Digitalisation in Clinical Trials

trends in connected sensor technology use

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Contents

Abstract

Objective. Connected sensor technologies are remote measurement technologies that offer an objective measure of patients' certain symptoms in their daily routine. Although there is an interest in implementing these technologies into clinical trials, adoption has been slow. Currently, there is no complete overview of connected sensor technology use for clinical drug development, analyzing the studies by the technology, year, study phase, endpoint positioning, and disease area. This overview can provide insight into the effects of different events and serve as a basis for future analysis.

Methods. Studies were selected from 2 sources: the DiMe Library of Digital Endpoints and literature indexed in PubMed. Studies in DiMe Library in which product type was indicated as "drug" or "biologic" were included. A search query was developed, and the resulting articles were screened by their titles, abstracts, and text according to the inclusion criteria. Data regarding study registry year, connected sensor technology, digital clinical measure, the indication of the test drug, study phase, and endpoint positioning was extracted, and trends were compared in aggregate and over time.

Results. 71 studies were identified, 63 from the DiMe library, and 8 from the literature review. Activity monitors were the most used devices (71.8%) and were the only devices observed in 2005-2014. The next most used devices were continuous glucose monitors (14.1%) and heart activity monitors (5.6%). Interest in phase 4 studies in 2015-17 was observed to shift towards phase 2 studies, the most common study phase (36.6%). More than half of the studies used connected sensor technologies to support secondary endpoints (56.3%). The most commonly addressed disease group was diseases of the nervous system (19.7%), followed by diseases of the respiratory system (18.3%), endocrine diseases (14.1%), and diseases of the circulatory system (12.8%). Most of the indicated conditions required long-term disease management.

Conclusion. The use of connected sensor technologies in clinical trials was already an ongoing process for a long time. We conclude that multiple factors are contributing to increasing interest. Major factors are increased regulatory guidance and acceptance and acceleration by the COVID-19 pandemic. In the coming years, a growing interest is expected in digital measures that offer objective measurement of established endpoints, increasing the knowledge and regulatory maturity in the domain. Once the quality standards and acceptance by all the industry stakeholders are established, a steep increase in innovative digital endpoints may be observed.

Layman's Summary

Clinical trials are part of the drug development process, where the drug is tested for efficacy and safety in humans. Once all the required steps in clinical trials are successfully completed, an application to the health authorities is filed to bring the drug to the patients. Traditionally, patients who participate in a clinical trial are carefully chosen, and the tests related to the clinical trial are carried out in highly controlled clinical trial environments to ensure validity and objectivity. However, there are some unwanted effects such as difficulty representing real-life situations where patients are more diverse and may have multiple diseases, and difficulty finding enough patients willing to travel to the clinical trial site as often as required. Currently, connected sensor technologies are receiving a lot of attention from companies, health authorities, healthcare providers, and patients as a possible solution to these problems.

Connected sensor technologies (CSTs) are devices that patients can use on their own, to monitor some of their symptoms. Continuously collected information enables healthcare providers to compare the disease/recovery progression of a patient. For example, a patient who recently had knee surgery is expected to be more active over time, wrist-worn activity monitors (similar to smartwatches) can be used to monitor the patient's mobility instead of the patients visiting the clinic for a mobility assessment. Connected sensor technologies enable more accurate measurement and decrease the burden of visiting the clinic.

Although CSTs are very promising, it is an emerging technology, and their implementation into clinical trials stays limited. Collaboration of technology developers, healthcare providers, companies, and health authorities is crucial to improving CSTs. Currently, it is not possible to find a complete overview of which CSTs were successfully implemented in clinical trials and what was measured with the device. This information is submitted to the health authorities by the companies. However, the information stays confidential, making it difficult to understand the current status of CSTs.

Currently, the DiMe Library of Digital Endpoints provides the most detailed publicly available information. The presented information is submitted by companies voluntarily. Therefore, the library offers mostly industry-sponsored studies. It is important to keep in mind that companies do not share all the clinical trials that may be relevant due to confidentiality. Lastly, the library does not contain information regarding any eligible clinical trial that may have been published as an article.

In order to provide a broader overview of CSTs use, we analyzed the studies in the Library and carried out systematic research to identify published studies that used CSTs for drug assessment. In total, 71 studies were found, 63 from the library, 8 from the article research. We observed slow and steady adoption starting from 2005 and a sudden increase in 2020-21. Overall, the most used CST was activity monitors (71,8%), used to measure patients' daily activity

and sleep. We identified two main factors in steady adoption: technology becoming cheaper and increased familiarity and use of technology in our daily lives. We identified two more factors that may have contributed to the increase in the last years: increased guidance and acceptance by health authorities and the COVID-19 pandemic.

We conclude that CSTs are valuable technologies in improving clinical trials and will be used increasingly in the coming years. Once the CSTs become more commonly used, we expect to see new ways to measure the progress of diseases that are currently not possible. Further research into other databases such as clinicaltrials.gov can contribute to this research to create an even broader view into CST use.

Introduction

Clinical trials are an essential part of drug development as they ensure the efficacy and safety of drugs before the drug reaches the market. Traditionally, randomized clinical trials (RCT) are the gold standard where only carefully selected patients are enrolled. During an RCT, all the clinical measures are preferably carried out in highly controlled environments at clinical trial sites to ensure validity and objectivity. However, various limitations hamper the conduct of RCTs. These include difficulty recruiting suitable patients, failing to provide information on safety and efficacy in the real population due to homogenous patient group selection, and lack of objective measurement methods for diseases. An increase in innovations and accessibility to new technologies during the past years provide new options to overcome some of these limitations and, as such, help minimize the gap between clinical trials and clinical care[1; 2].

One technological advancement that gathers attention is connected sensor technologies (CSTs) that process data captured by the mobile sensor using algorithms to generate behavioral and/or physiological function measures. CSTs offer objective, continuous, and non-invasive measurement options that reflect the patients' functions, symptoms, and behaviors in their day-to-day lives, in contrast to episodic and periodic measures at the trial site as is current practice. It is to be expected that these new technologies can provide the information needed for health authorities and companies to make better-informed decisions. Additionally, these technologies enable remote measurements and decrease the need for patients to visit the clinical trial site, making clinical trials more accessible and patient-focused [2; 3].

Although CSTs are not new, their implementation in clinical trials stays limited [4; 5]. Some of the main barriers in adoption are poor interdisciplinary collaboration in developing CSTs and digital endpoints, poor collaboration across countries on standardization of terminology and regulatory requirements, risk-averse nature of the pharmaceutical companies and healthcare practitioners, and data processing issues (data access, transfer, analysis, interpretation, etc.). Fortunately, there are many work streams, bringing companies, regulatory bodies, and other stakeholders together to improve the landscape and accelerate the adoption of CSTs[6]. One of the critical initiatives is the Digital Medicine Society (DiMe), working on improving collaboration and standardization in digital medicine. DiMe published The Playbook, offering standard definitions and a guide for successfully developing and deploying CSTs[7]. DiMe also started the Library of Digital Endpoints, a crowdsourced library, to overcome the lack of publicly accessible knowledge on which digital endpoints were successfully used in clinical trials[8]. Clinical Trials Transformation Initiative (CTTI) is another important initiative, offering a database compiling all the published CST feasibility studies to minimize the duplication of efforts in CST development[6; 9].

However useful, these initiatives reflect a fragmented landscape, where one must collect different information across different databases and websites to obtain a complete picture. Today, it is not possible to find comprehensive information on which CSTs have been

successfully implemented in clinical trials and the frequency, other than the Library of Digital Endpoints. Although this information is submitted to the regulatory authorities, most of the time, it stays confidential. DiMe library was launched to address this problem. However, the library focuses primarily on industry-funded clinical trials and does not contain information from other possible resources such as peer-reviewed articles. Additionally, contributing companies submit the data on a voluntary basis; hence, not all the trials carried out by a contributing company are indexed in the library. To our knowledge, there is also no literature review compiling peer-reviewed articles on clinical trials utilizing CSTs to assess the safety or efficacy of a drug. Bringing data from the literature and the Library of Digital Endpoints together enables a broader overview of CST use. This information can be used to visualize trends in CST adoption and assess the effects of past and future events on the landscape.

In this review paper, we aim to provide a broader overview of trends in CST use in clinical trials. To achieve this, we will identify studies that utilize CSTs in clinical drug development from January 2014 to December 2021 indexed in PubMed and the Library of Digital Endpoints. Data from selected studies and library entries will be analyzed to reveal trends in CST use, digital clinical measure, indication of the trial drug, study phase, and endpoint positioning in aggregate and by years.

Methods

The primary aim of this study was to provide a holistic view into types of CSTs used in clinical trials of new medicinal products or new applications of existing medicinal products. We used two different data sources, the DiMe Library of Digital Endpoints, and evidence from a systematic review of peer-reviewed articles indexed in PubMed. The information about the type of devices used, digital clinical measure, endpoint placement, and study phase was extracted from qualified studies. Data were analyzed for general trends and trends over time to present a broad overview of the landscape.

Data Sources

DiMe Database

Digital Medicine Society (DiMe), founded in 2019, is a non-profit organization convening experts from all disciplines comprising digital medicine and has been recognized as one of the most critical efforts [10]. DiMe aims to address three main challenges in digital medicine: lack of evidence, fragmentation and lack of alignment, and isolated silos of progress. One of their essential accomplishments is "The Playbook: The essential guide to digital clinical measures," offering standardization in nomenclature and describing how to develop and deploy CSTs effectively, which we base the foundations of our research on[7]. DiMe also launched The Library of Digital Endpoints due to community members expressing that digital endpoints used in clinical trials are one of the least transparent areas. The library focuses on industry-sponsored clinical studies using connected sensor technologies in assessment of new medical products or new applications of existing medical products. Inclusion and exclusion criteria for connected sensor technologies were defined as: collects clinical or health data, has a software component, has a biometric sensor, data is remotely collected, connected to the internet or other technology, and used by the patient (**Supplementary Material 1**)[7]. Data is entered by the 69 sponsors, voluntarily. The following data points are collected: listing data of the study, study phase, endpoint positioning (exploratory, primary, secondary), endpoint, technology type, health concepts, digital clinical measure, indication, sponsor, product type (drug, biologic, device, other), technology manufacturer, analytics company, patient-reported outcomes, clinicaltrials.org URL, sponsor and/or PI contact, and publications. On 17 November 2021, the library contained 225 digital endpoints from 101 clinical trials, and the oldest entered clinical trial was first registered to clinicaltrials.gov in 2005[8].

Systemic Literature Review

A systematic literature review was performed on 17 November 2021 to identify clinical trials that utilize CSTs for remote measurement that were indexed in PubMed. A search string was developed to identify all peer-reviewed literature describing a clinical trial using a connected sensor technology, published between 1 January 2005 – 17 November 2021, resulting in 447 results (**Table 1**). This time frame was selected due to the oldest entry in the DiMe library being from 2005.

Table 1. Search string used in PubMed.

Search string:
(("sleep" OR "activity" OR "locomotion" OR "scratching" OR "blood" Or "heart" OR "wrist" OR "skin" OR "adhere") AND ("wearable" OR "patch" OR "tracker" OR "digital" OR "smart" OR "sensor" OR "camera" OR "accelerometer" OR "actigraphy" OR "gyroscope" OR "mobile" OR " continuous") AND ("track" OR "measure" OR "monitor" OR "detect")) AND ((clinicaltrial[Filter]))) Filters: Clinical Trial, from 2005 - 2021

Articles were included based on the following inclusion criteria: data was collected from human participants, the study was designed to test a drug (efficacy, side effects, safety), at least one connected sensor technology was used for remote measurement. DiMe Library's criteria of connected sensor technologies were used to assess the articles (**Supplementary Material 1**). Studies were excluded if the study was conducted only to test and compare one or multiple devices.

Data Extraction

Once eligible studies were selected from the DiMe library, information regarding clinicaltrials.gov registry year, indication for the drug under investigation, study phase, technology type, digital clinical measure, and endpoint positioning was collected on excel.

Initially, the article title and PubMed search result number were downloaded to carry out the article selection. This information was retained to ease the data extraction and analysis. Articles were selected according to the pre-defined inclusion/exclusion criteria. The same information as the DiMe library was extracted from the selected papers (**Table 2**). If a clinicaltrials.gov registry number was available in an article, this was compared to the DiMe library to avoid duplication. The first entry year was recorded if the registry was available in clinicaltrials.gov or any other platform. If this information was not available, the publication year was recorded. Similarly, if trial phase or endpoint positioning was not available, the absence was recorded. If a study was classified as phase 1-2, this was accepted as a phase 2 study.

Table 2. Data fields extracted from DiMe library entries and selected articles.

Variable	DiMe Library	Literature review
Article title	N/A	X
Search result number	N/A	X
Clinical trial year	X	X (If not available, publication year)
Indication	X	X
Clinical trial phase	X	X
Connected sensor technology	X	X
Digital clinical measure	X	X
Endpoint positioning	X	X

Outcome

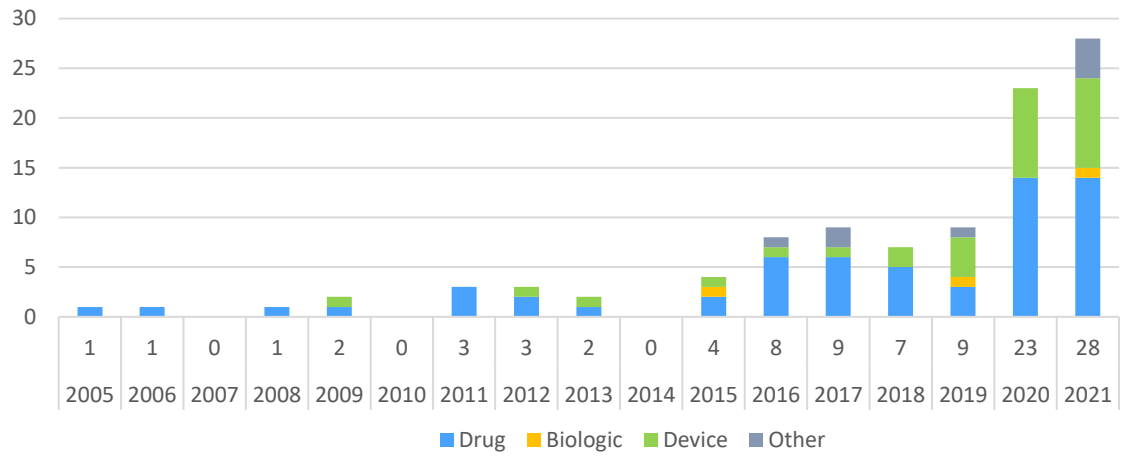
This study aimed to provide an overview of CST implementation in clinical trials for drug development. Extracted indications were grouped according to ICD-11[11]. Data were analyzed for general trends such as most implemented devices, overall preferences toward trial phase, endpoint positioning, and disease areas. Later, the data regarding CST type, clinical trial phase, endpoint positioning was compared by registry year of the studies.

Results

Library of Digital Endpoints

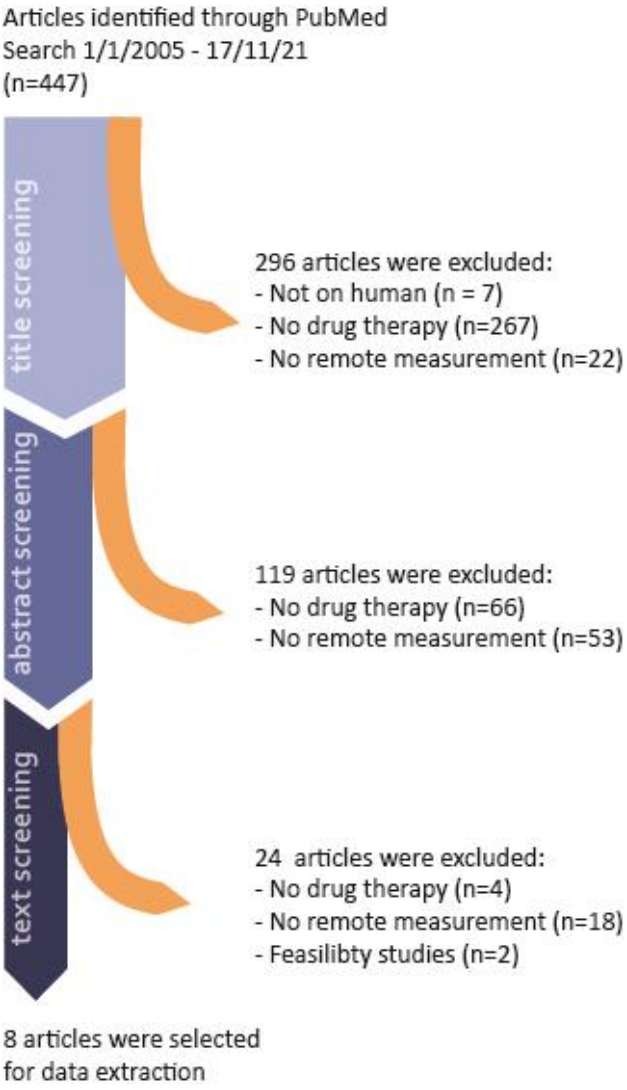
Out of 101 clinical trial entries in the Library of Digital Endpoints, 38 clinical trial entries were excluded due to product type recorded as “device” (n=30) or “other” (n=6). 65 remaining entries were marked as “drug” (n=60) or “biologic” (n=5). Despite being categorized as “biologic” for the product type, trial phases of two studies were classified as N/A. Upon further inspection, it was seen that both studies were registered in clinicaltrials.gov as dietary supplements. Therefore, these two studies were also excluded, leaving 63 studies for analysis. Indexed studies dated back to 2005, most of the recorded studies were registered after 2014, with a significant increase in 2020 and 2021 (**Figure 1**). Detailed information (used CST, study phase, indication, registry year) per study is given in **Supplementary Material 2**.

Figure 1. Studies registered in the Library of Digital Endpoints. Studies are shown by year and product type. The total number of studies in each year is given above the year.



Literature Review

Figure 2. Meta-analysis flow diagram



The initial search retrieved 447 articles. More than half of the articles (n=296) were eliminated in the title screening due to the study not being on human subjects (n=7), lack of drug therapy (n=267), or lack of a CST (n=22). 79% of the remaining articles were excluded in abstract screening due to lack of drug therapy (n=66) or a CST (n=53). The remaining 32 of the articles were screened further, 24 articles were excluded due to lack of drug therapy (n=4), or a CST(n=16), and being a feasibility study (n=2), leaving 8 articles for data extraction (**Figure 2**)[12-19]. Among the articles excluded due to lack of drug therapy, some included different interventions such as meditation, physiotherapy, online coaching, and supplements. Studies excluded due to lack of a CST included devices that were only used in clinic settings, or some were using only patient-reported outcomes to motivate their results. The studies excluded as feasibility studies included both CST and drug therapy; however, these studies were designed to compare devices and were not meant to assess the drug therapy. Selected studies were from the period of 2007-2018. Only 2 of the trials indicated the clinical trial phase, one was phase 3, and one was both phase 1 and 2, which was recorded as phase 2. Three of the trials used CSTs to support primary endpoints and one supporting secondary endpoint, whereas 4 of the studies did not indicate endpoint positioning (**Table 3**). Detailed information (measurement device, study phase, indication, registry year) per study can be found in **Supplementary Material 3**.

Connected sensor technologies

Library of Digital Endpoints revealed 13 CST types, and the literature review revealed 5 CST types, 2 of which were not used in the studies indexed in the DiMe library, holter, and MEMS (medication event management system) cap. The most used technology in both sources was activity monitors (71,8%), followed by continuous glucose monitors (14.1%) and heart activity monitors (5.6%). Both the library (n=1) and the article review (n=1) revealed studies that used accelerometers (**Supplementary Material 2-3**). These were grouped with activity monitors as accelerometers are used for measuring activity. Activity monitors also contain accelerometers, among other sensors. Similarly, MEMs cap and ingestible sensor were grouped in adherence monitors; ECG, holter, and heart rate monitor were grouped under heart activity monitor. Other CSTs indexed in the DiMe library included chest contact sensor, pulse oximeter, thermometer, camera, electrodermal activity sensor, home spirometer, and microphone.

Most studies were phase 2 (36.6%) studies, and digital endpoints were mostly positioned as secondary endpoints (56.3%). In total, 15 main categories from ICD-11 were addressed. Diseases of the nervous system were the most common indications (19.7%), followed by diseases of the respiratory system (18.3%) and endocrine diseases (14.1%) (**Table 3**). Some CSTs were used to measure different parameters, such as activity monitors measuring sleep-wake hours and/or daily activity, holter being used for measuring blood pressure, heart rate, and electrocardiogram. All the CSTs and their use-cases are given in **Table 4**.

Table 3. Connected sensor technologies identified from DiMe and the scientific literature.

	Variables	**All** 71 Studies	**DiMe** 63 studies (88,7%)	**Literature review** 8 studies (11.3%)
Connected sensor technology	Activity monitor	51 | 71.8%	46 | 73.0%	5 | 62.5%
	Adherence monitor	2 | 2.8%	1 | 1.6%	1 | 12.5%
	Camera	1 | 1.4%	1 | 1.6%	
	Chest contact sensor	3 | 4.2%	3 | 4.8%	
	Continuous glucose monitor	10 | 14.1%	9 | 14.3%	1 | 12.5%
	Electrodermal activity sensor	1 | 1.4%	1 | 1.6%	
	Heart activity monitor	4 | 5.6%	3 | 4.8%	1 | 12.5%
	Home spirometer	1 | 1.4%	1 | 1.6%	
	Microphone	1 | 1.4%	1 | 1.6%	
	Pulse Oximeter	2 | 2.8%	2 | 3.2%	
	Thermometer	2 | 2.8%	2 | 3.2%	
Clinical trial phase	Phase 1	5 | 7.0%	5 | 7.9%	
	Phase 2	26 | 36.6%	25 | 39.7%	1 | 12.5%
	Phase 3	15 | 21.1%	14 | 22.2%	1 | 12.5%
	Phase 4	19 | 26.8%	19 | 30.2%	
	N/A	6 | 8.5%		6 | 75.0%

Table 3. (Continued).

	Variables	All 71 Studies	DiMe 63 studies (88,7%)	Literature review 8 studies (11.3%)
Endpoint positioning	Primary endpoint	16| 22.5%	13 | 20.6%	3 | 37.5%
	Secondary endpoint	40 | 56.3%	39 | 61.9%	1 | 12.5%
	Primary & secondary endpoint	8 | 11.4%	8 | 12.7%	
	Exploratory endpoint	3 | 4.2%	3 | 4.8%	
	N/A	4 | 5.6%		4 | 50.0%
Indication Class (ICD-11)[1]	Certain infectious or parasitic diseases	2 | 2.8%	1 | 1.6%	1 | 12.5%
	Development anomalies	1 | 1.4%	1 | 1.6%	
	Diseases of the blood or blood-forming organs	1 | 1.4%	1 | 1.6%	
	Diseases of the circulatory system	9 | 12.8%	8 | 12.6%	1 | 12.5%
	Diseases of the digestive system	1 | 1.4%	1 | 1.6%	
	Diseases of the genitourinary system	1 | 1.4%	1 | 1.6%	
	Diseases of the musculoskeletal system or connective tissue	3 | 4.2%	2 | 3.2%	1 | 12.5%
	Diseases of the nervous system	14 | 19.7%	13 | 20.6%	1 | 12.5%
	Diseases of the respiratory system	13 | 18.3%	13 | 20.6%	
	Diseases of the skin	3 | 4.2%	2 | 3.2%	1 | 12.5%
	Diseases of the visual system	1 | 1.4%	1 | 1.6%	
	Endocrine diseases	10 | 14.1%	9 | 14.3%	1 | 12.5%
	Mental, behavioral or neurodevelopmental disorders	4 | 5.6%	2 | 3.2%	2 | 25.0%
	Neoplasms	1 | 1.4%	1 | 1.6%	
	Sleep-wake disorders	7 | 9.9%	7 | 11.1%	

[1] Certain infectious or parasitic diseases: HIV, COVID-19; Development anomalies: Rett syndrome; diseases of the blood or blood-forming organs: sickle cell anemia; diseases of the circulatory system: chronic stable angina, heart failure, atrial fibrillation; diseases of the digestive system: reflux; diseases of the genitourinary system: menopause; diseases of the musculoskeletal system or connective tissue: osteoarthritis; diseases of the nervous system: Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington disease; diseases of the respiratory system: pulmonary arterial hypertension, asthma, chronic cough, cystic fibrosis, chronic obstructive pulmonary disease; diseases of the skin: atopic dermatitis; diseases of the visual system: blepharospasm; endocrine diseases: type 1 and type 2 diabetes mellitus; mental, behavioral or neurodevelopmental disorders: major depressive disorder; neoplasms: cachexia in lung and pancreas cancer; sleep-wake disorders: insomnia, sleep disturbance, restless leg syndrome

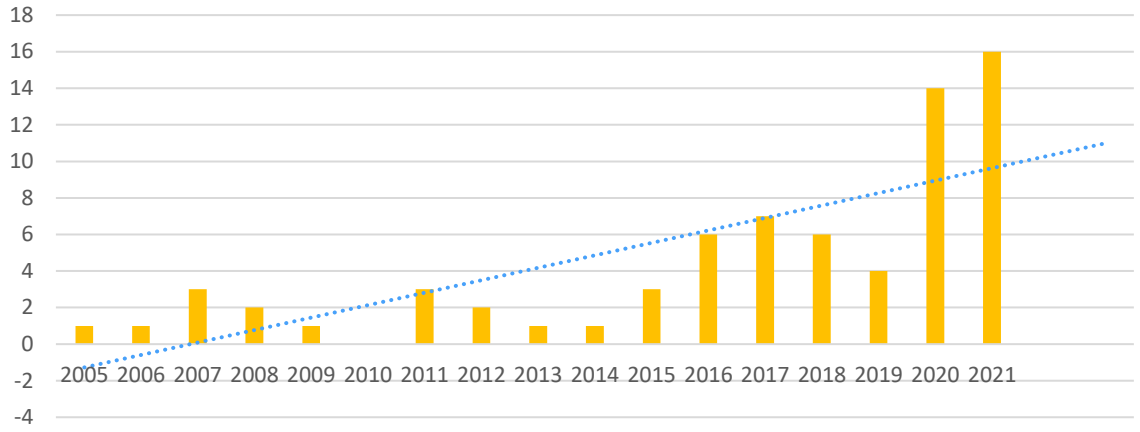
Table 4. Indexed digital measurements per device.

Device	Digital Measure
Activity monitor	Activity count, sleep measures, tremor
Electrodermal activity sensor	Seizure activity assessment
Heart rate monitor	Heart rate variability
Thermometer	Body temperature tracking
Ingestible sensor	Adherence tracking
Chest contact sensor	Cough count
Home spirometer	Lung function test
Microphone	Voice biomarkers for Alzheimer's disease
Pulse oximeter	Blood oxygenation
Continuous blood glucose monitor	Glucose variability, glycemic variability, mean glucose
Camera	Facial movement
Accelerometer	Tremor rating, activity count
MEMS Cap	Adherence
Holter	Heart rate, blood pressure, electrocardiogram

Implementation of CSTs Over Time

Extracted data were analyzed by year. Increased use of CST was observed starting from 2016, peaking in 2020 (**Figure 3**). Studies carried out in 2005-2015 (n=12) indexed in DiMe library and studies carried out in 2007-2014 (n=5) obtained from the literature review were only utilizing activity monitors. Activity monitors were used for tracking the status of various diseases/conditions that influence daily movement and sleep quality or cause involuntary movement such as post-operative recovery, atopic dermatitis, and Parkinson's disease, consecutively (**Supplementary Material 2-3**).

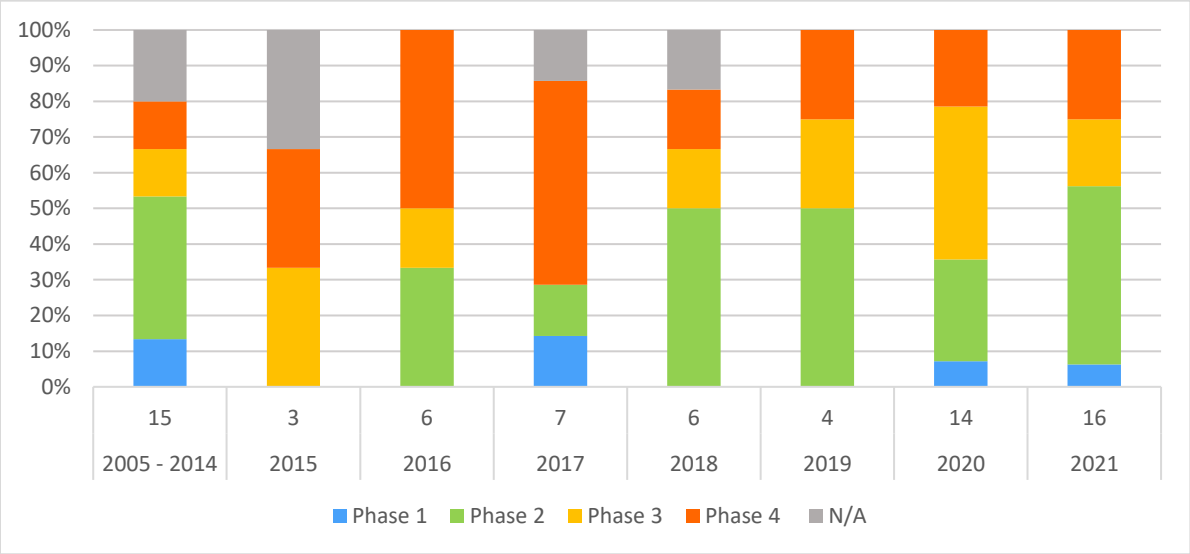
Figure 3. Number of clinical trials utilizing CSTs by years. Reported numbers combine results of literature review and DiMe Library. Linear forecast is given as a blue dotted line.



Between 2016 and 2021, activity monitors were still the most utilized device type (33 studies) recorded in the DiMe library. However, other devices were also implemented in this period, such as continuous glucose monitor (n= 9) for type 1 and type 2 diabetes and chest contact sensor (n=3) for cough count in chronic cough patients. Other utilized devices were electrodermal activity sensor to gather sleep measures in sleep-wake disorders, heart rate monitor for Rett syndrome, thermometer to measure fever in Rett syndrome and COVID-19, ingestible sensor to measure adherence in asthma patients, home spirometer for COPD, microphone to target voice biomarkers in Alzheimer's disease, pulse oximeter for sickle cell anemia and COVID-19, ECG for atrial fibrillation and to follow blinking activity in blepharospasm patients, and camera to track facial movement in Huntington patients (**Supplementary Material 2**). Selected articles revealed similar results where the studies after this period utilized different CSTs (continuous glucose monitor, holter, and Medication Event Management System cap) but earlier than the DiMe library (starting from 2015).

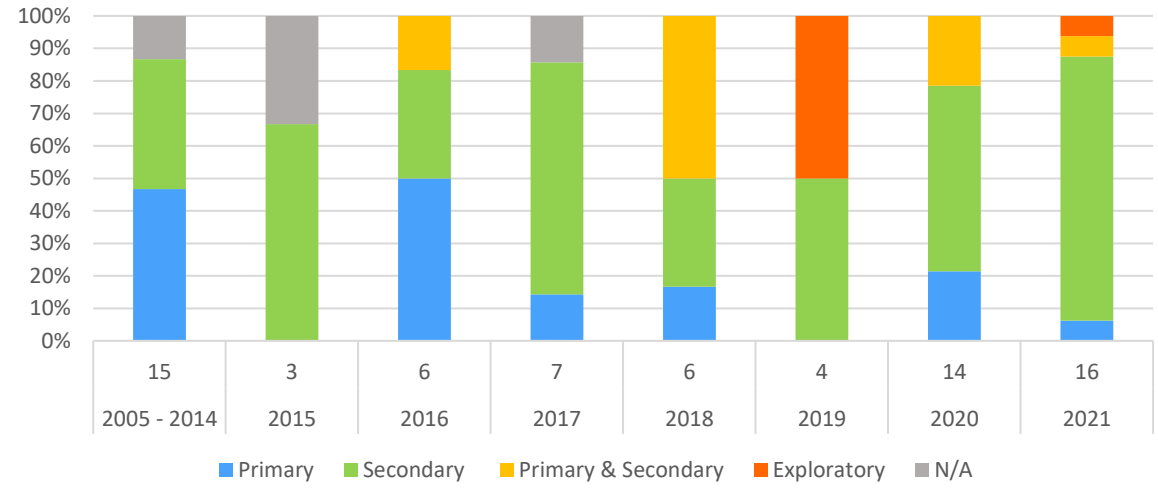
When trends in study phases are considered, a higher interest in phase 1 and 2 studies was observed in the early years (2005-2014) CSTs. In 2015-17, this interest shifted towards phase 4 studies. Starting from 2018, main interest was towards phase 2 studies, which accounts for more than half of the trials overall (**Figure 4**). Information regarding the study phase was missing in the majority of studies identified through the article review.

Figure 4. Trial phases by years. The years 2005-2014 were collapsed due to the low number of trials. The total number of trials per year is given above each year.



When endpoint positioning preferences are considered, a significant interest in primary endpoints is observed in 2005-2014. This interest was observed to shift towards secondary endpoints (except 2016). In 2020-2021, most CSTs were used to support the secondary endpoints (2020: 64.3%, 2021: 81.2%). Some studies used CSTs to support both primary and secondary endpoints **(Figure 5**). Half of the studies retrieved from PubMed did not indicate a clear endpoint positioning in the article.

Figure 5. Endpoint placement of CSTs in clinical trials. The years 2005-2014 were collapsed due to the low number of trials. The total number of trials per year is given above each year.



Discussion

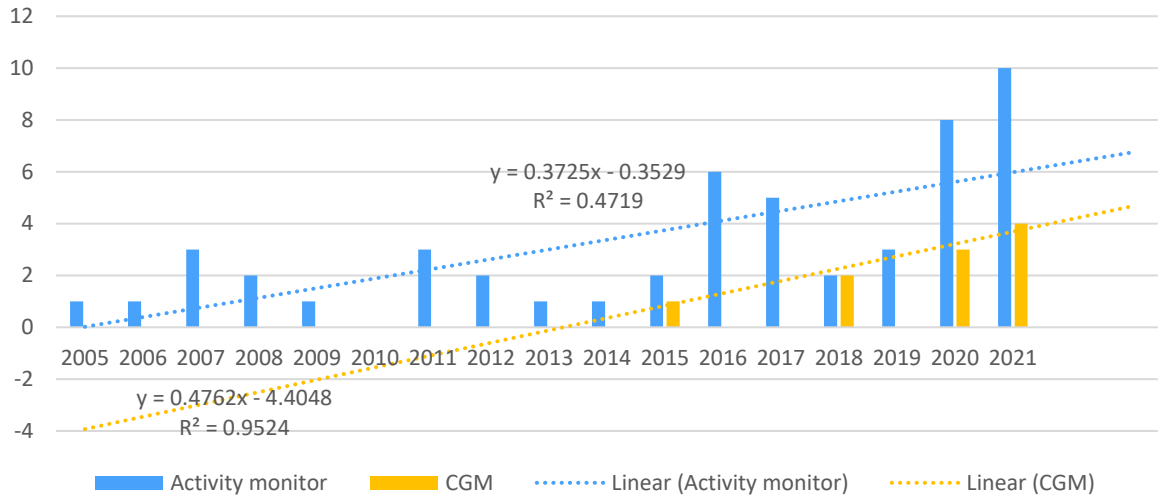
We have analyzed 71 studies, 63 acquired from DiMe Library of Digital Endpoints and 8 from the literature review. Until 2014, the only device used for remote measurement was activity monitors. Although other devices were implemented after 2014, activity monitors (two were specified as accelerometers only) stayed the most implemented technology (69.0%). Studies implementing activity monitors were addressing a wide variety of disease areas such as diseases of the skin, circulatory system, respiratory system, nervous system, and digestive system; musculoskeletal system or connective tissue disease; sleep-wake disorders; behavioral or neurodevelopmental disorders. Most of these diseases, conditions, and symptoms affect mobility and/or sleep quality. Traditionally, these parameters are measured consecutively by 6-minute walk test (6MWT) and in-laboratory polysomnography. 6MWT reflects only a short segment of the patient's life, which may fail to represent patients' daily mobility needs (e.g., going upstairs in their house multiple times a day)[20]. Similarly, in-laboratory polysomnography may not represent patients' sleep problems due to reasons unrelated to their disease/condition, such as sleeping problems due to sleeping in a different place. Implementing in-lab polysomnography test is also very costly. Activity monitors offer non-invasive, continuous data collection on patients' mobility and/or sleep in their daily routine, enabling an objective view into patients' status over a period. They are cheap to implement and patient-focused: enabling remote measurement and measuring meaningful aspects to patients[20; 21].

The next most implemented (14.1%) device was continuous glucose monitors (CGM), enabling diabetes patients to monitor their glucose levels in near-real time without much effort. Traditionally, diabetes patients have to check their glucose levels multiple times a day by pricking their fingers to draw blood and carry out the measurement with a glucose meter. CGMs significantly decrease the need for skin puncturing without compromising the data the patients need. CGMs also helps patients keep their blood glucose levels in the desired range by notifying the patient when blood glucose is too low or too high. Well controlled glucose levels are crucial in decreasing the risk of diabetes-related complications[22]. Although CGMs address an unmet need of diabetes patients, they are still costly and more challenging to use compared to activity monitors, which are the main limiting factors to their wide adoption in healthcare[22; 23]. However, when we look at the trends in the clinical trials, we can see that their implementation is following the trend of activity monitors (**Figure 6**).

Similar to CSTs, some disease categories were addressed more often. When all the indications were classified based on ICD-11, 14 main categories were addressed, from which the most indicated category was diseases of the nervous system (19.7%), followed by respiratory system (18.3%), endocrine (14.1%) and circulatory system diseases(12.8%). Although indicated diseases

seem to be all different, they were all chronic or long-lasting diseases/conditions that require long-term disease management. COVID-19 was an exception, which is primarily an acute viral infection. However, the lockdown requirements made it necessary to monitor patients at their homes. Interestingly, neither of our data sources revealed any study regarding epilepsy where CSTs were available as early as 2010, and by now, there are multiple FDA-cleared devices[24]. This may be stemming from possible competitive advantage or risk averse attitude.

Figure 6. Trends of activity monitor and continuous glucose monitor (CGM) implementation.



When we look further into trends in the trial phase and endpoint placement, we can see an interest in phase 4 studies which shifted towards phase 2 in recent years. Phase 4 studies are carried out after drug approval is achieved to provide further safety information to the regulatory authorities and/or provide further efficacy data to support marketing. Whereas phase 2 is the first time a drug is tried on the patient population to show safety and preliminary efficacy. This shift in interest may be due to more prominent regulatory acceptance and lower patient numbers in phase 2 studies which reduce the implementation costs of the CSTs. It is also observed that digital endpoints are more frequently positioned as secondary endpoints. This may be due to lower trust towards digital measurements and the need to further validate digital measures compared to traditional measures. Proven acceptance from regulatory authorities may lead to more utilization in primary outcomes; however, more research is required to assess this hypothesis.

Although CSTs hold the potential to make clinical trials more patient-focused and offer objective endpoints, their implementation has been slow. A notable trend is observed in 2020-21, which seems to be a sudden increase in CST implementation, accounting for 46.0% of eligible studies indexed in the DiMe library. We believe there are several contributors to this trend. Firstly, some traditional measurements used in clinical trials were not objective enough, but the industry did not have better ways of measurement. As discussed earlier, activity

monitors illustrate this situation clearly, where major to minor sleep disturbances and all the daily activity light to vigorous can be measured in patients' day-to-day lives without causing much inconvenience. More accurate measurement of patient status is key to more precise measurement of drug efficacy [25]. Another main reason is the decreasing costs of CSTs and increasing accessibility of similar devices to the general public, which had been developing slowly for a long time. Nowadays, many people have access to technologies similar to some CSTs (e.g., smartwatches, smartphones), and they are happy to track their wellbeing, increasing the overall trust towards emerging digital technologies. Some examples of what people can commonly measure with their everyday devices are step count, sleep measures (e.g., sleep time, time spent in deep sleep, wake after sleep onset), heart rate measurement, blood oxygen measurement [26]. We believe these two factors were important in creating an attractive landscape that enables successful implementation in the first place, increasing acceptance of CSTs by patients and caregivers. However, these changes were ongoing for a long time, leading to a more subtle and steady increase in the adoption of CSTs. Two important factors may have accelerated the adoption: acceptance by regulatory authorities and the COVID-19 pandemic. Clear interest from FDA with 21st Century Cures Act, signed in December 2016, established interest in patient-focused clinical trials, continued by Digital Health Innovation Action Plan in 2017, solidified by the launch of Digital Health Center of Excellence in 2020 [6; 27]. Although some advancements in the area had previously been made, the COVID-19 pandemic acted as an accelerator, creating an urgent need for remote trials. During this period, both EMA and FDA released temporary guidance documents [27; 28].

On the contrary, the trend of increased implementation in recent years (2020-21) was not observed in the literature review results. In fact, the trend was quite the opposite where more studies using CSTs were identified in 2007 compared to the DiMe library, and no studies were identified after 2018, unlike what we expected. However, we note that most of the identified articles were excluded due to the absence of drug therapy (366 out of 447), suggesting high interest in implementing CSTs to measure the efficacy of other interventions such as meditation and coaching. This difference may stem from different motivations in clinical trials conducted by the industry and academia. Companies try to bring a drug to the market and must carry out clinical studies to complete a submission dossier to the regulatory authorities. Whereas academia is more interested in understanding the disease and its mechanism [29]. Similarly, according to Marra et al., who carried out similar research to this on clinicaltrials.gov, only 13% of the studies on the clinicaltrials.gov database that used connected digital products (including wearables, ingestible, adherence applications, and ePROs) were designated as development stage trial (phase 1-3) or post-marketing trial (phase 4). This finding also supports more extensive use of CSTs out of drug development purposes [30]. Additionally, according to DeMets et al., high costs of clinical trials for drug development are also creating a barrier for the conduct of academic clinical trials, overall decreasing the number of academic clinical trials [31].

The strengths of this study were providing data from 2 different sources to create a broader view into CSTs implementation and analyzing the combined data by years. However, there were

also some limitations. Industry's tendency to keep information confidential and/or poor interest in publishing, combined with low numbers of academic clinical trials made it difficult to form a complete view on the adoption of CSTs. DiMe library was created to address the lack of information regarding the implementation of CST, and they provide the most comprehensive and user-friendly information available. However, the information is given by their stakeholders voluntarily, and we see that not all the trials carried out by the stakeholders are listed. An example is the successful study by Bayer utilizing activity monitors, used for label expansion of a pain medication, mentioned in the article of Godfrey et al.[26]. Further research into databases like clinicaltrials.gov can be effective in extending the view on the landscape we have provided in this research paper.

Conclusion

COVID-19 pandemic demonstrated the benefits of CSTs and accelerated the adoption of digital health components in patients' lives, old and young. In this period, guidance and acceptance by the regulatory authorities visibly increased, encouraging companies to adopt CSTs further. Based on our research output, we foresee an increasing implementation rate in the coming years, although it may not be as steep as the implementation rate in 2020-21. The highest implementation is expected to be in disease areas where patients have to take part in long-term disease management and where comparing patient data over time can be helpful. Established endpoints are likely to receive more interest where all the industry stakeholders learn from these experiences, increasing regulatory guidance, and acceptance. Heart activity monitoring, an emerging area according to our results, is likely to be the next most implemented CST in the near future, given that heart activity parameters are already established endpoints and some parameters (e.g., heart rate) can already be easily measured by publicly available devices like smartphones and smartwatches. It can be expected that implementation of novel digital endpoints (e.g., speech biomarkers for Alzheimer's) will stay scarce until a higher maturity level is achieved in this domain (e.g., standardization, regulatory guidance) and then follow the same increasing trend we have so far observed. Overall, an increase in the adoption of CSTs measuring established endpoints can be expected, facilitating acceptance by all the pharmaceutical industry stakeholders, followed by an increase in the implementation of CST supporting novel endpoints.

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Supplementary Materials

Supplementary Material 1. Inclusion/exclusion criteria for connected sensor technology. The same criteria as the DiMe library were used for the literature review to select connected sensor technologies[7].

Category	*Examples*	*Inclusion Criteria*						*Scope*
		1. Collects clinical or health data	2. Software Component	3. Biometric Sensor	4. Remotely Collected (e.g., could be used off-site)	5. Connected to internet or other tech	6. Patient use (incl. non-expert caregiver/parental)	
Connected sensors technologies (e.g. BioMeT)	**Activity trackers, heart rate monitors, smart scales, sensors embedded in smartphones** (e.g. microphone)	✓	✓	✓	✓	✓	✓	Included
	Ingestibles such as smart pills (e.g., MyCite)	✓	✓	✓	✓	✓	✓	Included
	Implantables (e.g., pacemaker, subdermal wearable)	✓	✓	✓	✓	✓	✓	Included
	Medical expert-operated (e.g., Butterfly portable ultrasound)	✓	✓	✓	✓	✓	✗	Excluded
Non-internet connected sensor	Personal thermometer, at home blood pressure cuff	✓	✓	✓	✓	✗	✓	Excluded
Mobile Apps (w/o sensor)	Lifestyle mgmt. & adherence programs	✓	✓	✗	✓	✓	✓	Excluded
Assessments via Mobile Platform	iPad-administered tests, ePROs collecting clinical metrics via smartphone	✓	✓	✗	✓	✓	✓	Excluded
Electronic Health Records	Communication portals, ePrescribing	✓	✓	✓	✓	✓	✗	Excluded
Products with Digital Display	Digital display scale, digital pregnancy test	✓	✓	✓	✓	✗	✓	Excluded
Large, stationary equipment	Rehabilitation robots, Smart treadmills, CT machine	✓	✓	✓	✗	✓	✓	Excluded

Supplementary Material 2. Usage of connected sensor technologies for different disease areas by years. COPD: chronic obstructive pulmonary disease, MDD: major depressive disorder, HF: heart failure, PAH: pulmonary arterial hypertension, CF: cystic fibrosis, MS: multiple sclerosis.

Device	# of Studies	Indication
2005		
Activity monitor	1	Restless leg syndrome (measuring periodic limb movements)
2006		
Activity monitor	1	Alzheimer's Disease
2008		
Activity monitor	1	Sleep disturbance
2009		
Activity monitor	1	Atopic dermatitis
2011		
Activity monitor	3	Atopic dermatitis, cachexia in lung or pancreas, diabetic peripheral neuropathy
2012		
Activity monitor	2	Osteoarthritis, Alzheimer's disease
2013		
Activity monitor	1	Chronic stable angina
2015		
Activity monitor	2	COPD, osteoarthritis
2016		
Activity monitor	6	Insomnia, MDD, Rett syndrome, CF, HF
Electrodermal activity sensor	1	Sleep-wake disorders
Heart rate monitor	1	Rett syndrome
Thermometer	1	Rett syndrome
2017		
Activity monitor	5	PAH, reflux, neuromyelitis optica spectrum disorder, MS, HF
Ingestible sensor	1	Asthma (measuring treatment adherence)

Supplementary Material 2. Continued.

2018		
Activity monitor	2	Parkinson's disease, T1DM
Chest contact sensor	1	Chronic cough
Home spirometer	1	COPD
Continuous glucose monitor	2	T1DM
2019		
Activity monitor	3	Postoperative recovery, allergic asthma, diabetic peripheral neuropathic pain
Microphone	1	Alzheimer's disease (voice biomarkers)
2020		
Activity monitor	8	HF, essential tremor, Parkinson's disease, sickle cell anemia, menopause, MDD, asthma, sleep-wake disorders
Pulse oximeter	2	Sickle cell anemia, COVID-19
Thermometer	1	COVID-19
Continuous glucose monitor	3	T1DM, T2DM
Chest contact sensor	2	Chronic cough (cough count)
2021		
ECG	2	Atrial fibrillation, blepharospasm
Activity monitor	9	Restless leg syndrome, PAH, Huntington disease, cognitive impairment, sleep disturbance, Parkinson's disease, HF, MDD, CF
Continuous glucose monitor	4	T1DM, T2DM
Camera	1	Huntington disease (facial movement)
Accelerometer	1	Essential tremor (tremor rating)

Supplementary Material 3. Device type, phase, outcome placement, and indication data from selected articles (n=8). MDD: major depressive disorder, HIV: Human Immunodeficiency Virus, T1DM: Type 1 diabetes mellitus.

Device Type	Phase	Outcome placement	Indication
2007			
Activity Monitor [14]	N/A	Primary & Secondary	Rheumatoid arthritis
Activity Monitor [17]	Phase 3	Primary endpoint	MDD
Activity Monitor [18]	N/A	N/A	Alzheimer's
2008			
Activity Monitor [13]	N/A	Secondary endpoint	Opioid addiction
2014			
Accelerometer [15]	Phase 1 and 2	Primary endpoint	Heart failure
2015			
Continuous glucose monitor [19]	N/A	N/A	T1DM
2017			
Holter [12]	N/A	N/A	Hair loss reduction
2018			
Medication event management system (MEMS cap) [16]	N/A	Primary endpoint	HIV