rare diseases, including DMD (n = 6), HD (n = 6) and mucopolysaccharidosis (n = 5). Due to the low prevalence of rare diseases, patient recruitment for clinical trials is often limited. DHTs pose a viable option for decentralized patient recruitment into clinical trials for rare diseases while providing objective continuous measurements. This is a welcome opportunity for clinical trials for rare diseases, which often face difficulties in demonstrating treatment effect because of a lack of objective measurements and the small patient numbers.[p20],[p21]

DHTs proposed primarily for efficacy endpoints

The DHTs proposed within the SAs were focused on the measurement of efficacy endpoints (n = 62), mainly secondary endpoints (n = 29), followed by tertiary or exploratory outcome measures (n = 22) and primary endpoints (n = 11). In a minority of the SAs, the DHT was proposed to measure a safety endpoint (n = 6). In addition, in 13 cases, the applicant did not specify the type of endpoint for which the DHT would be utilized. No clear distinction was observed between the types of DHTs proposed for different endpoints; similar technologies were suggested across varying endpoint types. DHTs were proposed for multiple study phases within a single advice, most often to measure endpoints during phase 2 and phase 3 trials.

Questions posed by applicants, and issues and concerns raised by the Committee for Medicinal Products for Human Use

The inductive thematic analysis resulted in four main topics for questions: device specifications, digital endpoints, clinical trials, and other (Figure 2). Interestingly, despite the regulatory oversight provided by notified bodies for medical device approval, applicants still raised questions about device conformity. This underscores the need for further guidance in this area, as evidenced by the recent EMA pilot program focused on orphan medical devices.[p22] This initiative highlights an ongoing demand for regulatory advice and support surrounding medical devices.

When reviewing the main recommendations from the Committee for Medicinal Products for Human Use (CHMP) provided in the SAs, QAs and QOs, most were found to align with the categories identified by Dekker *et al.*,[p10] including (i) the relevance of the (novel) outcome measure for the disease; (ii) validation of the novel outcome measure; (iii) analytical performance parameters such as precision, accuracy, sensitivity, and specificity of the novel endpoint; (iv) strategies for ensuring patient compliance and handling of missing values; (v) appropriateness of the sampling interval; and (vi) procedures for data handling, accessibility, and privacy.[p10]

In our analysis of the advices issued between 2020 and 2022, we identified additional considerations beyond these topics (Table 1). A recurring issue raised by the CHMP with regard to DHTs was the lack of alignment between the proposed use of a DHT and its defined context of use, which serves as a critical reference point for evaluating the scientific justification and regulatory acceptability of a device. The context of use should therefore be clearly discussed as early as possible in the qualification procedure. Another important aspect for acceptance of DHT-derived endpoints, particularly for novel outcome measures, was their added value over existing disease outcome measures. Clarity regarding how the digital measurement enhances the drug development process plays an important role determining in whether the DHT is accepted as a replacement for an established outcome or as a complementary tool. The CHMP emphasized the importance of first evaluating digital biomarkers within a single, well-defined disease context before considering their use across multiple conditions. Such evaluations ensure the validity and relevance of the biomarkers by assessing their performance in each disease,

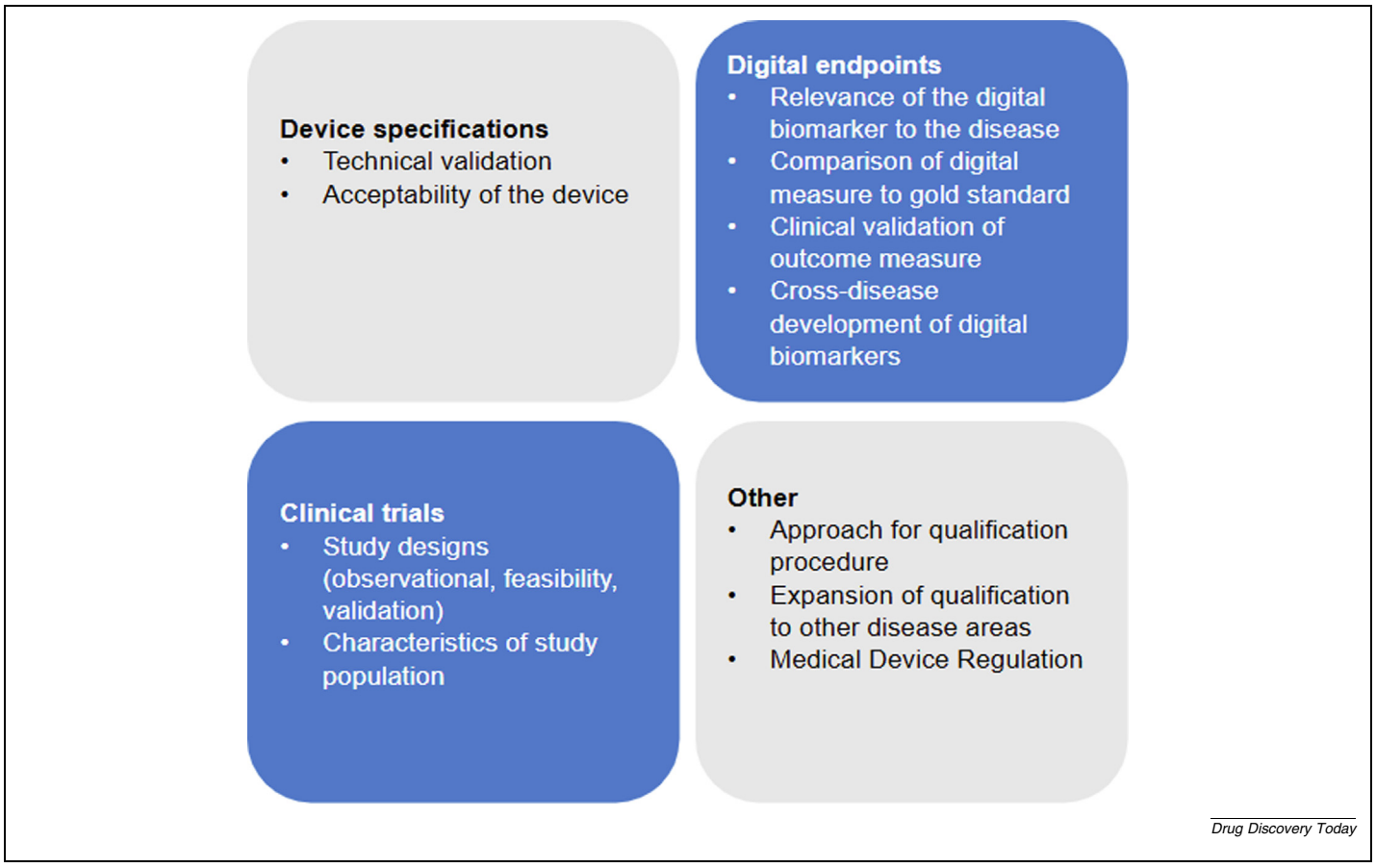

FIGURE 2

Types of questions posed by applicants in advices issued between 2020 and 2022 (n = 35). The questions were categorized into four main topics: device specifications, digital endpoints, clinical trials, and other.

although from an efficiency perspective, it is vitally important that an extrapolation pathway across different diseases is agreed early in the development process. Disease-specific evaluations also determine the suitability and reliability of digital biomarkers as measures of disease progression, treatment response, and other outcomes. Moreover, they provide valuable insights into the potential impact of digital biomarkers on patient care and outcomes within the specific context of each disease. In line with the objective of implementing a patient-centric approach in drug development processes, the CHMP also frequently raised their concerns about the burden imposed on patients during clinical trials with a DHT. In addition, caution was advised when dealing with diverse patient populations, such as patients who have differing disease courses, different levels of disability, differing ages, when extrapolating data to another population. From a broader perspective, the CHMP tailors its response in advices to the questions posed by the applicants. A comprehensive and well-supported question is more likely to elicit an extensive response. Consequently, applicants are strongly encouraged to submit a thorough briefing document, including relevant sources, to provide as comprehensive a context as possible.

Concluding remarks

Our review consolidates data on the use of DHTs for endpoint measurement in recent EMA advice procedures from 2013 and 2022, expanding upon the findings of the study by Dekker *et al.*.[p10] Although no clear association was observed between the number of regulatory advices relevant to DHTs and the COVID-19 pandemic, there was a notable rise in the development of DHTs for endpoint measurement over the study period, as evidenced by the increase in QAs related to DHTs. It is important to highlight that qualification is a voluntary process and not a prerequisite for the use of DHTs in clinical trials. Thus, the absence of qualification does not preclude the possibility that additional DHTs were deployed in clinical trials during the pandemic.

This study provides just a small glimpse into the broader landscape of DHT development. For instance, the Digital Medicine Society (DiMe) curates a Digital Endpoint Library, which focuses on industry-sponsored studies on new medicinal products and applications.[p23] DiMe has also introduced a framework designed to guide the development of meaningful digital measures, providing valuable tools for developers who are working on these innovations.[p24] The EMA recently released an action plan to future-proof the qualification process for novel methodologies.[p25] Key initiatives include publishing methodology-specific Q&A documents, updating existing guidance (such as the Q&A on the qualification of digital technology-based methodologies to support the approval of medicinal prod-

TABLE 1

Overview of Committee for Medicinal Products for Human Use (CHMP) considerations mentioned in the advices issued between 2020 and 2022, in addition to the recommendations described in Dekker *et al*.[p10]

Category	Main considerations	Quotes
Device characteristics	Device agnostics should be taken into account	"Regarding the qualification of different sensors, a device agnostic approach is in principle appreciated and it is noted that the algorithms [X] and [Y] have been designed to be device agnostic with some appropriate pre-processing steps applied to raw signals."
	Equivalence between software versions should be ensured	"The presented data equivalence testing is not considered to provide confirmatory evidence of data equivalence from version 1 and version 2 of the [application] . . . It is considered that variation in results from one version to the other could be attributable to failure to replicate the test in the same manner. The applicant should clarify the rationale for conducting testing one after the other."
	Risk control measures should be defined and documented	"Risk control measures should be defined and documented to ensure no impact on the app's essential performance characteristics, i.e. data capture and processing capability. The software validation report does not consider other risks/harms associated with software bugs, hardware issues, Wi-Fi etc. nor reflect any harms due to change in version."
Digital endpoints	The context of use should be well defined	"The proposed context of use (CoU) is very broad and use of the new tools is not limited to a specific clinical development phase or study design. . .. It was discussed that refinement of the CoU and validation steps in addition to the proposed first validation study are envisaged."
	Caution should be taken when extrapolating data derived from healthy volunteers to patients	" . . . use of algorithms developed in healthy volunteers that derive data for physical activity levels can be suitable in [condition] patients. This is considering that the validation study is exploratory and that, from the perspective of physics of raw data generation and processing of these data, the application in healthy volunteers and [condition] patients would be similar. However, it is currently unclear if the proposed thresholds for the endpoints can be transferred from healthy volunteers to patients with [condition] to achieve a sensitive measure."
	Added value of digitally derived measures in addition to what is currently captured using accepted outcomes should be defined	"The value of the additional disease aspect(s) measured by the [device] in addition to what is currently captured using accepted outcomes should be clarified further."
	It is preferable to first develop and validate the digital biomarker in one, well-defined and not too heterogeneous condition	"However, the rationale for and the feasibility to (right from the start) develop and validate a cross-disease biomarker was questioned. It was believed that a better approach could be to first develop and validate the biomarker in one, well-defined and not too heterogeneous condition."
	The impact of confounding variables needs to be cautiously recorded and be accounted for in the analysis of digital endpoints	"It is also noted that measures will be influenced by the use of concurrent treatment of [symptom 1] and [symptom 2] (including OTC products, emollients or medicinal products otherwise interfering with [symtom1/symptom2]). These would therefore need to be cautiously recorded and be accounted for in the analysis of this endpoint, and their potential impact should also be taken into account during the validation exercises."
Clinical trials	The study population should include a sufficient number of patients of different disease courses and levels of disability as well as different age groups	"However, as the app is expected to be suitable for all [disease] subtypes, the applicant should include a sufficient number of patients of different disease courses and levels of disability . . . the applicant is encouraged to include children in an early development stage and patients from different centres."
	The effect of the device on the patients daily functioning should be documented as well as the guarantee of safety of study participants	"The (clinical) relevance and meaningfulness to patients of changes in the test performances need to be established, i.e., how changes in test performance translate into an effect on daily functioning and/or disability would have to be shown. This is specifically relevant for domains covered by app challenges for which no generally accepted

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TABLE 1 (*CONTINUED*)

Category	Main considerations	Quotes
		endpoint is currently available or a minimal clinically important difference is not unambiguously established."
		"Safety of the study participants needs to be guaranteed: for this exercise capacity test, a nearby physician needs to be available in case safety issues occur, which is not unlikely for this in part severely ill and vulnerable study population."
Other	Recommendation for seeking qualification advice	"The CHMP recommends the applicant to apply for qualification for the digital measures of motor function as endpoints in [disease area]."
		"The CHMP recommends the applicant to seek qualification advice regarding the device."
	Expansion of qualification to other disease areas	"The CHMP sees potential for [endpoint] to be used as a secondary endpoint in other neuro diseases as the measurement properties can also be observed in those cases. However, as the diseases mentioned are heterogenous, the sensitivity to change must be determined separately for each condition."
	Medical device regulation	"The applicant may apply for the inclusion of drug effects on [device] measures in the drug labelling, which may then motivate decisions by health care providers. Since such a scenario is not considered unlikely, it is, therefore, recommended to consider [device] and derived measures, respectively, as medical devices (or software)."

ucts), and providing targeted training for methodology developers who may be less experienced in regulatory engagement. These efforts underscore the EMA's commitment to advancing and supporting the qualification of novel methodologies, including DHTs. Such initiatives reflect the observations of Colloud *et al.*,[p26] who highlighted the challenges of regulating DHTs that fall within the scope of both medical device and medicinal product regulations in the European Union.

To conclude, although we observed no clear association between the frequency of regulatory advice regarding DHTs and the COVID-19 pandemic, there was a notable increase in the development and consideration of DHTs during this period, particularly as reflected in a rise in QA submissions. These efforts represent a significant stride toward unlocking the full potential of DHTs, advancing their qualification, and ultimately enabling their broader adoption to capture patient outcomes. The rapid evolution of this field will require ongoing collaboration and engagement among stakeholders to ensure the robust and meaningful development of DHTs for years to come.

Author contributions

KJ: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. HG: Investigation, Writing – review & editing. PM: Investigation, Supervision, Writing – review & editing. AP: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

Competing interests

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.drudis.2025.104388.

Data availability

The data that support the findings are available from EMA. However SAs and QAs are confidential. For further information or access to specific documents, please contact the corresponding author.

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