Ebook

The place of connected medical devices in health today

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SUMMARY

I - Introduction

In recent years, non-compliance has become a major problem in the treatment of chronic diseases worldwide. This impacts patients, health care professionals and pharmaceutical companies.

The connected medical devices (CMDs) could provide an effective response to this problem. These products are expanding rapidly in the e-health market.

How did we end up in a CMDs race? Why did these devices became so prized?

The aim of this ebook is to present CMDs around one main issue:

How do CMDs improve patients' quality of life?

The first part will be focused on non-compliance. What is the rate of non-compliance among patients? How can this rate be explain? What are the impacts on the concerned sectors ?
We will then look at CMDs and the benefits for patients / health care professionals / industries. How is the CMDs market? Are they reimbursable? What are the advantages and disadvantages of CMDs?
Finally, a case study will be presented to illustrate the changes brought by the connected medical device Mallya in the daily life of a patient with diabetes.

II - Non-compliance in patients with chronic diseases

What is the compliance?

Several definitions have been published in recent years, to define the term "compliance" for long-term treatment. In 2003, the Word Health Organisation (WHO) published a definition based on the definitions of Haynes [1] and Rand [2]:

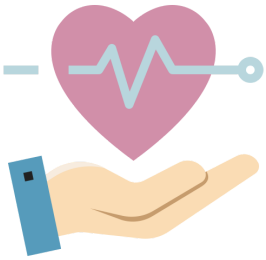
"*The extent to which a person's behaviour (taking medication, following a diet, and/or executing lifestyle changes), corresponds with agreed recommendations from a health care provider.*" [3]

Compliance is therefore the fact of scrupulously respecting the health care professional's prescription in the context of a treatment. This includes respecting the dosage, number of doses, the time of intake and the recommendations for lifestyle changes (e.g.: specific diet, quit smoking, etc.).

What is the non-compliance?

Non-compliance is the failure to comply 100% with the health care professional's prescription for a given treatment. This may include: forgetting to take a drug, not taking it at the correct interval, taking the wrong dosage, etc.

For long-term treatment, it can be more complicated to comply with prescriptions. A high rate of non-compliance is often observed in patients with chronic diseases.



Definition of chronic disease

In a 2003 press release, the WHO defines the chronic disease as:

"*Diseases which have one or more of the following characteristics: they are permanent, leave residual disability, are caused by non-reversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care.*" [3]

So, a chronic disease is defined as incurable, as well as having definitive consequences for the patient. Treatments require a lifelong care and aim to control and to reduce symptoms.

a. Global figures and problems faced

It is the rate of patients with chronic diseases who are poorly compliant with their treatment [4]. This is a problem in all geographical areas, but the rate is higher in developed countries, according to the WHO [3].

What are the consequences of non-compliance?

Non-compliance leads to reduce effectiveness of treatment [5]. There are several reasons for this:

- Dosages are set to ensure the best rate of efficacy for patients. If the dosages are not respected, the patient does not benefit from this rate.
- This means that health care professionals cannot properly adapt the treatment because data are not reliable.

Studies show that patients with poor compliance have a reduced response to treatment, increased resistance to treatment, poorer prognosis, higher relapse rates, and increased medical visits and hospitalisations across all chronic diseases [6].

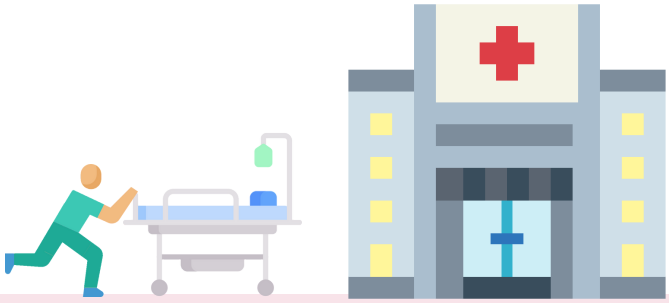
These compliance problems can have more serious consequences for patients. It is estimated that 275 000 patients die each year worldwide due to poor compliance [6].

In addition to the health consequences for patients, non-compliance has economic repercussions for both the health system and pharmaceutical industries.

What are the costs of non-compliance?

Pharmaceutical industries

Non-compliance creates costs for manufacturers, as it leads to a drop in product consumption and therefore a drop in sales. Furthermore, since in product effectiveness is not what the company promises, it can damage the industry's brand image [7].
It is currently difficult to quantify exactly the cost of non-compliance worldwide [8]. However, one study has estimated the lost revenue of $290 billion in 2019 in the United-States [9].



Health system:

The health system is also greatly impacted by non-compliance, as a decrease in treatment effectiveness leads to additional health care services. Indeed, as explained above, non-compliance increases the risk of relapse, poor response to treatment and therefore worsening of the disease. Patients then require additional care, sometimes in a hospital setting, which requires additional equipment and staff. Furthermore, an increase in treatment resistance leads to increase investment in research and development of new drugs to compensate for resistant variants that are more likely to develop with non-compliance [3].

All of this comes at a cost for the health system: one study estimated the loss at $1 trillion per year worldwide [9].

b. Why don't patients comply with their prescriptions?

The causes of non-adherence are multiple, and can be psychological and/or physical:

Psychological reasons:

- Mental burden of treatment: in the case of chronic diseases, medication is taken several times per week or even several times a day. It can be difficult for patients to remember to systematically take their medication on time. According to one study, 38% of people suffer from mental burden imposed by their treatment [10].
- Patient does not understand his diseases: 46% of non-compliance is because the person has a poor understanding of his prescription and recommended dosages [7]. Indeed, some patients do not understand their disease; they feel less concerned and will be less involved in their treatment.
- When symptoms decrease; patients forget their treatment: 29% stop their treatment at the first signs of improvement, when they no longer feel sick [7].

Physical reasons:

- Restrictive administration: some treatments must be administrated by injection. It can be embarrassing for the patient to self-administer a drug in a public place or in society.
- Lack of product: the patient may run out of medication and cannot purchase it in a short term.

All of these factors underline the fact that long-term treatment compliance can be difficult to respect scrupulously. This explains the 50% rate of non-compliance among patients with chronic disease.

c. How to solve the problem of non-compliance ?

The factors for non-compliance can be different, but there is common thread in the psychological reasons: lack of motivation and feeling of involvement in the treatment.

To address this, it is important that patients are educated and understand their disease. Self-management programs may be an option to help patients manage their own treatment and understand the course of their disease. Studies have shown that self-management patients who are supported in the initial phase, show improved cognitive control of symptoms, improved disability management and greater sense of involvement in the disease [3].

Next, to support patients in their regular treatment, health industries aim to offer innovative technologies that can help and psychologically relieve people suffering from chronic disease. Among them, connected medical devices have proven their effectiveness in this respect.

III - Connected medical devices

What is a medical device?

Based on the section 201(h) of the Food and Drug Administration (FDA), a medical device is:
"*[...] An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:*
- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and
which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o)." [11]

In this eBook, we will focus on a medical device qualified as tool for self-administration treatments, for a frequent use and outside health care institutions.

What is a connected medical device?

The French National Authority for Health published in April 2018,
an article about the evaluation of medical device and health Technology. In this document, it precises that CMD are tools:

"*Used for telesurveillance and teleconsultations or generating an action for the patients for an auto-administration or auto-compliance.*" [12]

And they meet these three conditions:

"*1. Destinated for medical use,*
2. used by the patient,
3. with a telecommunication function." [12]

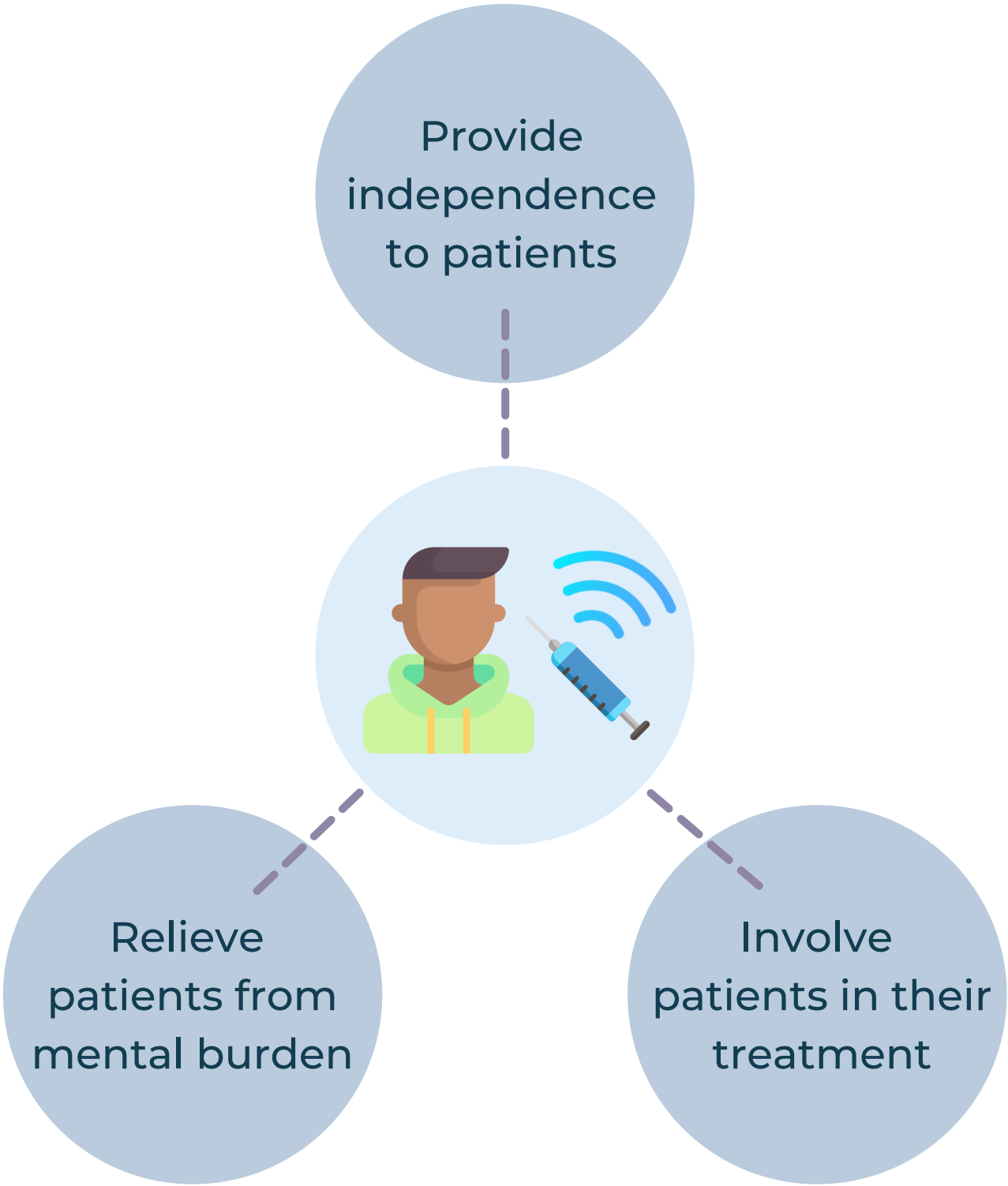
⚠ Warning ! ⚠

It is important to differentiate the connected medical device from the connected health object. In fact, this one does not have a declared medical purpose. It belongs to the "well-being" category. For examples: connected scales, connected watches, etc [13].

a. Objectives through the connected medical devices

I. For patients

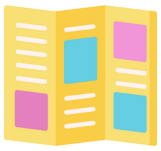
The functions and options offered by CMDs may vary depending on the product or the company offering it, but the objectives remain the same:



Provide independence to patients

Some patients choose to go to a health facility to have their treatment administrated by a professional when their treatment can be self administered. This may be due to a lack of confidence and knowledge in the proper handling of the device.

To address these issues, CMDs offer to accompany the patient during the injection, in several ways (non-exhaustive list):



- Instructions for successful self-administration with explanation

- Indicator light to show whether or not the administration is running smoothly

- Audible signal to indicate the end of the administration

Thus, by accompanying patients during the administration, CMDs allow them to be independent by letting them to manage their own treatment.

Involve patients in their treatment

46% of non-compliance is due to a lack of understanding of prescription and dosages from patients [7].

The lack of understanding may be due to a lack of interest in the disease and this subject may be complex. Some medical information is accessible by the medical professionals in terms of understanding. The patient may not feel concerned by his disease; it may seem too complicated to understand. However, according to a study of cancer patients, 80 to 87% of them indicate that it is important to see and follow their medical file to improve their compliance [14]. Thus, by giving them access to their medical data, patients would feel more involved in their treatment.

In response to this challenge, the CMDs offer monitoring of disease progressing by providing patients an electronic diary where patients can enter their symptoms. The person can see improvements due to the treatment directly on the electronic diary, which is also available to the health care professional. This also allows to space out appointments with the caregivers.

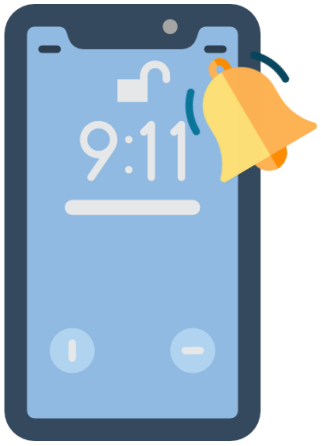
Noted: a CMD does not replace a medical appointment.

Relieve patients from mental burden

Treatments for chronic diseases involve frequent dosing, usually several times a month to several times a day. Remembering each dose can be a heavy mental burden. Sometimes, the patient forgets to take a dose or cannot remember whether he has taken it or not.

Based on a study, about 40% of patient with a chronic disease say they cannot sustain the investment of time and energy on their treatment over time [10].

To help people comply with their treatment, CMDs can save and display administrations in a software for smartphone. In addition, by configuring dosages and frequency of administration, the smartphone can send notifications to remind patients to take the prescribed dose. This solution allows to soothe the mental burden of the treatment.



II. For health care professionals

Health care professionals follow several patients with chronic disease, often in multidisciplinary care with other doctors or specialists. They have to make a diagnosis and to monitor the progress of the disease, with regular medical appointments with their patients. On average, these appointments are made every six months to follow a chronic disease. Depending on the results and the patient's feedback, the health care professional will have to adapt the treatment and vary the dosage in order to provide the best rate of effectiveness.

For this, his diagnostic will be based solely on the patients' feedback. However, to establish the evolution of the disease, the doctor will need quantified and reliable data, particularly in the event of forgotten treatment.

With the electronic symptom diary system linked to the CMD, the patient can regularly enter and save the "parameters" that he needs to monitor. This gives to the doctor access to reliable data on symptoms and side effects.
In addition, the CMDs records administrations of the treatment. Thus, in case of poor compliance, the health care professional can justify the lack of treatment effectiveness by a lack of respect for the dosage and remind the patient to respect the prescription.

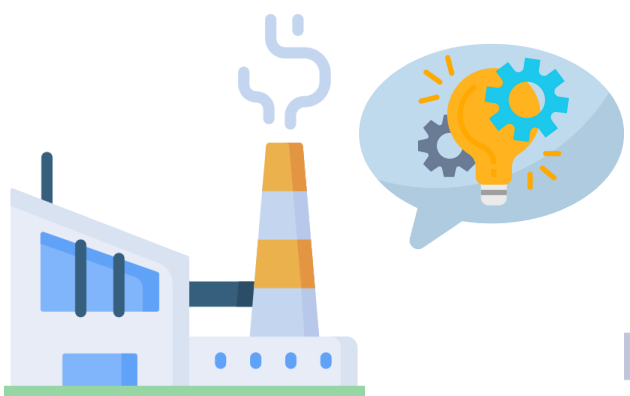
III. For the patient-doctor relationship

According to the WHO, studies have shown that the quality of the relationship between the patient and the health care professional has a real impact on compliance [3].

To help improve these relationships, it is important that the patient feels involved and in a collaborative mode with the doctor. As explained earlier, CMDs help provide independence to patients and empower them. In addition to helping them understand their disease, it improves their relationship with the health care professional. Indeed, according to a study published on 2019, the English literature has studied this subject, they have demonstrated that the use of health software linked to CMD has a positive impact on communication and relationship between the patient and his doctor [15].

IV. For pharmaceutical companies

As explained earlier, the problem of non-compliance has a financial impact for companies, but also a negative impact on their brand image. It is therefore important for companies to offer solutions to improve patient compliance.



b. The connected medical device market

The e-health market is growing rapidly

E-health is the application of information and communication technologies to health, [16] which includes CMDs.

According to the consulting firm Frost & Sullivan, the value of global e-health market is expected to grow by 160% between 2019 and 2023. This can be explained by the democratisation of digital tools in our daily lives, particularly with a new generation that masters and consumes new technologies. It is therefore natural that CMDs have made their appearance in the patient's care pathway [17].

Is there a real demand in the CMD market?

CMDs are mainly intended to accompany patients in their long-term treatment. This problem concerns more and more people as we observe an increase in the rate of chronic disease in the world, especially in developed countries [18]. Scientifics explain this hight rate in northern countries by the lifestyle adopted (pollution, tobacco, alcohol, sedentary, etc.) in addition to ageing population.

In the word, 1 in 3 adults live with at least one chronic disease [18].

CMDs help improve compliance with the treatment of chronic diseases. Today, the percentage of people affected by one of these pathologies is on the rise, and they are increasingly in demand for support from a CMD. In fact, according to a study, 57% of patients want remote monitoring for medical follow-up via connected devices at home [19]. So there is now a real plebiscite for CMDs.

This fact has been observed and confirmed by A2Z Market Research, which published in 2019 a CMDs market research report, where it stated that there is a growing interest among people for CMDs. This demand will lead to a strong expansion of this market between 2021 and 2027 [20].

Today, many companies are already specialising in the CMDs sector, with some which are already leaders on this market [20]:

- GE Healthcare
- Medtronic
- OMRON Corporation
- AgaMatrix
- Boston Scientific Corporation
- F. Hoffman-La Roche

We are now witnessing a CMDs race. Compagnies want to join the e-health world by bringing out their own connected product. The competition is tough and strong in this market.

However, designing and developing CMD has a cost, and this can be reflected in the price for the consumer. The solution to sell and make accessible a high-tech product to everyone, is to be covered by health insurance organisations.

c. Regulatory context

Medical devices and connected medical devices

Technological acceleration as well as regulatory clarifications put the spotlight on CMDs, which, like all other MDs, must meet the general data security and performance requirements of the Medical Device Regulation in order to be placed on the market.

In other words, MCDs must meet the same requirement level as any other medical device and benefit from an assessment adapted to their technology and purpose.

Regulation, including the regulatory framework and the issue of data protection was often mentioned as a limit on the expansion of CMDs, but it is now becoming clearer.

Mobile apps

Health professionals are raising the issue of the reliability of mobile applications, which is why the HAS is currently formalising a set of specifications to assess these tools. The aim is not to issue a label, but to formulate recommendations for manufacturers, doctors and users.

In addition, since 2011, the FDA (Food and Drug Administration, the American health authority), has also developed a draft recommendation for the approval of medical applications. This is not an approval, only an indicative recommendation.

Compliance of a product with EU legislation

The marketing of connected medical devices takes place within a European regulatory framework. This framework sets out the health and safety "core requirements" with which manufacturers must comply to ensure the safety. and reliability of their devices placed on the market.

The CE marking affixed by the manufacturer guarantees this conformity.

How to obtain the CE mark?

To ensure the conformity of the product with all applicable EU-wide requirements, it needs to be determined whether the manufacturer can assess the product himself or whether he needs a notified body to compile a technical file proving the conformity of the product, draw up and sign an EU declaration of conformity. [21]

Compliance of a product with the laws of the US

The US Food and Drug Administration (FDA) is the US government agency that, among other things, has the mandate to approve the marketing of drugs and medical devices or connected medical devices in the United States.

How to obtain FDA approval?

The FDA provides comprehensive guidance documents, application guides and databases that manufacturers of medical devices can use to achieve regulatory compliance.

Examples include:
- General Controls for Medical Devices ;
- General Principles of Software Validation;
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
- Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software use in Medical Devices. [22]

c. Reimbursement of connected medical device in France

In France, reimbursement of CMDs is possible if the product meets certain criteria. To guide manufacturers, which want to apply for a refund, the French National Authority for Health published in 2019 a press release to explain clinical evaluation methods for CMDs.

A CMD is eligible for the clinic evaluation, if [23]:

- It has the status of a medical device
- It has the CE marking
- It is for individual use (without a health care professional intervention)

If the CMD meets these three criteria, then the company can apply for reimbursement of the CMD at the French National Authority for Health.

d. Advantages/disadvantages of connected medical devices

CMDs seem to be an innovative and essential turning point in the health market. However, this sector has some limits and disadvantages for companies to launch their own CMDs.

To summarize the information given in this ebook, here is a comparison of the advantages and disadvantages of CMDs.

Advantages :

- Relieves the mental burden
- Gives patients continuous access to their medical data
- Improves compliance
- Allows a remote medical monitoring
- Gives to health care professional accurate and numerical data for the compliance of the patient
- High patient demand
- Growing market

Disadvantages:

- R&D for CMDs is expensive
- Environmental impact of electronic components in addition to plastic waste
- Very competitive market
- Technological barrier for some people (e.g. seniors)
- Health professionals need to be convinced by the product to recommend it and then use it with their patients.
- Data security risks
- Limited time for the doctor to analyze the connected data
- Reimbursement framework still in its infancy and lack of uniformity at European and global level.

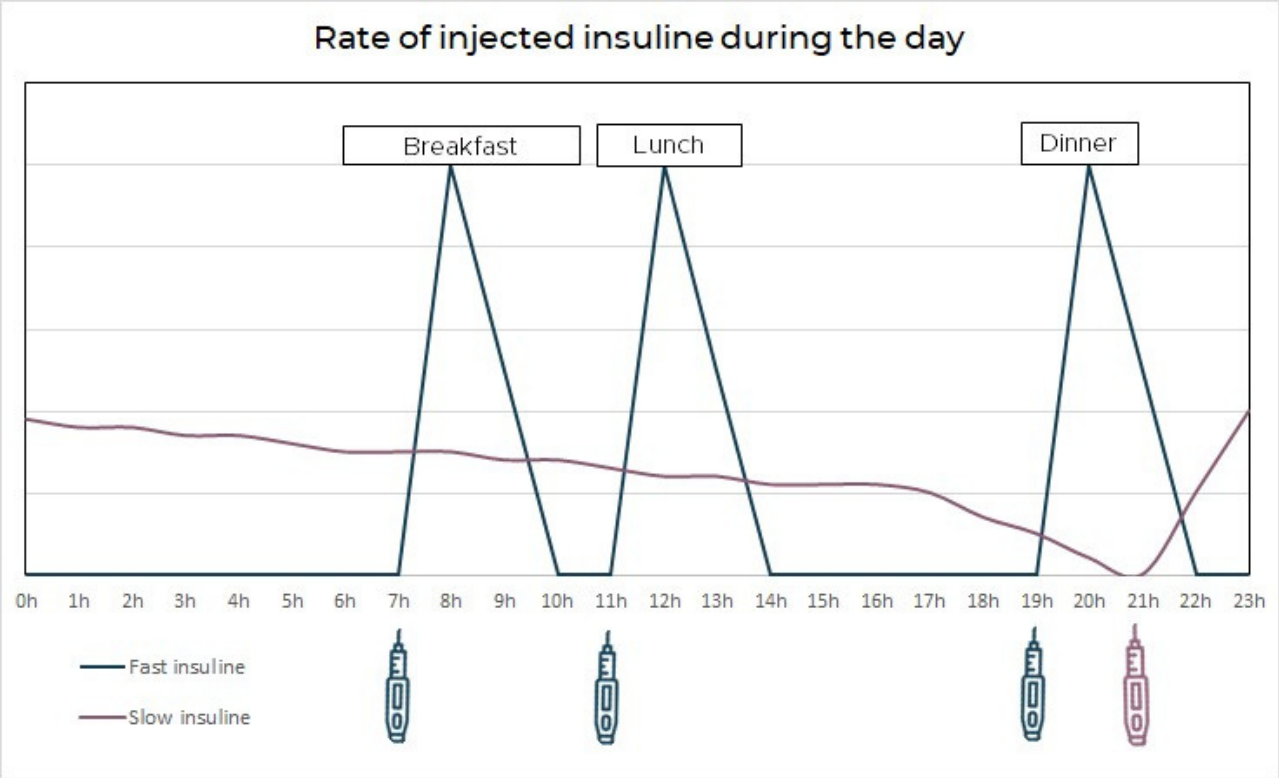
IV - Case study

Mallya

The connected medical device which turns your insulin pen into a smart device!

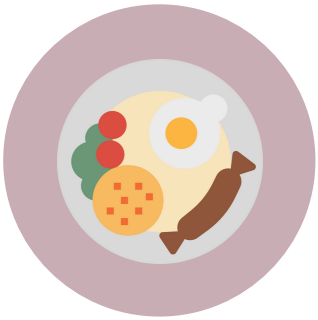
To assess the usefulness of CMDs, we will analyse the daily life of a patient with a chronic disease, before and after the use of a CMD in his treatment management:

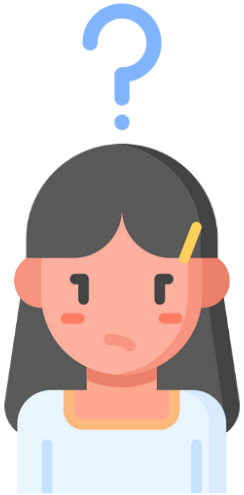
Marie is a 26 year-old working woman from Taiwan who was diagnosed Type 1 diabetes since she is 8 years old. With her doctor, they agreed on a multi-injection treatment with a disposable insulin pen.
Her injections are distributed throughout the day as follow:



In addition to her injections, Marie has to monitor her treatment. To do this, she has the FreeStyle Libre, which continuously measures the glucose level. She has to scan the device regularly with her phone, to transfer data to the software. During the day, Marie has to handwrite these following indications in her diabetes management booklet:

- Insulin dose injected (before each meal)
- Glycemia rate with trend arrow (before and after each meal)
- Observations (changes, physical activities, symptoms, etc)





Marie is very active and involved in her job, where she has a lot of responsibilities. Injecting insulin has become a banal and repetitive act. In her daily life, she sometimes forget to take her medication. She may forget to write in her diary, she may inject twice before a meal, or she may not remember What she has been doing.
The mental burden of her treatment takes up lot of her time, in addition to her work and family life.

Lastmonth, her doctor has recommended the CMD Mallya. This device is simply placed on her insulin pen and is connected to a diabetes management software on her smartphone.

After pairing Mallya with her smartphone and selecting the insuline type that Marie is using, the device dectects the dose of insulin injected, the time and the date. Next, data are directly sent to the software via Bluetooth.

In addition to saving injections data, Mallya accompanies the patient during the administration. At the time of injections, a sound and luminous indicator warns of the right running.

Marie no longer has to worry about monitoring her treatment. In case of any doubt, her software tells her whether the injection has already been given or not.

Marie can now share her data with her doctor by sending a PDF of the information collected by Mallya. Thus, her health care professional has access to accurate and quantified data. This enables him to monitor Marie's compliance, to discuss about it in case of regular omission and to adapt her treatment based on the efficiency of the injected insulin.

Today, Marie has regained control of her diabetes, while strengthening her monitoring with her doctor. With Mallya, Marie is relieved from the mental burden of her treatment and her doctor adjusts the treatment according to the data collected by the device.

V - Conclusion

In this new high-tech word, the e-health market is booming. With a high increase in demand from patients, companies are entering the CMDs race. Their objective? To support patients in their treatment, to relieve them from mental burden, to provide health care professional with accurate and quantified data, to enable personalised treatment based on those data. For compagnies, it is also an opportunity to develop innovative products and to stand out to the public.

For patients and health care professionals, CMDs are synonymous with reliability, accuracy, and convenience. The connected aspect allows them to take the regain control of their treatment by empowering them and giving them the access to their medical data. Then, patients can follow the evolution of their conditions according to their treatment and better understand their pathology and the importance of good compliance.

For compagnies, the ad of the connected system on medical devices gives a significant added value. By developing state-of-the-art products, pharmaceutical compagnies are now getting a place on the high-tech industry market.

CMDs open the door to a market with unlimited solutions to improve and accompany people with chronic disease. Nevertheless, questions arise concerning the impact of those CMDs on human relationship.

In fact, will the development of remote monitoring deteriorate the human relationship between doctor and patient? Where is the balance between medical technological innovation and the breakdown of human links? Will doctors have the same involvement and the same diagnosis for remote patients?

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Question? A Feedback?
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Sources

[1] Haynes RB.Determinants of compliance: The disease and the mechanics of treatment. Baltimore MD, Johns Hopkins University Press, 1979.

[2] Rand CS. Measuring adherence with therapy for chronic diseases: implications for the treatment of heterozygous familial hypercholesterolemia. American Journal of Cardiology,1993, 72:68D-74D.

[3] Adh.200x260/0 (who.int)

[4] Battling Nonadherence: What Actually Works (medscape.com)

[5] 17-suppl_A-8.pdf (silverchair.com)

[6] How Medication Non-Adherence Impacts Brand Management (pharmexec.com)

[7] https://www.ondrugdelivery.com/adherence-to-self-injection-regimens-can-be-enhanced-by-connected-devices/

[8] Economic impact of medication non-adherence by disease groups: a systematic review - PubMed (nih.gov)

[9] Cost of Prescription Drug–Related Morbidity and Mortality - Jonathan H. Watanabe, Terry McInnis, Jan D. Hirsch, 2018 (sagepub.com)

[10] Is My Patient Overwhelmed? - Mayo Clinic Proceedings ; Étude ComPaRe sur le « fardeau du traitement » : près de 40% des patients chroniques estiment ne pas être en mesure de supporter, sur le long terme, la charge de leurs soins | APHP

[11] https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device#step1

[12] Fiche Mémo (has-sante.fr)

[13] http://thesesante.ups-tlse.fr/2282/1/2018TOU31105.pdf

[14] https://www.pharmexec.com/view/how-medication-non-adherence-impacts-brand-management

[15] https://www.sciencedirect.com/science/article/abs/pii/S0738399118308723

[16] https://www.has-sante.fr/jcms/c_2056029/en/e-sante

[17] https://www.sanofi.fr/fr/labsante/e-sante-les-grandes-tendances-d-un-marche-en-pleine-expansion

[18] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6214883/

[19] https://www.accenture.com/_acnmedia/PDF-118/Accenture-2020-digital-health-consumer-survey.pdf

[20] https://myurgence.com/rapport-complet-sur-le-marche-des-dispositifs-medicaux-connectes-2021-tendances-demande-de-croissance-opportunites-et-previsions-jusquen-2027/

[21] https://europa.eu/youreurope/business/product-requirements/labels-markings/ce-marking/index_fr.htm

[22] http://www.eliealalam.com/blog/dispositifs-medicaux-les-reglementations-selon-les-pays

[23] https://www.has-sante.fr/jcms/c_2905546/fr/evaluer-les-dispositifs-medicaux-connectes-y-compris-ceux-faisant-appel-a-l-intelligence-artificielle