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Using connected objects in clinical research☆

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Introduction

The development of the internet of things (IoT) is transforming many objects in our environment into objects referred to as ‘connected’. A connected object (CO) can be defined as an object that has an internet connection and/or algorithm added for additional value in terms of functionality, interaction or information. By extension, mobile health apps are included in this definition, whether or not they are connected to an object. The CO establishes a communication (sending and/or receiving information) with its environment and with a server or the ‘cloud’ via an internet connection. COs have invaded the health world, through activities of well-being (nutrition, sports, etc.). They appeared in clinical research 15 years ago, even though proportionately they are relatively little used in this field. For instance, approximately 3% of clinical trials on neurodegenerative diseases have integrated COs into their studies [1]. Use of COs in clinical research raises various questions related to their impact on the various steps in a clinical study. The objectives of the round table were to provide an overview on the typology and validation of COs, their current use in clinical research, and discuss the benefits and limitations of these objects, as well as regulatory and ethical questions that arise from their use in clinical research.
Typology and validation of connected objects

There has been a twofold evolution for the past ten years. Medical devices (MD), previously analog, are now digital and becoming "communicative". These MDs, initially connected to a proprietary network and a dedicated platform, are now connected via an internet link that allows the user direct access to applications and services opened by the MD.

The COs developed initially without a medical purpose (for sports, well-being and the "quantified self", enabling each person to measure, analyze and share their personal data, such as weight, exercise, heart rate, etc.), making large amounts of data available in relation to health issues that could potentially be used in clinical research. Under certain conditions (CE marking, French health authority [HAS] approval), these "general public" objects, materials or software can become MDs.

The different typologies of connected objects

Fig. 1 summarizes the different CO typologies and the "process" to implement them for use in clinical research or treatment. These objects are used by the patient, placed in the center of the device, and linked to investigators and the clinical research team, and/or, if applicable, caregivers.

Smartphones and tablets, the first COs, are a first level platform for collection, storage, or even data processing. They allow information to be entered by the patient (questionnaires, etc.) and exchanged with the medical team. The patient is identified and localized, information is dated, then transmitted to a platform for their treatment. This information helps make data collection safer and faster. The connection to other information systems and/or to the "cloud" allows additional data (laboratory, genomics, imaging) to be linked and to access online treatment algorithms, if needed.

To information filled in by the patient, data can be added from sensors connected to:
- biosensors, whether an MD or not, worn by the person or placed in their environment, which can, through various physiological parameters (weight, physical activity, heart rate, blood pressure, blood oxygen saturation level \(\text{SpO}_2\), etc.) directly measure or collect laboratory parameters from a sample (blood, urine, exhaled air, etc.);
- environmental sensors (temperature, hygrometry, atmospheric pollutants, etc.), cameras or movement detectors may be used to acquire additional data that is useful to the research.

All data from the patient, treated locally or remotely, can automatically (artificial intelligence algorithms) provide decision support for the patient or medical team, with or without intervention from a medical team. In this case, information (alerts, tips, instructions, prescriptions, etc.) will then be returned to the patient via their connected smartphone or tablet, as a potentially regulated closed-loop system, enabling optimized treatment. In this loop, the processed information may order actions via connected actuators worn by, or implanted in the patient, such as a pump for dispensing active ingredients, or a pacemaker or stimulator (cardiology or neurology). In the latter case, the object must necessarily be an MD.

Validation and risk management

COs are used in clinical research for data collection, with added value in terms of communication or algorithmic analysis. Their use should respond to a prior validation based on three approaches: technical and clinical reliability, data protection and cybersecurity.

Depending on the nature and typology of these objects, Table 1 provides a structure for the validation process.

The development of MDs responds to technical requirements, risk analysis, usage aptitude tests and verification.
Table 1  Validation of connected objects based on their typology.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>PRO</th>
<th>Measuring devices (meters)</th>
<th>Sensors</th>
<th>Actuators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile applications (scales)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validation</td>
<td>With medical purpose = non medical device</td>
<td>De novo creation: paper and digital validation</td>
<td>Validated existing scale: validation of the digital transposition</td>
<td>Validation of the measurement system adapted to the risk level (calibration, standardization, reproducibility)</td>
</tr>
<tr>
<td>With medical purpose = medical device</td>
<td>Stand alone medical device software CE marking</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cybersecurity</td>
<td></td>
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<td>Protection of data</td>
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CE: European compliance; PRO: patient-related outcome.
and validation, which aim to ensure their performance and safety. In addition, MD softwares follow a process involving specifications, design, development, testing and rollout, etc.

The objects or software applications that are not in the MD field must also comply with a validation procedure prior to their use in clinical research:
• for software applications, known as stand alone, the transposition of a collection scale onto a digital medium must go through a validation step;
• for measuring devices, sensors and active devices, it is essential to validate the device, which must be adapted to the level of risk incurred (calibration, standardization, reproducibility).

Examples of connected objects used in clinical research

The aim of this chapter is not to provide a comprehensive review of the literature [2–4], but to provide some examples of studies in which COs are involved.

It is necessary to distinguish:
• observational studies where all participants have a CO in order to evaluate its proper functioning and ergonomics;
• randomized interventional studies where only one group has a CO, mainly to investigate its impact on monitoring the patient’s condition and/or treatment;
• randomized interventional studies, much rarer but currently in full expansion, where both groups have a CO, which is then used as an actual support tool for assessing clinical research (Fig. 2).

Observational studies

A typical example is the validation of applications associated with algorithms or artificial intelligence. All medical specialties are involved. Once validated, they will be able to more specifically measure symptomatology or a response to treatment in clinical research. In psychiatry for example, in the field of mood disorders, many smartphone applications aim to assess mood, enabling improved patient self-assessment [5]. They are sometimes associated with physiological measurements (heart and breathing rate), behavioral measurements (frequency of use of messaging, exercise) or voice measurements (speech rate, voice prosody) that can improve the detection and measurement of a depressive condition or psychomotor excitation (manic episode) [6]. A team from Barcelona developed the application Simple for patients with bipolar disorder [7–9]. This application involves answering 5 questions each day that will help assess different areas associated with bipolar disorder, and to produce suitable psycho-education or alert messages.

A second example, focused on data collection for better patient monitoring, is illustrated by the Cardiauvergne device [10], which monitors weight in class 3–4 heart failure via a connected scale: weight change is a reliable reference for the start of decompensation, regardless of the cause. This device is associated with a remote, coordinated care service. Pharmaceutical and laboratory monitoring is also downloaded. All data is analyzed by an expert system that generates alerts, managed by the coordination cell 7 days per week (Fig. 3). An e-cohort was created, monitoring 1,084 patients included after 4 years of operation. Mortality, readmissions and average length of stay were strongly reduced compared to a historic cohort, corresponding to € 4,500 in savings per patient, deducting the cost of the Cardiauvergne.

A recent randomized multcenter study, evaluating the efficacy of a CO and remote device in the same population, showed no significant difference in terms of mortality and readmission at 6 months [11]. However, the coordination cell was managed by nurses and not by physicians, as mentioned for Cardiauvergne, and mortality and especially the rate of readmission was much higher. This highlights the importance of the human element in managing data from the CO and the alerts generated, which confirms another study, which monitored weight loss in obese patients [12].

Interventional randomized studies in which only one group gets a connected object

They study its impact on monitoring the patient’s condition and management. The first example is from the DIABEO
Secure hosting of computerized records
Expert System that generates alerts and alarms

Figure 3. Cardiauvergne: at-home monitoring of patients with severe heart failure. Courtesy: Jean Cassagnes, Cardiauvergne.

Figure 4. Efficacy of DIABEO on HbA1c level over time.

device [13], which guides patients with type 1 diabetes on the insulin dose to administer. This is an application downloaded onto a smartphone that incorporates the medical prescription, made on the website, for adjusting insulin doses. Based on this prescription, the system proposes a dose, taking into account various information provided by the patient (blood glucose, quantity of carbohydrates in a meal, physical activity). Data collected in the smartphone is then sent to the website. An automatic data analysis system generates alerts that will be sent to the caregiver's mailbox. This looped system reacts immediately. The Télédébi-1 study showed that in patients with persistent treatment failure (HbA1c > 8%), the DIABEO system enabled improved glycemic control at 6 months (Fig. 4) [13]. If remote monitoring by the caregiver has little added value for patients complying with the system, it is extremely beneficial for less compliant patients. The automated alerts allow the caregiver to promptly intervene, leading to final results that are as good as the results from the subgroup of compliant patients [14]. These results should be confirmed by those in the Télésage study, a nationwide study conducted in approximately 700 patients over 2 years.

The second example comes from the Institut inter-régional de cancérologie (Inter-regional cancer institute) in Le Mans (France), where it was shown that, in a population of patients treated for localized lung cancer, the monitoring of a number of symptoms through a mobile application can detect disease progression earlier than clinical evaluations and scans. This translates into a survival benefit for patients [15]. Another project is ongoing at the Gustave-Roussy Institute, the CAPRI trial, in which patients receiving oral treatment for cancer are randomized between classic monitoring and monitoring by a coordinating nurse with a dedicated internet platform. The primary objective is to show better dose-intensity of the treatment through coordinated care [16].

Randomized interventional studies where both groups get a connected object

The object is now used as a support tool for assessment. These studies are rare due to the device needing to be technically and clinically tested before the trial, but, on the ClinicalTrials.gov registry, many such studies are in process. For example, a study demonstrating the effect of melatonin, magnesium and zinc on insomnia using a rollover motion sensor as an assessment tool, combined with questionnaires [17], or another study showing improved walking in children with cerebral palsy by visual or auditory signals, using sensors and movements paired with a computerized analysis interface [18].

COs, after an initial technical and clinical feasibility validation phase, will increasingly be part of the arsenal of clinical research tools.
Contributions and limitations of connected objects as an assessment tool in clinical research

COs provide real opportunities as assessment tools in clinical research, but they also have limitations, even dangers, that need to be well understood [19].

Data collection and data quality

The advantage of using COs in the collection and quality of data includes the collection of objective, accurate, reproducible measurements, with, in theory, less missing data than a non-instantaneous and non-systematic collection. Systematic collection facilitates numerous and repeated measurements at a reduced cost, with long follow-up with no loss of data, more representative of "real life," as well as the detection of significant events. Simple algorithms can generate less random integrated measurements (e.g., weekly mean values instead of one value per week). The gain in terms of data accuracy may result in a potential reduction in the number of subjects.

However, the use of COs in clinical research is currently limited by the lack of clearly validated tools and uncertainty about technological imperfections (breakdowns, artifacts, disconnections, etc.) which may result in data loss or acquisition of incorrect values, requiring a backup solution or a hotline. The multiplicity and incompatibility of the different platforms available, particularly in the context of international studies, are also an impediment to their use. Finally, the investment cost is currently difficult to understand in terms of profitability.

Patient compliance/adherence

The development of COs in many other areas of everyday life facilitates patient familiarization and contributes to better acceptability when they are included in studies. Also, technological advances make these COs very easy to use, even fun, and very discreet if necessary, enhancing patient compliance with the research.

By creating a functional link between the patient and the staff in charge of the clinical study, COs are in line with a telemedicine-type approach. This allows "virtual study visits," which limit travel, a major obstacle in recruitment and patient compliance when the patient lives a long way from investigational sites, or is too tired or not available for the many study visits. This facilitates the conduct of the study for the patient, the investigator and the study sponsor.

COs allow for more frequent measurements without disrupting the patient’s daily life, and result in less missing data. They thereby allow for better compliance from patients with adherence to the tools, better follow-up, fewer patients lost to follow-up or withdrawn from the study.

The benefits of COs can be emphasized, particularly in the context of chronic conditions. They are, in fact, sought by manufacturers developing new perspectives on treatment, management and support for patients in their daily lives. Treatment is not only taking a medication, but also using a CO that collects a given amount of data and analyzes it, which provides valuable information to the caregiver, and also allows the patient to have a complete view of the treatment for their condition.

Connected to pharmacovigilance

If the use of COs is today mainly focused on efficacy endpoints, everyone knows that treatment trials also aim to evaluate the tolerability of the studied treatments. In this regard, COs may provide a benefit on two levels.

First, they may improve patient safety by their ability to manage alerts or alarms triggered automatically by one or more body sensors. The signal may be received and interpreted by the patient themselves and/or by a healthcare professional, who may interact with the patient or family to relieve the adverse effect in the best way.

The completeness of data collected about adverse effects may also be improved. In fact, the CO can ask the patient at regular intervals, either with an open question, such as, "Have you felt any abnormal phenomena during the past night and day?", or use targeted questions about certain expected adverse effects. Furthermore, COs can themselves detect possibly subclinical adverse effects. These can be asymptomatic episodes of hypoglycemia, sleep apnea, loss of balance without an actual fall in various neurological conditions, etc. The problem that then arises is how to determine thresholds, which will be used to decide whether it is truly an adverse effect.

Representativeness of the patient population

The use of connected tools in clinical research may allow a broader recruitment of eligible patients, including patients that live far from investigator sites. However, this democratization of access to research, with better representativeness of the target population, risks being counterbalanced by a selection of more "technophile" patients, or at least patients open to innovation.

This should be considered in study protocols that must provide for alternative solutions (paper documents, nurse home visits, etc.) to compensate for a selection bias that may impact representativeness.

E-cohort potential

The use of a CO is a great opportunity to try to build data warehouses for testing research hypotheses, at no additional cost and immediately, in a way similar to the creation of biobanks.

Societal limitations and risks

The benefits listed above are undeniable, but they have some limitations, even certain societal risks.
First, the status of COs might change from "virtuous" to "destroyers of freedom" [20]. In fact, the often intrusive nature of certain parameters collected by the COs as part of clinical research can lead to difficulties in patient acceptability [21].

If the CO becomes the companion of a treatment during its development phase, it is worth remembering that its use after marketing will be unavoidable in benefitting from the therapeutic innovation. It is highly likely that our health care system will take into account the use of the CO and its reimbursement conditions, which may lead to renouncing certain individual rights in order to benefit from the innovation. This is the case, for example, with the use of a medical device to treat sleep apnea [22,23].

Sometimes greater reluctance is noted among the investigator staff. In fact, the staff will need to be trained and then guide the patients taking part in the research, ensuring optimal use of the tools, resolve certain technical problems, etc. This represents a change in the duties of the investigator staff (technician or clinical research nurse and investigator), with additional jobs that may concern them.

Finally, from an industrial viewpoint, the validation requirements for COs and resultant implementation timelines are, aside from the cost, an obstacle to the broader roll-out of their use.

Misuse of purpose

The COs used in clinical research generate health data, sometimes on a massive scale. Their digitization opens the door to potential misuse that should be foreseen by paying particular attention to securing the methods of transmission and qualification of data hosts.

This leads to the importance, for patients participating in research, of being fully informed about what the COs are that they will be offered. They should know precisely the nature of the information collected and the period when their data will be collected by these technologies.

Strict regulations should therefore be defined to protect the individual participating in research.

Regulatory and ethical specifics when using a connected object in a clinical research project

In order to address these questions, we will assume that the CO involved has already undergone scientific validation adapted to its use.

If the CO generates data, which may be considered health data, the applicable regulatory context is doubled, since it combines research involving humans (RIH) and the data protection act [24,25]. The study sponsor will have to define the type of research, based on the level of intervention related to the CO, and describe the CO’s operating technique, the data generated and interpretation limitations in the research documents (protocol, information leaflet, application submitted to foreign or French authorities), as well as how the information will be sent from the sensor to the database, whether or not via "cloud"-type hosting sites. The sponsor must also ensure that each project fits in the application fields for reference methodologies of the French data protection authority (Commission nationale de l’informatique et des libertés [CNIL]), or if applicable, undertake the necessary steps.

Data usage and security

For data usage, it is commonly accepted that the data cannot be subject to a change of purpose for other types of subsequent treatments without express authorization from the CNIL. However, it is possible to provide that the data, once coded, can be kept for use in future research that may have a different objective from the objectives of the main research, but only if this new objective is scientific knowledge and/or the development of new treatments. In this case, the patient should specifically accept their storage and this new usage. This point regarding data use is more sensitive, as some COs can generate ongoing measurements without the patient’s intervention. The status of the collected data for operating the algorithm appears to need careful consideration.

With regard to data hosting, it is necessary to identify where the data will be hosted at all stages of the data flow. Currently, data from COs are frequently hosted in the "cloud," therefore separate from the clinical database. In this case, it is also necessary to accurately document the data flow, in order to inform both patients and healthcare professionals and to ensure adequate security. Data storage by a licensed "health data" host seems necessary.

Communication and information

Special care must be given to writing the "information document/consent form," so that the patient has clear and sufficiently detailed information about the CO, the data generated and resultant treatments, and their storage conditions. The patient should clearly consent to the collection of their health data by the CO and its associated risks as part of the study in which they are planning to participate. In fact, the simple and fun aspect, popularized, may make people forget about the nature of the collected data, health data, which is personal and sensitive. Finally, a clear reminder should be included in the consent form, indicating that the patient has the right of access and rectification, the right to object, the right to be forgotten (erasure of personal data), and the "right to disconnect" [26].

It seems necessary to submit a file to the ethical review board (ERB) that provides sufficient documentation on all aspects related to the CO. It must be an educational effort, and specifically document all uses of a CO in the research. This will probably contribute to improving participants’ knowledge and facilitate the use of COs in future research. In practice, we recommend applying the guidelines formulated by the HAS in October 2016 [26].

Summary of guidelines

Beyond application of best practices on health applications and COs (mobile health or mhealth) described in the
Connected in-depth training of their involvement in the computer and other relevant aspects related to the CNIL, and the integration of potential regulatory actions specific to the CE marking of the object if necessary.

- a precise and documented definition of the data circuit, integrating compliance with current legislation related to access, storage and hosting, the transfer and use of these circuits in the respective countries, in order to avoid any misuse (cybersecurity).
- an analysis of potential risks related to the use of a CO appears necessary for each project. Data security must be managed during the collection, transfer, hosting, processing, or interpretation stages. Concerning this point, it is important to accurately know the algorithm that transforms the sensor’s (CO) signals into data that will be used in clinical assessment. The connection is critical to its proper function, and technical connection issues cannot be underestimated (including in the hospital).

- cybersecurity is also a subject to discuss (see the recent debate around a potential hacking of connected pacemakers) [27]; therefore the risk analysis should provide for any potential misuse or corruption of data, and advocate encryption;

- training and commitment of all participants with regards to the specifics of data collection and processing. The involvement of users starting from the study design, with a clear definition of the role of the patient in the use of the CO in clinical research, and attention to this dimension in the patient information leaflet. Representativeness of the patient population should also be considered, as well as potential screening bias (age groups, geographical or socio-professional coverage) resulting from using a CO. Also the value of a feasibility stage should be kept in mind, which allows procedures to be tweaked, facilitates risk analysis and finds technical solutions, and the provision of clear and detailed information for the patient for participation in the research, particularly on the nature and scope of data use, and their consent to this use;

- projects with COs often rely on external partnerships, involving various structures, start-ups, manufacturers and computer companies. Effective hotline solutions should be provided for patients and healthcare professionals, and a contingency plan in case of a technical problem.

Partners involved should be assessed by the sponsor to ensure their sustainability (multi-year research), in order to anticipate technological developments and ensure long-term maintenance.

A guide to best practices is also expected on a European scale for 2017 on this topic and will complement these recommendations.

We recommend providing a patient-card, outlining the use of a CO in a research project.

As COs are set to become widespread in the context of research, and as various research participants are still fairly new to them and their guidelines for use, our latest recommendations will go to the Health Authorities. In order to facilitate the appropriate use of COs in studies, the French national agency for medicines and health products safety (Agence nationale du médicament et des produits de santé [ANSM]) may organize a workshop, “Use of COs in Clinical Research”, so as to strengthen the skills of all participants. The Centre national des RIPH [French national RH center] may also take the initiative, so that ERBs have sufficient and standardized expertise.

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The other authors declare that they have no competing interest.

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