MASTER IN BIOMEDICINE PROFESSIONAL FOCUS

E-Pertension Study

Proof Of Concept Of An Enablement Suite For The Self-Measurement Of Blood Pressure In Hypertensive Patients

Noël, Cyril

Award date:
2019

Awarding institution:
University of Namur

Faculté de Médecine

E-PERTENSION STUDY: PROOF OF CONCEPT OF AN ENABLEMENT SUITE FOR THE SELF-MEASUREMENT OF BLOOD PRESSURE IN HYPERTENSIVE PATIENTS

Mémoire présenté pour l'obtention

du grade académique de master en sciences biomédicales (Master 120)

Cyril NOEL

Janvier 2019

Université de Namur
FACULTE DE MEDECINE
Secrétariat des départements
Rue de Bruxelles 61 – 5000 NAMUR
Téléphone: + 32(0)81.72.43.22
E-mail: manon.chatillon@unamur.be – http://www.unamur.be/

E-pertension study: Proof of concept of an enablement suite for the self-measurement of blood pressure in hypertensive patients

NOEL Cyril

Abstract

Background: Arterial hypertension is a major health concern. It affects more than a billion of people worldwide and is known as a *"silent killer"*, which impact the patients' therapeutic adherence and thus their treatment efficiency. A potential way to improve the therapeutic adherence is the use of blood pressure self-measurement in combination with new technologies such as the mobile health (mhealth).

Aim: Proof of concept study aimed at developing and evaluating, in terms of functionality, feasibility and performance, a digital platform to improve the self-management of hypertensive patients.

Methods: The platform was developed in collaboration with the "Connected Health" team from Nokia Belgium. Once the platform was ready to be tested, 8 patients were recruited. The patients were added in the platform and they were given a blood pressure monitor device (Withings BPM-801) in order to perform their self-measurements. The devices are to be used with a smartphone application, the "Nokia Health Mate" and all the data collected in the smartphone application are sent to the platform, where a healthcare professional can manage them. The patients have to take their blood pressure twice a week during two months (8 weeks) and they will receive reminders, warnings or encouraging messages according to their blood pressure or measurements performed or not.

Analysis: The platform was shown to be functional and efficient with 187 out of 223 measures correctly transferred (83,85%). A database issue occurred at the initiation but was rapidly corrected and another issue occurred at the end of the study but was not related to the platform itself. The patient compliance to the protocol was relatively high with 223 out of 252 measures done (88,5%). Regarding the blood pressure data, the study sample was too small to see significant differences but some slight changes can be seen in several patients. For the feasibility, 7 out of 8 patients found this system very helpful and were ready to extend this practice.

Conclusion: The platform need to be more robust in order to prevent the issues encountered and need some slight adaptation but it was showed to be functional, efficient and useful for the patients. A further study might then be envisaged in order to test the potential benefit in poor or non-adherent hypertensive patient.

Keywords: arterial hypertension, adherence, self-measurement, connected device, home blood pressure monitoring

Mémoire de master en sciences biomédicales

Janvier 2019

Thesis Supervisor: Marc Tomas

Acknowledgment

All this work wouldn't have been possible without the help of many people.

First of all I would like to thank Dr Marc Tomas, my thesis supervisor, for this wonderful project. We had ups and downs but he was always optimist, in good mood and encouraging me to do my best. He often had great ideas and a good expertise which allowed me to go through this work without hesitation.

I thank Dr Philippe Delmotte for his participation and advices as an investigator and Pr Alexandre Persu for reviewing and keeping an eye on this project.

I particularly thank Pascal Dal Farra, Roel Vanstiphout and the other members from the "Connected Health" team at Nokia Belgium for all the work they did on the platform, for their support and their dedication to the project.

I express my deep gratitude to my parents and my family for allowing me to do all these years of study and for their support. I also thank my friends for their support during these years and during this project.

Finally, I thank the people who will take time to read this manuscript.

"Whatever can go wrong, will go wrong"

-Murphy's Law

"Success is no accident. It is hard work, perseverance, learning, studying, sacrifice and most of all, love of what you are doing or learning to do"

-Pelé

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I. Abbreviation

ABPM	Ambulatory Blood Pressure Monitoring
ACC	American College of Cardiology
ACE	Angiotensin Conversion Enzyme
ACTO	Access to Care and Therapy Optimization
AHA	American Heart Association
AHT	Arterial Hypertension
AIDS	Acquired Immune Deficiency Syndrome
ARMS	Adherence to Refills and Medication Scale
ASH	American Society of Hypertension
BMI	Body Mass Index
BMQ	Brief Medication Questionnaire
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
HBPM	Home Blood Pressure Monitoring
HPLC	High Performance Liquid Chromatography
ICER	Incremental Cost Effectiveness Ratio
MARS	Medication Adherence Rating Scale
MMAS	Morisky Medication Adherence Scale
MPR	Medication Prescription Ratio
PDC	Proportion of Days Covered
QALY	Quality Adjusted Life Years
QoL	Quality of Life
SEAMS	Self-Efficacy for Appropriate Medication Use Scale
WTP	Willingness to Pay

II. Introduction

a. Arterial Hypertension

Arterial hypertension is defined by an increase of the arterial systolic pressure above 140mmHg and/or an increase of the arterial diastolic pressure above 90mmHg [1]. This increase must be confirmed by several measures of the blood pressure [2]. More recently the new American guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA) revised downward the threshold of arterial hypertension by defining an elevated blood pressure when above 130/80 mmHg regardless the age [3]. However, the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines define a systolic blood pressure target less than 140mmHg for the majority of patients and less than 130mmHg for the patients younger than 65 years [4]. The total number of hypertensive people reaches one billion worldwide and arterial hypertension is more prevalent in African countries (46%) than in high income countries (35%) [2].

About 95% of arterial hypertension cases are of essential origin which means that the etiology is unknown. Nevertheless some risk factors can be distinguished such as age (>60 years old), obesity, absence of physical activity or high sodium chloride intake [2]. Secondary forms of arterial hypertension also exist. Those forms can usually be cured and include: iatrogenic hypertension due to the uptake of alcohol or drugs such as oral contraceptives, cyclosporine, tacrolimus, illicit drugs (cocaine, amphetamines); hypertension due to renal artery stenosis and "adrenal" hypertension as a consequence of an adrenal tumour or hyperplasia with a hypersecretion of aldosterone, catecholamine or cortisol. "Masked" and "white coat" hypertensions should also be distinguished. The masked hypertension shows normal results of blood pressure at the physician's office but high blood pressure in self-measurement at home while the white coat hypertension shows normal results in self-measurement but high blood pressure at the physician's office [2, 3].

The diagnosis should include the hypertension state, assess the presence of secondary forms of arterial hypertension and evaluate the cardiovascular risks. The measurement of blood pressure at the office is performed with auscultatory or oscillometric semiautomatic sphygmomanometers placed at the upper arm. Beside the office's measurement it is also possible to perform ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM). Those techniques allow multiple measurements away from the medical environment [1]. ABPM is the measurement of blood pressure for a period of 24 hours or more with the use of automatic and wearable manometer. The measurement is usually performed every 15 minutes during the day and every 30 minutes overnight. HBPM consists of the auto-measurement of blood pressure at home during at least 3 consecutive days following the European Union (EU) guidelines [1]. These measurements are done with arm or wrist devices, but these latter are less recommended [5]. In the HBPM, the measurements should be done at least twice a day (in the morning and in the evening). In the long-term

follow-up, less frequent measurements can be performed aimed at reinforcing adherence. This provides data from the everyday routine which are more reliable [2]. These two lasts types of measurement are useful for patient's follow-up. The ABPM was considered as the best way to measure the blood pressure at home. However, the HBPM is more and more considered as a complementary method to the ABPM. Monaco et al. (2016) compared the two methods and demonstrate that HBPM cannot substitute the ABPM. Indeed, there was not a high degree of agreement between the two methods. The discrepancies come from the fact that in the HBPM there could be inaccuracy in patients' measurements. Patients' training and the development of the HBPM technology (e.g. devices connected with smartphones) may reduce this discrepancies [6].

Once the measurements are done, a therapeutic decision can be taken. If the blood pressure is lower than 130/80mmHg, no intervention is needed. If it is in the high average (130-139 and 85-89mmHg) a primary prevention should be considered such as reducing the risk factors. If it is above 140/90mmHg and confirmed, anti-hypertensive drugs should be considered (Figure 1).

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
1–2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
≥3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • BP drugs targeting <140/90	• Lifestyle changes • Immediate BP drugs targeting <140/90

Figure 1. Table adapted from the ESC 2013 guidelines [1] containing the therapeutic decisions that can be taken in regards with the patient's condition.

Those values correspond to the Office Blood Pressure Measurement but they are not the same for ABPM and HBPM. In Europe, the threshold is 130/80mmHg for ABPM (corresponding to the mean of day and night measures) and 135/85mmHg for HBPM [2]. Anti-hypertensive drugs are divided in different classes: diuretics, beta blockers, calcium channel blockers, angiotensin-converting- enzyme inhibitor and sartans (angiotensin II receptor antagonists). An association of those drugs may be also envisaged. Alpha blockers, vasodilators and central anti-hypertensive drugs are less indicated [7].

This proof of concept study consists of developing and testing a digital platform to be combined with the HBPM technology and is a precursor of a further study in which we will evaluate the impact of this platform on the therapeutic adherence among hypertensive patients that are non- or poor adherent.

b. Therapeutic Adherence

Therapeutic adherence is defined as *"the process by which patients take their medication as prescribed"*. When patients did not follow their medication scheme correctly, there are called "non-adherent". Different terms such as compliance, persistence, and concordance are often used interchangeably to define different aspect of this process (e.g. concordance is used to describe the relationship between the general practitioner and the patient) and that may lead to confusion. Vrijens et al. (2012) thus proposed a new taxonomy. They defined *"Adherence to medication"* and *"Management of adherence"* as *"the process by which patients take their medication as prescribed"* and *"the process of monitoring and supporting patients' adherence to medication by health care systems, providers, patients, and their social network"* respectively. There are different forms of non-adherence: absence of initiation by the patient; poor execution (the patient delays, omits or take extra doses); the patient discontinues his treatment (non persistence) (Figure 2) [8].

The non-adherence can be unintentional or intentional. The unintentional cause is the forgetfulness while the intentional causes may be having other things to do, intentional decision to omit the treatment, a lack of information or emotional factors. The adherence is poor when the medication's frequency of intake is high thus simple dosing (one pill a day) helps to improve the adherence [9]. The new taxonomy proposed by Vrijens et al. (2012) also emphasized the physician's role in the management of adherence (Figure 2). There are some hurdles leading to poor adherence and these hurdles may be addressed to the physician instead of the patient. Indeed, according to Devine et al. (2018) [10], the most frequent reason of non- or poor adherence is the patient's lack of motivation driven by depression which can be translated into physician's perspective as an *"Inadequate effort to address depression"*. There's then a need for the physician to screen depression and give appropriate treatment to the patient. Another frequent reason of non- or poor adherence is the patient's fear about a potential adverse event which can also be translated as an *"Inadequate transmittal of information about medication"*. Tackling this problem and thus emphasizing the physician's role is a way to improve the adherence [10]. Non-adherence might also be driven by the disease itself, by the treatment, by a bad patient-physician relationship, by the treatment's cost and/or the financial status of the patient or by the system of treatment reimbursement.

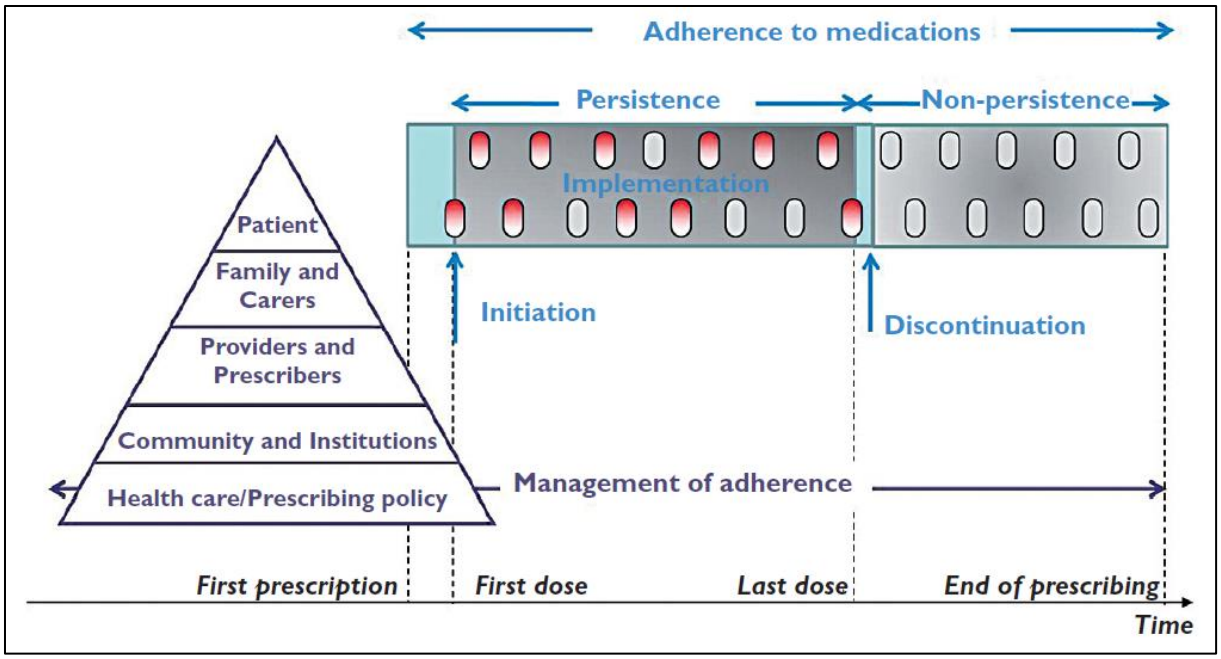


Figure 2. Illustration from Vrijens et al. [8] showing the process of adherence and the actors involved in the management of adherence.

A low adherence to medication is generally observed in hypertensive patients. Such conclusion has been obtained by different methods like the High Performance Liquid Chromatography (HPLC) urine analysis showing that 25% of a 208 hypertensive patients' cohort are totally or partially non-adherent [11] or by self- reported non adherence using a scale like the *"Morisky Medication Adherence Scale"* (MMAS) where 40.7% of 897 participants were showed non-adherent [12]. Other questionnaires exist to measure the adherence such as the Hill-Bone compliance scale, the SEAMS *(Self-efficacy for Appropriate Medication Use Scale)*, the BMQ *(Brief Medication Questionnaire)*, the MARS *(Medication Adherence Rating Scale)* or the ARMS *(Adherence to Refills and Medication Scale)* [13]. These questionnaires also cover the measurement of adherence for certain disease other than arterial hypertension like coronary heart diseases, diabetes, psychosis, acquired immune deficiency syndrome (AIDS), osteoporosis and smoking cessation. Most of them show a good internal consistency reliability with a high Cronbach's alpha coefficient (>0.8) [13]. There are other ways to measure the adherence like calculating the "Proportion of Days Covered" (PDC) or the "Medication Prescription Ratio" (MPR) which are defined by *"the number of doses dispensed in relation to a dispensing period"*. The PDC can have a maximum value of 1 (complete adherence) whereas the MPR can have a value above 1 if there is any oversupply of the medication [14]. A way to improve the adherence in hypertensive patient is the use of HBPM [15]. However the successfulness of such methods remains unclear in the long-term [16].

The relationship between the adherence and blood pressure control in arterial hypertension has been studied. Bramley et al. performed a retrospective study from 1999 to 2002 in the US on a population of 840 hypertensive patients taking a monotherapy. This study showed that the highly adherent patients are more likely to have a controlled blood pressure than the medium

or low adherent ones (Figure 3) and that a higher total number of medication is associated with a lower control of blood pressure [17]. However, only 43% of highly adherent patients achieved a controlled blood pressure (<140/90mmHg).

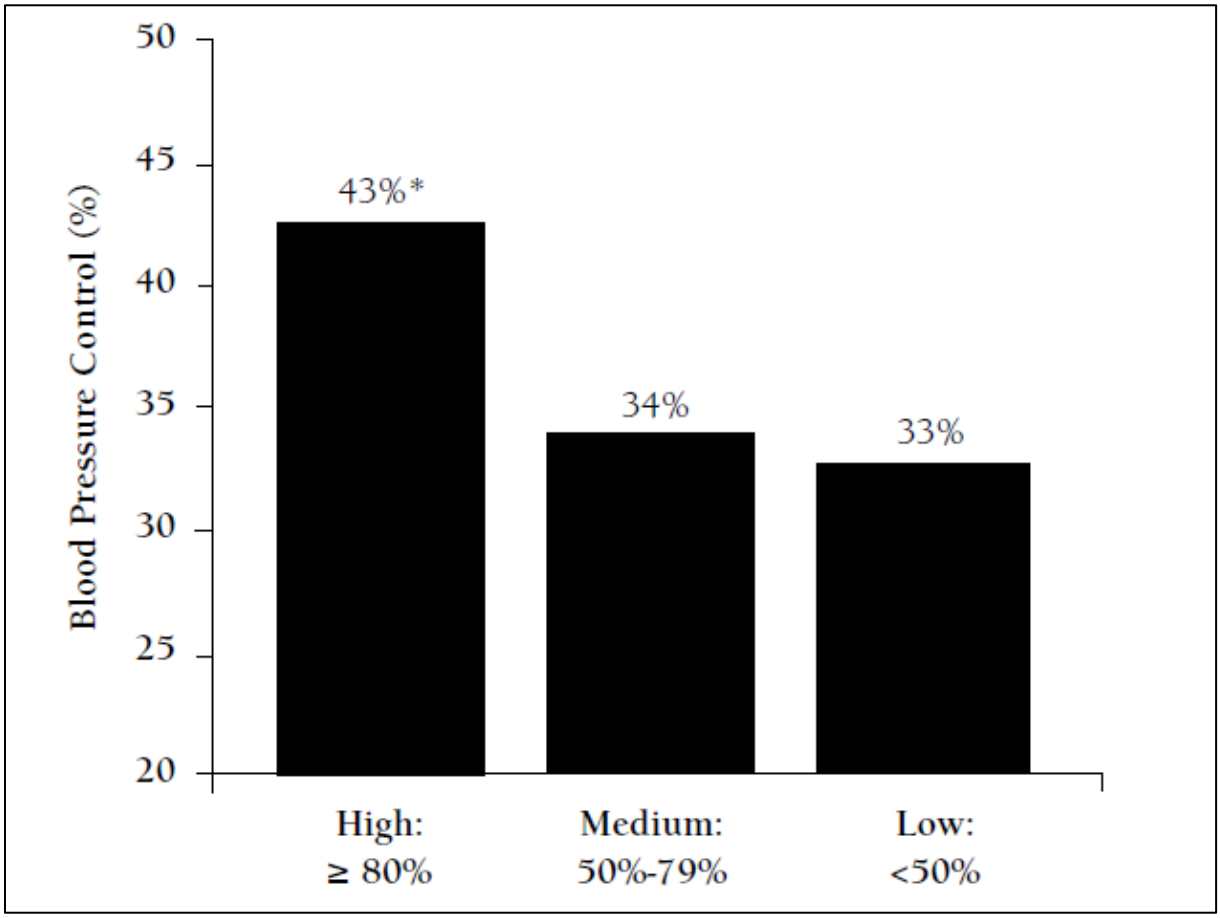


Figure 3. Figure from Bramley et al. [17] showing the percentage of patients achieving blood pressure control (<140/90mmHg) according to their level of adherence to the medication.

The relation between the adherence to antihypertensive drugs and the risk of cardiovascular events was assessed by Perreault et al. [18]. They made a retrospective study on a cohort of 83 267 patients treated with antihypertensive agents between 1999 and 2004. The rate of cardiovascular events was determined with respect to the adherence level to antihypertensive drugs which was calculated using the MPR. It was then found that a higher level of adherence was associated with a risk reduction of cardiovascular events [18].

The adherence was also studied according to the class of antihypertensive agents [19]. The meta-analysis performed by Kronish et al. found that there was a relationship between the adherence to antihypertensive agents and the drug class. Indeed, the diuretics and beta-blockers were associated with a lower adherence compared to the angiotensin-II receptors blockers and angiotensin conversion enzyme inhibitors which are associated with a better adherence. These differences are probably due to the side effects brought by the drug class (e.g. the diuretics induce and increase urinary frequency) or due to the patients' beliefs about medication [19]. This might then be factors to modify in order to increase the adherence.

The American Society of Hypertension (ASH) published in 2010 a position paper emphasizing the importance of therapeutic adherence and persistence to control blood pressure [20]. They identified the problem's scope of a lack of adherence and they reviewed scientific background to support the importance of adherence while taking medication. Eventually, they provided some recommendations such as to focus on the clinical outcomes to maintain a goal blood pressure over time; to empower, inform the patients and make them more active in their treatment, they have to learn how to take care of themselves; to implement a team approach to deliver a collaborative care and to be more patient-centred; to advocate for health authorities to increase the awareness about the importance of therapeutic adherence [20].

c. Digital Health and telemonitoring

With the development of science and technology occurs a new way to diagnose and follow diseases. Digital health, e-health or telemedicine have appeared and with it mobile health (mHealth) and connected medical devices [21]. The mHealth consists of using portable devices with digital applications in order to follow patient's health condition. With billions of mobile phone users, such way to enhanced healthy behaviours has to be considered [22]. There are different types of devices like the *"Smartphone-connected rhythm monitoring devices"*, the *"Wireless and wearable devices"* and even *"Implantable and ingestible sensors"* (Figure 4). With that type of technology, a question to ask is "Are the patients ready to use these connected devices and will it improve their condition?" Several telemedicine trials show encouraging results with improvement of patients' condition [21]. Indeed, Kim et al. (2016) [23] performed a trial with hypertensive patients distributed between a monitoring and a control group in order to evaluate the influence of a self-monitoring program on the health behaviours, the therapeutic adherence and the control of blood pressure. The monitoring group had an improvement of the health condition, showing that hypertensive patients are receptive to that type of program. There was no difference in their therapeutic adherence (measured with a Morisky scale). However the patients were already relatively adherent (with a median Morisky score at 7.0) and probably had a higher health literacy because of working in a hospital. This results in a selection bias. Further study is then needed to evaluate the impact on the adherence [23].

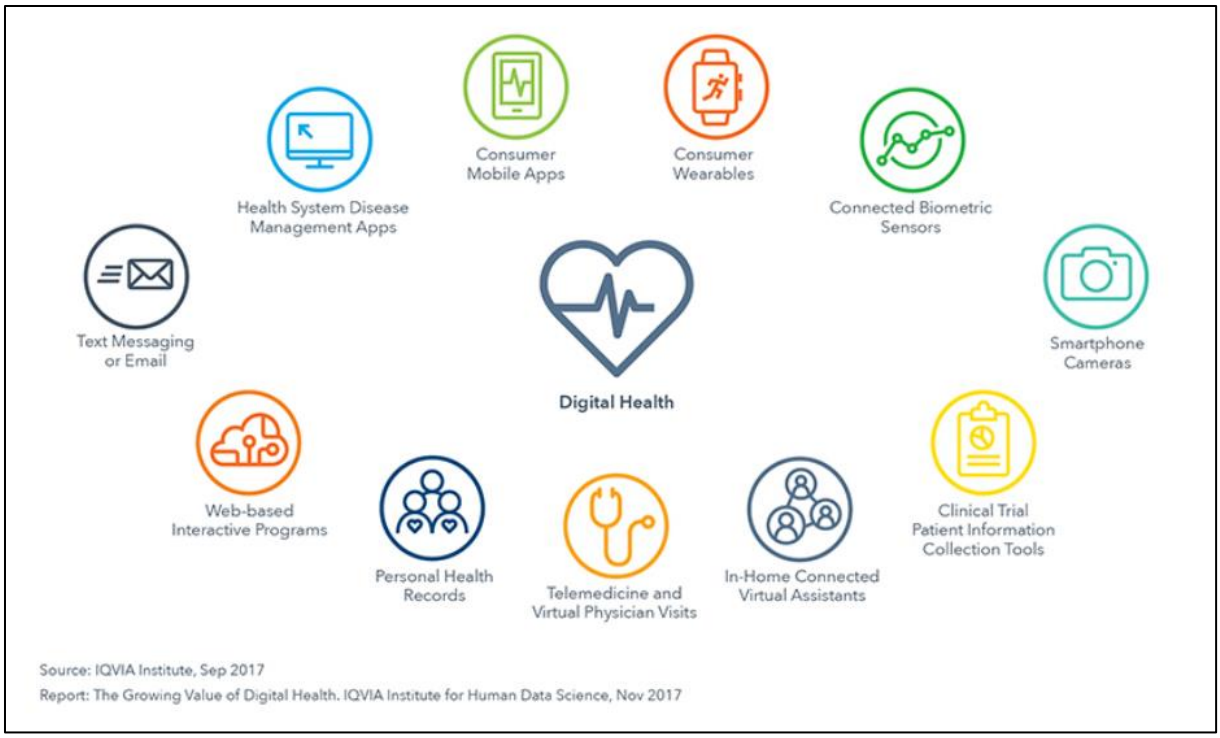


Figure 4. Chart from the IQVIA 2017 report "The Growing Value of Digital Health" showing different tools in the field of digital health.

To have a better management of the arterial hypertension, software for self-interpretation of blood pressure measurement results were created to work with connected devices. These softwares are based on an algorithm that will help the users (the patients) to interpret their blood pressure results. The patients have to enter their personal information such as the age, the weight and height in order to calculate their Body Mass Index (BMI), their medication scheme, their comorbidities, and then they can enter their values of self-measurement of blood pressure. The software will then check the data and reject the abnormal values (in the case of the Hy-result software, a systolic blood pressure below 60mmHg and a diastolic blood pressure below 40mmHg are considered abnormal). A blood pressure mean will be calculated and messages will be sent to the patients whether or not they have to go to their general practitioner or to adapt their medication schedule. Such softwares have been evaluated and have been proven to be at least as accurate as the physician's assessment [24].

Nevertheless the healthcare professionals remain reluctant to this kind of technology. Despite being more personalized for the patient and its ability to share easily the information about diseases, there are still some hurdles to pass like lack of confidence in such technology, legal issues concerning data protection or reimbursement issues [25]. There might also be a legal liability issue if a patient die while the general practitioner received the patient's data but didn't react to an abnormal value. Moreover, this type of technology needs a social dimension to be effective and it needs to be in harmony with what matters to people. To assess this need of social dimension, Greenhalg et al. (2015) performed a 3-phase study. The first phase consisted of an interview of technology and service providers. The second phase was an ethnographic study of patients in order to get information about their lives with a disease. For the last phase, they made workshops with patients and technology and service providers in

order to make them interact, identify the challenges and have new ideas. Both patients and providers found out that this kind of technology need to be customizable to meet the users' requirements. It has also been found that service providers are stuck with standard packages and have to deal with it. A greater pledge between service and technology providers is then required. Finally, patients emphasized that service providers have to interact more with them and create more personal relationships. In brief, a human effort is needed to improve the user's understanding and involvement in such technology [26].

The ESC took a position to enhance the e-health and to tackle these hurdles. They will play a pro-active role and developed an action plan that includes and covers: implementation of e-health; education and training; regulation and quality control; data security and confidentiality; emphasizing the research and cost-effectiveness; solving the reimbursement issue and assessing the benefits and risks of e-health. There is also a more specific issue with the mHealth. Indeed, there are hundred thousands of Apps available that have been downloaded millions of times but there is a lack of distinction between a medical App and a lifestyle App, there is an issue about privacy, confidentiality and data use, healthcare providers are then unsure about this technology. The ESC will then be a key stakeholder and works with the other stakeholder such as the patients' organization, health professionals, authorities and App developers to improve the global quality of these Apps. This mHealth is a way to move from care to prevention [25].

Regarding the costs, Kaambwa et al. performed a cost-effectiveness analysis of the TASMINH2 study which evaluate the effect of telemonitoring and self-management in the control of arterial hypertension. This study compared the use of automated sphygmomanometer and some equipment to transmit the measures to the usual care for 12 months. It was found out that the use of automated sphygmomanometers induced a reduction in blood pressure by 5.4/2.7 mmHg, made the patients take more medications and made them change their treatment at least once [27]. The cost-effectiveness analysis found an incremental cost effectiveness ratio (ICER) of 1891€ per QALY gained (Quality Adjusted Life Years) in men and an ICER of 5733€ per QALY gained in women. The self-management is then more costly than usual care but it provides a better quality of life (QoL) due to a decrease of cardiovascular events and is still more cost-effective than usual care when looking from a long term period of 35 years with a willingness to pay (WTP) threshold of 23 000€ to 35 000€ per QALY gained. These results show that the self-management of arterial hypertension with the help of telemonitoring reduce the blood pressure but is also cost-effective when compared to usual care [27].

III. Specific aims

In collaboration with the "Connected Health" team from Nokia Belgium, the ACTO research group of the University of Namur, Faculty of Medicine, developed a digital platform, the « Enablement Suite », to improve self-management of hypertensive patients, especially the non-adherent ones. The current study is a proof of concept phase aimed to evaluate the feasibility, usability and performance of such a platform in view of future clinical trials to be conducted to evaluate the benefit in poor-adherent patients.

IV. Methods

a. Literature review

The Pubmed database was consulted with the following key words: "arterial hypertension"; "adherence"; "self-measurement"; "HBPM"; "connected device"; "intervention". The articles older than 10 years were generally excluded.

The French website "Haute Autorité de Santé" has also been consulted in order to find general information about arterial hypertension.

b. Design and study sample

This trial is a proof of concept study on hypertensive patients. The web platform "Suite" was developed by Nokia with the collaboration of the promotors from the Namur University. After an approval by the ethics committee from the Ambroise Paré hospital (Mons), 8 hypertensive patients are recruited at the hospital from the consultation of Doctor Delmotte, following several inclusion and exclusion criteria (Table 1), in order to test the platform in combination with the connected device BPM[1] from Nokia. Patients will have to measure their blood pressure during 2 months. The arterial hypertension condition is based on their medical dossier and the prescription of anti-hypertensive compounds. According to the AHA recommendations, hypertensive patients presenting arrhythmia can't participate in this trial because the device might not give accurate measures due to this condition [28].

[1] https://health.nokia.com/eu/fr/blood-pressure-monitor

Inclusion criteria	Exclusion criteria
- Patients from at least 18 years old - Patients who have a smartphone able to run the platform and that allows access to Internet - Patients who are treated with at least one anti-hypertensive drug	- Patients with cognitive disorders - Patients without capability to follow a 2 months protocol - Patients who do not understand French and unable to understand the informed consent - Patients included in another trial - Patients with blood pressure above 200/110mmHg - Patients presenting significant arrhythmia

Table 1. Inclusion and exclusion criteria for participation in the study.

c. Platform development

The HBPM is performed using connected devices from Nokia: the BPM device (Withings BP-801). These devices were provided by Nokia and they are to be used with a smartphone application, the "Nokia Health Mate" (available on Apple and Android smartphones), with which the patients will be able to register the measurements (Figure 5). There is no digital interface on the devices, which make them unable to perform the measurements without a smartphone. During the follow-up period, in combination with those devices, the patients also get an access to the digital platform developed by Nokia and ACTO in order to follow their blood pressure and receive comments or advices (Figure 6). This platform contains one questionnaire at their inclusion in the study to collect their socio- demographic factors (gender, age, social status …), their clinical factors (treatments, comorbidities…) (Appendix 1) and a satisfaction survey at the end of the trial (Appendix 2).

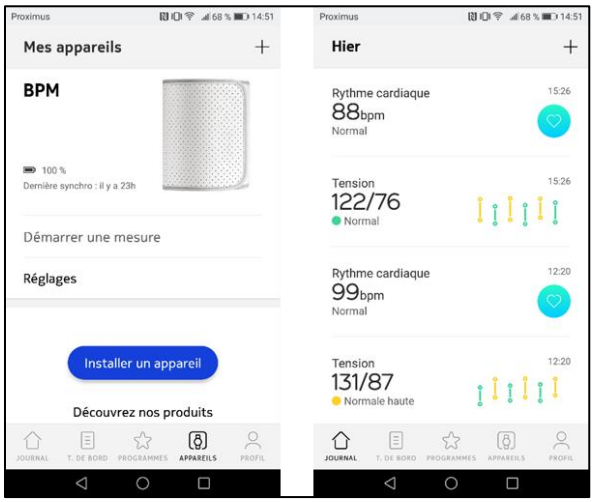


Figure 5. Nokia Health Mate smartphone application.

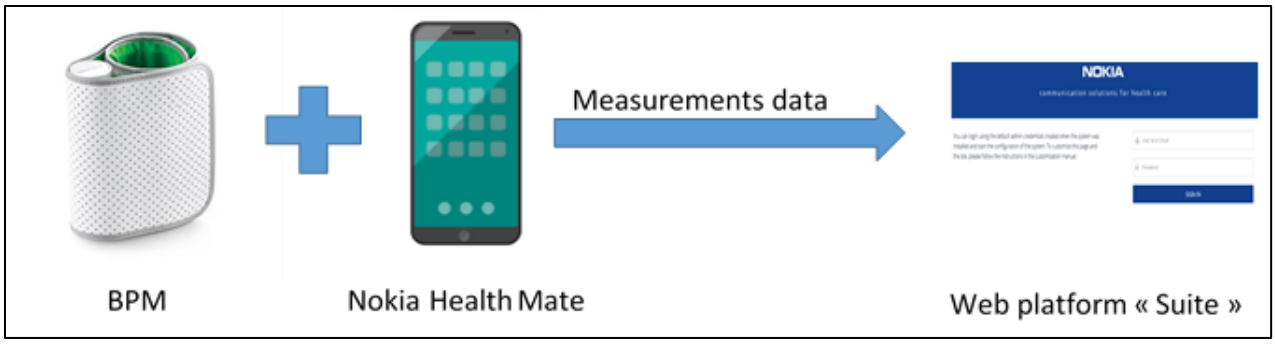


Figure 6. Summary of the whole system developed.

The platform also records their blood pressure values, the date and the hour of the measures. It sends warnings and messages to the patients. We developed 4 types of warnings:

- the measures are not performed
- there is a technical error
- abnormal values are detected
- warnings related to non-adherence to the protocol

The technical error may occur if the patient did not place the device correctly or move during the measurement.

The values are considered abnormal if there are under 90/50mmHg or above 200/110mmHg. These warnings are sent to encourage the patients to repeat the measurement or advise them to contact their general practitioner or their specialist (Appendix 3). Indeed this is only a monitoring tool and the general practitioners remain the only people able to treat the patient in case of an elevated blood pressure. Therefore in such case the patients are advised to contact them for a check-up or a refill if they are lacking of antihypertensive drugs.

In this platform, three types of accounts are available: epertension-admin, epertension-config and epertension-expert. Screenshots of the different tools present in the platform are available in appendix 5.

The “epertension-admin” account is used to add healthcare professionals and patients to the platform and gather them in “Care group” so that each professional can see the results from his patients and has no access to other patients from other professionals. Some “Tracking limits” were established that can be personalized by the physician if needed. These tracking limits are related to a color code which helps the physician to see quickly how his patients’ blood pressure is. The red is used for blood pressure measures that are outside the limits (>135/85mmHg or <100/60mmHg), yellow is used for blood pressure measures that are in the limits but almost outside (between 100/60mmHg and 110/75mmHg or between 120/80mmHg and 135/85mmHg) and green is used for blood pressure measures that are within the limits (110/75mmHg to 120/80mmHg). The tracking limits established in the admin account can be personalized in the expert account for each patient, allowing then a more personalized follow-up of blood pressure according to the patient condition (Figure 7).

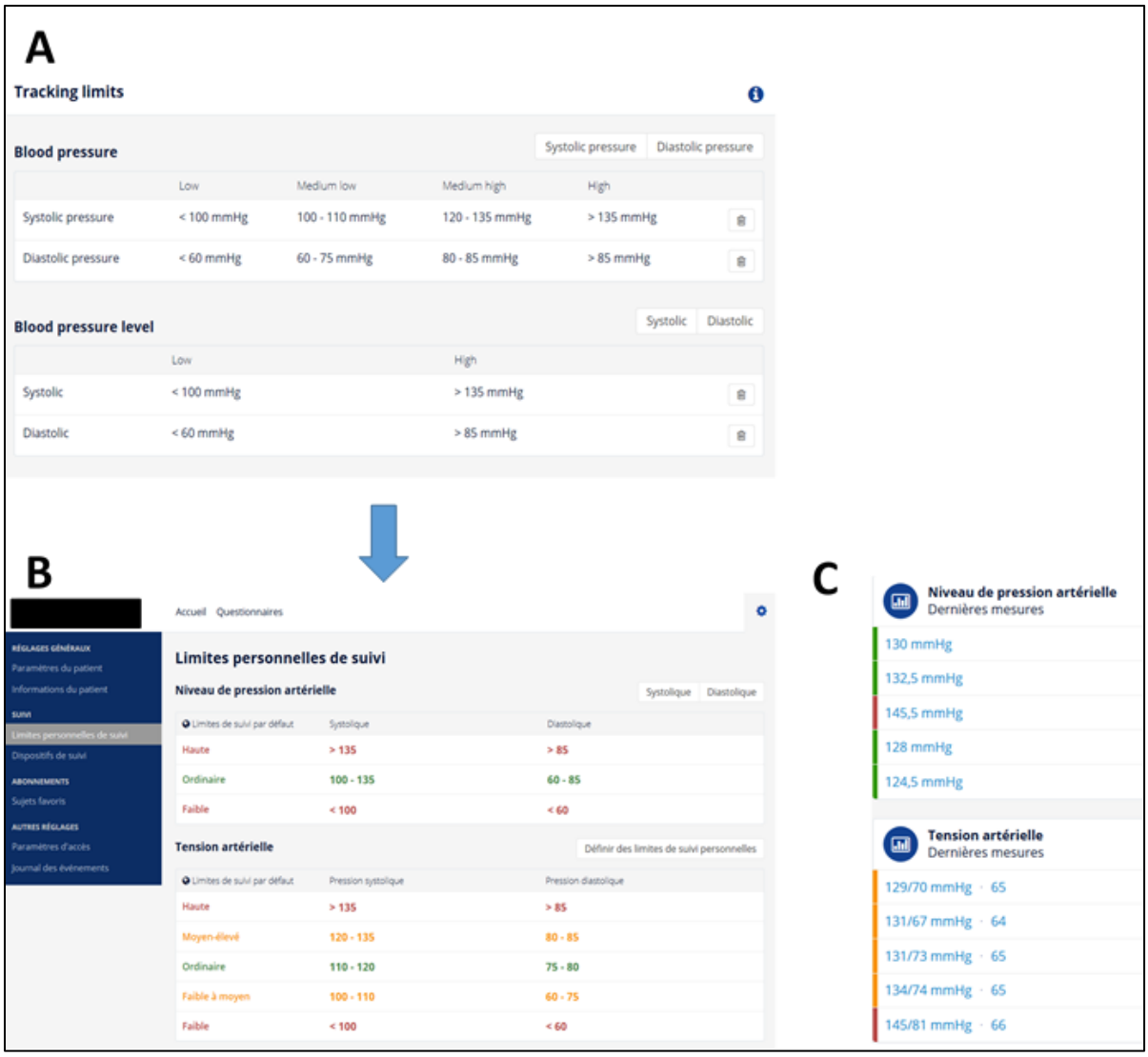


Figure 7. Tracking limits as seen in the admin account (A) and in a patient's profile in the expert account (B). The color code is visible next to the patients measures (C).

The "epertension-config" account is used to define different settings for the admin and expert accounts such as the questionnaire that will be submitted to the patients or the trackers that the admin and expert account can use like blood pressure, blood glucose, oxygen saturation and so on (Appendix 5).

The "epertension-expert" account is the account used by healthcare professionals. This account allows them to add their patients in the system as well as the "epertension-admin" account and to see their patients' profile. In the patient's profile, the latest measurements are shown as well as their answers to the questionnaires. The blood pressure measurements can be seen as a list or they can be plotted in a chart. The healthcare professionals also receive some alerts, called "cases" that are related to the alerts that the patients receive. A case is created if the patient is not compliant to the protocol, if the patient took more measures than asked or if the patient's blood pressure is out of range. The importance of these case is identified by a color code: green is for too much measurements than what was asked or a lack of measures during the first part of the week; orange is for less measurements than what was asked at the end of the week and

red is when the patient's blood pressure is out of range (<90/50mmHg or >200/110mmHg) (Figure 8).

Figure 8. Color code on the "Case" page from the expert account.

d. Patients' inclusion and follow-up

Hypertensive treated patients presenting at the consultation of arterial hypertension of the Ambroise Paré hospital and at the Dr Delmotte's private office are invited to participate to this proof of concept study. Due to a delay in the recruitment some patients were also recruited outside the Dr Delmotte's consultations. The patients are informed about the conduct of the trial and they receive an informed consent form to read at home. If the patients agree to participate, they are invited to come at a training session at the Ambroise Paré hospital. The patients coming from outside Dr Delmotte's consultations were seen in the place which they wanted.

During this training session, the investigator asked to each patient if they have any questions concerning the protocol or the inform consent form. The inform consent form is then signed by both the investigator and the patient who is then registered in the system. Firstly the investigator helped the patients to create an account on the "Nokia Health Mate" app on their smartphones. Secondly he created a patient account on the web platform and linked both accounts. The patients are then trained on how to use the device along with the app and how to answer to the general information questionnaire. Once these steps are done, the patient may return to home with the device.

The patients are contacted by phone during the period of the trial. These phone calls to the patients are done during:

- The first week
- At the end of the first month
- At the end of the second month

These calls are done by the research team in order to identify if they face any issue like a non-working device or difficulties to remember the use of the suite. Patients are also able to contact the research team at any time in case of problems. The patients' feedback is also collected at the end of the trial.

e. Blood pressure measurements

Patients were instructed to perform their self-measurements at home, at least 2 days a week, 2 times in the morning and 2 times in the evening. This schedule is in alignment with the guidelines from the ESH, that recommends a minimum of 3 days a week of measurements or 1 or 2 measurements a week in case of a long term follow-up [29]. A third measurement is asked if the second measure performed is significantly higher or lower than the first one (more than 20mmHg of difference in the systolic blood pressure). It is indeed expected that some stress can occur during the first measure. The platform collects all the raw data, meaning that in case of a third measure, all of them will be kept but the data are also computed in order to make the mean between the second and third measure (Figure 9). The first measures should be recorded no later than Wednesday evening and the second measures should be recorded no later than Sunday evening. A message is sent to the patient each time that the measures are not recorded on Wednesday or Sunday evening to remind them to measure their blood pressure. This reminder has the objective to test if it can improve their adherence. A message is also send to the patient each time they take correctly their blood pressure.

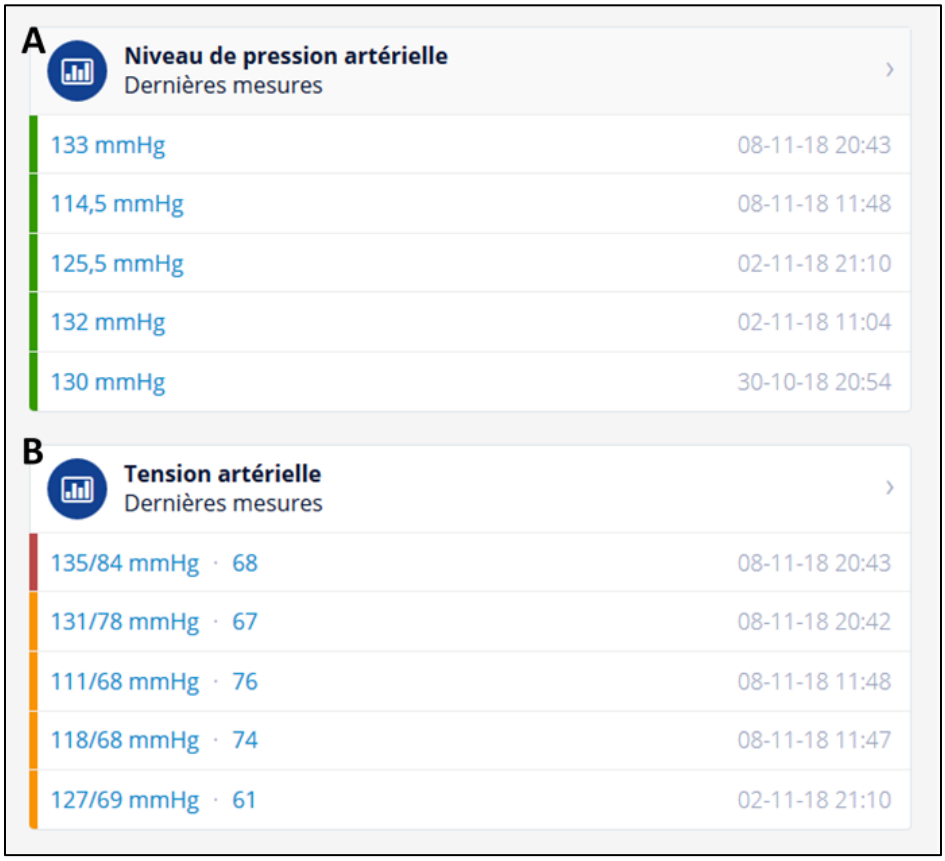


Figure 9. "Niveau de pression artérielle" (A) are the computed data and "Tension artérielle" (B) are the raw data in a patient profile. More details for the computed data can be obtained by clicking on them.

Patients were instructed to perform their self-measurements in a seated position, after few minutes of relaxing and to avoid talking during the cuff's inflation. A second measurement has to be executed directly after the first one. The cuff has to be placed around the upper arm, few centimetres above the elbow and the arm has to rest on a table during the measurement. All the information about the measurement's schedule and the use of the device are resumed in a patient leaflet received at the training session (Appendix 6).

f. Privacy and confidentiality

Patients' data will be collected only when they have read and signed the informed consent given to them at the inclusion visit (Appendix 4).
Patients' data will remain confidential and will be fully anonymised in case of publication. Individual data will not be accessible to the promotor or to Nokia Company.

g. Endpoints

The primary endpoint of this study is to identify the convenience of the Suite in terms of applicability and functionality.

Secondary endpoints are:

- Patients' feedback at the end of the 2 months. A questionnaire (Appendix 2) is addressed to the patients aimed to collect their level of satisfaction, perception of usefulness and willingness to eventually continue this self-measurement practice

- Percentage of measurements performed (compliance to the protocol)

- Percentage of measurements well performed and errors in measurements

- Patients' systolic and diastolic blood pressure evolution

- The evaluation of the technological reliability with the wrong or unsent messages

V. Results analysis and discussion

a. Patients' characteristics

Ten patients were screened but two out of the ten patients were not recruited. One patient refused to participate because of the time that should be invest in the study. The other patient didn't make the necessary proceedings to be added in the platform. In total, 8 patients (50% men) were included in the study. The average age was 66.125 ± 12.37 years (range 46-81). The mean BMI was 31.83 ± 6.14, 3 patients had a BMI below 25 (37.5%), one patient had a BMI between 25 and 29.9 (12.5%) and four patients had a BMI over 30 (50%). A majority of the patients (75%) were retired. Half of the patients had a higher education (university or high school) as the highest grade obtained.

The majority (87.5%) of patients were diagnosed more than 3 years ago but one of these patient is treated only since 1 to 3 years. The most used antihypertensive class of medication were the angiotensin conversion enzyme (ACE) inhibitors that were taken by 7 out of 8 patients (87.5%) followed by the diuretics taken by 3 out of 8 patients (37.5%). Four patients (50%) are in a monotherapy with ACE inhibitor. Two patients are in a polytherapy with ACE inhibitor or calcium antagonist combined to a diuretic. Two patients are in a polytherapy with a combination of ACE inhibitor, central antihypertensive drug and calcium antagonist or diuretic. Five patients take their drugs only in the morning, two patients take their drugs both in the morning and in the evening depending on the drug and one patient take the drugs only in the evening.

No patients had a history of myocardial infarction nor stroke which means that all the patients are in secondary prevention but two patients (25%) had a history of renal impairment. The patients take an average of 5.125 ± 2.80 tablets a day, including the antihypertensive medications. The patients visit their general practitioner for arterial hypertension more frequently than a specialist (2.62 ± 1.59 times per year *vs* 0.75 ± 0.7 times per year). Majority of the patients (87.5%) already took their blood pressure themselves with arm (57%) or wrist (43%) devices. Three patients have a wrist device, which are not preferentially recommended. One patient have no device at all. Despite of that, the patients don't take their blood pressure on a regular basis, 3 patients (43%) have a device but never took their blood pressure and four patients (57%) took their blood pressure only very few times a month. All these information are reported in Table 2.

n	8
Gender (males)	4 (50%)
Age (years)	66.125 ± 12.37
Professional situation (active)	2 (25%)
Professional situation (inactive)	6 (75%)
Highest grade (Higher education)	4 (50%)
Highest grade (High school)	4 (50%)
Weight (kg)	92.125 ± 25.53
Height (cm)	170 ± 8.86
BMI	31.83 ± 6.14

BMI < 25	3 (37.5%)
BMI 25-29.9	1 (12.5%)
BMI > 30	4 (50%)
ACE inhibitor	7 (87.5%)
Diuretics	3 (37.5%)
Calcium antagonists	2 (25%)
Central antihypertensive drug	2 (25%)
Hypertensive since 1 to 3 years	1 (12.5%)
Hypertensive for more than 3 years	7 (87.5%)
Treated for AHT since 1 to 3 years	2 (25%)
Treated for AHT for more than 3 years	6 (75%)
Diabetics	2 (25%)
Hypercholesterolemia	4 (50%)
Tablets per day	5.125 ± 2.80
Visits to GP for AHT per year	2.62 ± 1.59
Visits to specialist for AHT per year	0.75 ± 0.7
Previous history of myocardial infarction	0
Previous history of stroke	0
Previous history of renal impairment	2 (25%)
Previous history of HBPM	7 (87.5%)
Previous device for HBPM (arm)	4 (57%)
Previous device for HBPM (wrist)	3 (43%)
Previous HBPM frequency (never)	3 (43%)
Previous HBPM frequency (few times a month)	4 (57%)

Table 2. Patients' characteristics and clinical features.

b. Platform's functionality and convenience

Regarding the platform's functionality, some issues were encountered during the two first weeks of operation. Indeed, the addition of some of the patients in the system was not correctly performed, resulting in the appearance of duplicates in the database. These duplicates had led to a data mix up. The database was then cleaned and this issue didn't occur anymore.

At the first week call, the patients didn't report new issues and the patients stated that everything went fine. After one month, a second call was performed. During this second call, the patients didn't report any issues. Only one patient reported during the first month that there was a problem with the device which couldn't connect anymore to the smartphone. This issue was quickly resolved and was not related to the platform's functionality.

During the last week of follow-up another issue occurred which prevented the data to be transferred from the smartphone application to the platform. This issue was due to a slowdown in the smartphone application which caused delays, thus causing no data to be sent to the platform. This issue is not related to the platform, which was still fully functional, but some optimizations need to be made in order to have a more robust system which can support this kind of issue. The patients were informed about it and the latest data that have not been transferred were retrieved directly from the patients with their authorizations.

The last call, at the end of the two month, was not performed but the patients were seen face to face directly. This face to face interview allowed the investigator to get the devices back but also to collect the patients' feedback. During this interview, some patients, who were still under follow-up during the last week when the issue mentioned above occurred, only reported unsent messages and wrong reminders sent due to the issue. Except for the problems of the first and for the last week, the patients didn't report wrong messages received. One patient reported that one time he didn't receive a message when he had taken his blood pressure. Due to that he made one more day of measurements during that week.

83,85% (187 out of 223) of the data were treated correctly by the platform. 45 measures (20,18%) were not computed among which 8 measures were not computed because of the two first weeks issue and 9 measures were not supposed to be computed according to the business logic. Indeed, when the data were out of range, the data were not computed, a warning message was sent to the patient and a case was created on the expert account. Among these 45 measures, 18 were not collected by the system because of the last week issue and were retrieved directly from the patient during the feedback interview and 2 were sent directly by a patient to the investigator because this patient had a connection problem between the smartphone and the device but was willing to take the measurements in order to be compliant to the protocol. Beside the first and last weeks issues, only 8 measures (4,28%) were not treated correctly by the platform (Figure 10).

Patients	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8		Extra measures
1	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	+1 week 3 (Computed)
	V (Comp)	X	V	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	X	V (Comp)	V (Comp)	V (Comp)	X	+1 week 4 (Computed)
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	
	V	X	V	V (Comp)	V (Comp)	V (Comp)	V	V (Comp)	V (Comp)	V (Comp)	V (Comp)	X	V	V (Comp)	V	X	
2	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	+1 week 2 (Computed)
	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	+2 week 3 (Computed)
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	+2 week 5 (Computed)
	V	V	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V	V	V (Comp)	X	V (Comp)	V (Comp)	V (Comp)	X	+1 week 8 (Computed)
3	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	
	V	V	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	
	V	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	
4	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	
	V	X	V	V (Comp)	X	V	V	X	X	V (Comp)	V (Comp)	X	X	V (Comp)	V (Comp)	V (Comp)	
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	
	V (Comp)	V (Comp)	X	V (Comp)	X	V (Comp)	V	X	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	
5	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	
	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	
	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	
6	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	+1 week 6 (Computed)
	X	X	X	X	X	X	X	X	X	V	V (Comp)	V (Comp)	V (Comp)	V	V	X	+1 week 8
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	
	X	X	X	X	X	X	X	X	X	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V	V	X	
7	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	
	V	V	V (Comp)	V	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V	V	V	+1 week 1 (Computed)
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	
	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V (Comp)	V	V	V	V	
8	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Morning	Not performed		+1 week 5
	V (Comp)	X	V	V (Comp)	V (Comp)	V (Comp)	V	X	V (Comp)	X	V (Comp)	V	V	V			
	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening	Evening			
	V (Comp)	X	V (Comp)	V (Comp)	V	V (Comp)	V	X	V (Comp)	V (Comp)	V (Comp)	V	V	V			

V (Comp) Measures received and computed

V Measures received, not computed and not correctly treated (platform issue)

V Measures received,not computed but correctly treated (out of range measures)

V Measures not received and retrieved afterwards from the patient

X No measures done

Figure 10. Summary of the measures done by the patients and their management by the platform.

Based on the data received or not, 80 cases were created in the expert account among which 16,25% (13 out of 80) were “red” cases (out of range); 48,75% (39 out of 80) were “yellow” cases (incomplete measures, missing one day of measurement in a week or no measures done at all during the week) and 35% (28 out of 80) were “green” cases (no measures done before Wednesday evening or too much measurements in a week). 11,25% (9 out of 80) of these cases were abnormal and were not supposed to be created. These abnormal cases came from duplicated data during the two first weeks issue.

c. Compliance to the protocol

The patients showed generally a high compliance with 88,5% of compliance to the protocol (223 out of 252 measurements done) (Figure 10 and Figure 11). But despite this high compliance, the patients didn’t take their measurements at regular moment during the day (Figure 12).

One patient was recruited late in the study and thus only performed 7 weeks instead of the two months (8 weeks). Only one patient had a low to moderate compliance with 43,75% of measures done (14 out of 32) because he initiated the measurements more than one month after his recruitment and addition in the platform. The patient was asked why he didn’t initiate the measurements on time and he replied that he was abroad for a month without his device. Two patients are above 100% of compliance because they made extra-measures during the study.

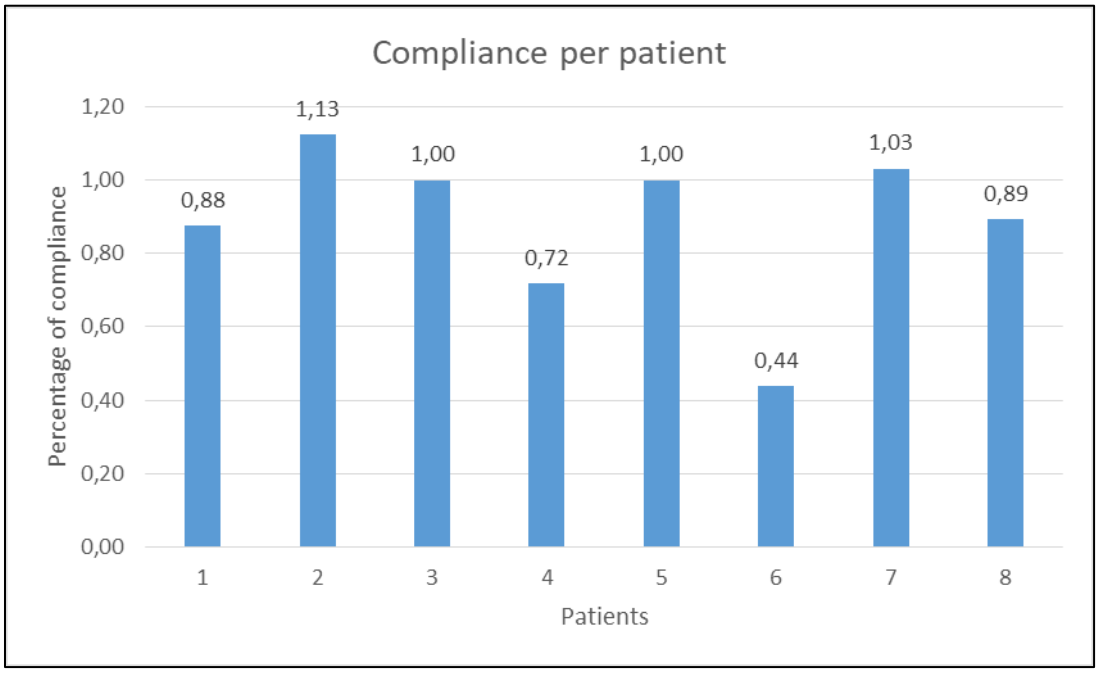


Figure 11. Percentage of compliance per patient.

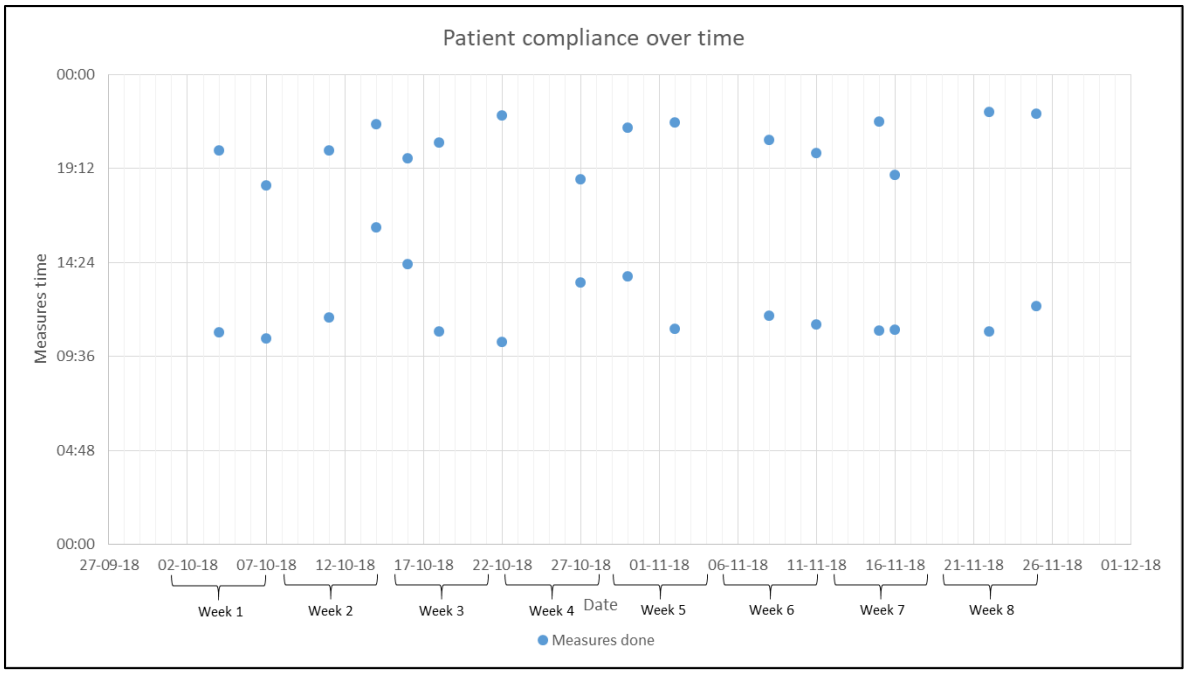


Figure 12. Patient's compliance over time. The blue dots represent each measure at which time and date. This patient had a 100% compliance but the measures are not made on regular moments.

One patient showed a sporadic lack of compliance (23/32 measures made; 71,8% of compliance) (Figure 13). During the feedback, the patient said that she was compliant but she had difficulties to take her blood pressure with the device. The blood pressure was then taken with the help of the investigator. The cuff was correctly placed and inflated correctly but for an unknown reason, the device was sometimes unable to give the results. It took several times to get a result, which is the reason why the patient sometimes gave up to take her blood pressure. The device was then tested successfully on the investigator and the patient reported to have no arrhythmia which could be a reason of this issue. According to the *"Regulatory information"* leaflet delivered with the device, other factors than arrhythmia might impact the results such as ventricular premature beats, atrial fibrillation, arterial sclerosis, poor perfusion, diabetes, age, pregnancy, pre-eclampsia or renal disease (Figure 14). When looking to the patient's profile, renal disease would be the cause of this issue. Another patient also reported having this issue once. The use of the device might then not be appropriate for every patients.

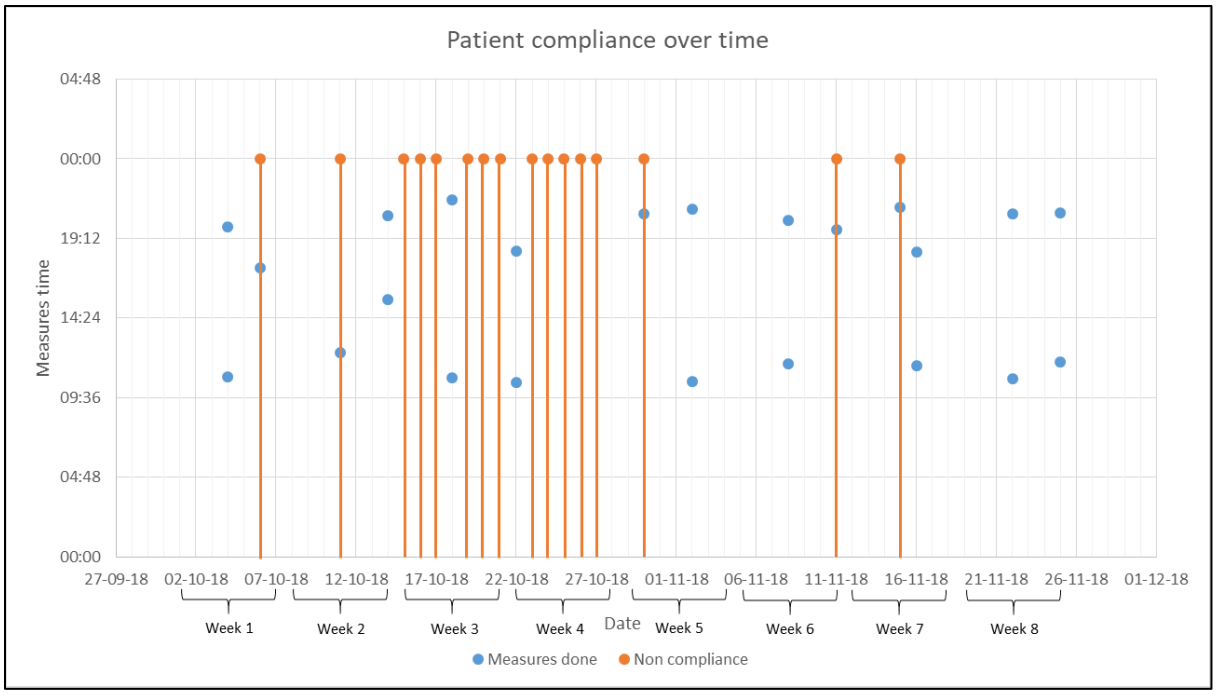


Figure 13. Patient's compliance over time. The blue dots represent each measure at which time and date. The orange lines represent the lack of compliance. A lack of compliance is considered when there is no measures at all in a week, only one measure done in a day or when there is only one day of measurement in a week.

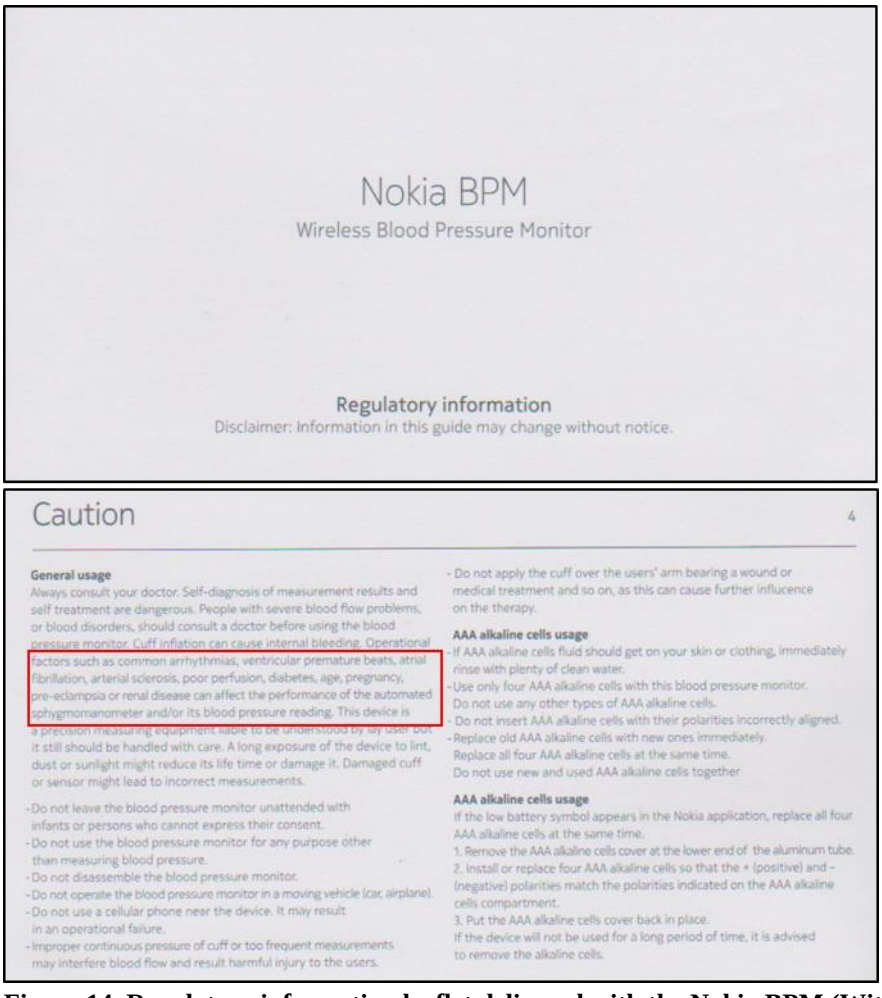


Figure 14. Regulatory information leaflet delivered with the Nokia BPM (Withings BP-801).

Conversely, some patients made more measurements than what was planned. One patient with a high compliance (30/32 measures made; 93,75% of compliance) made 6 more periods of measurement than asked in the protocol. One of them was made inadvertently, two were made because he didn't receive the message confirming that he took his blood pressure (as mentioned before), two were made because he forgot to make a third measurement that was asked by the platform and the last one was made because one day he forgot to take his blood pressure in the evening (Figure 15). This patient then achieved a compliance of 112,5% with 36/32 measures made.

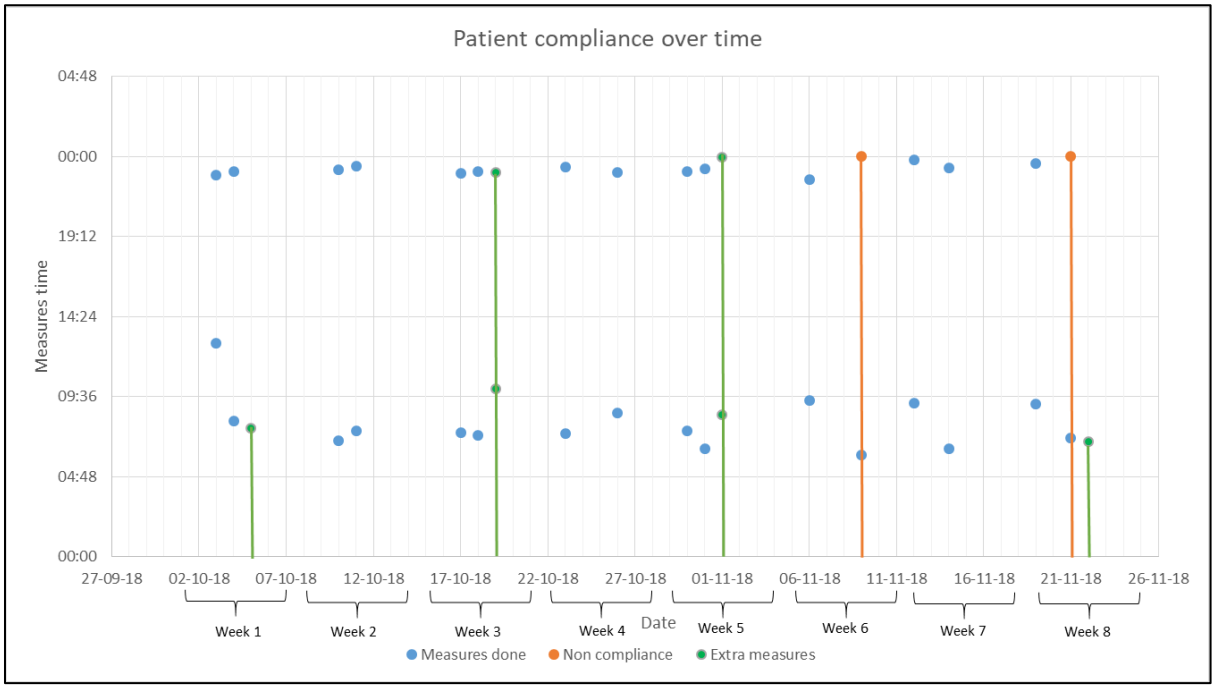


Figure 15. Patient's compliance over time in a patient with more than 100% compliance. The blue dots represent each measure at which time and date. The orange lines represent the lack of compliance. A lack of compliance is considered when there is no measures at all in a week, only one measure done in a day or when there is only one day of measurement in a week. The green lines represent the extra days of measurement.

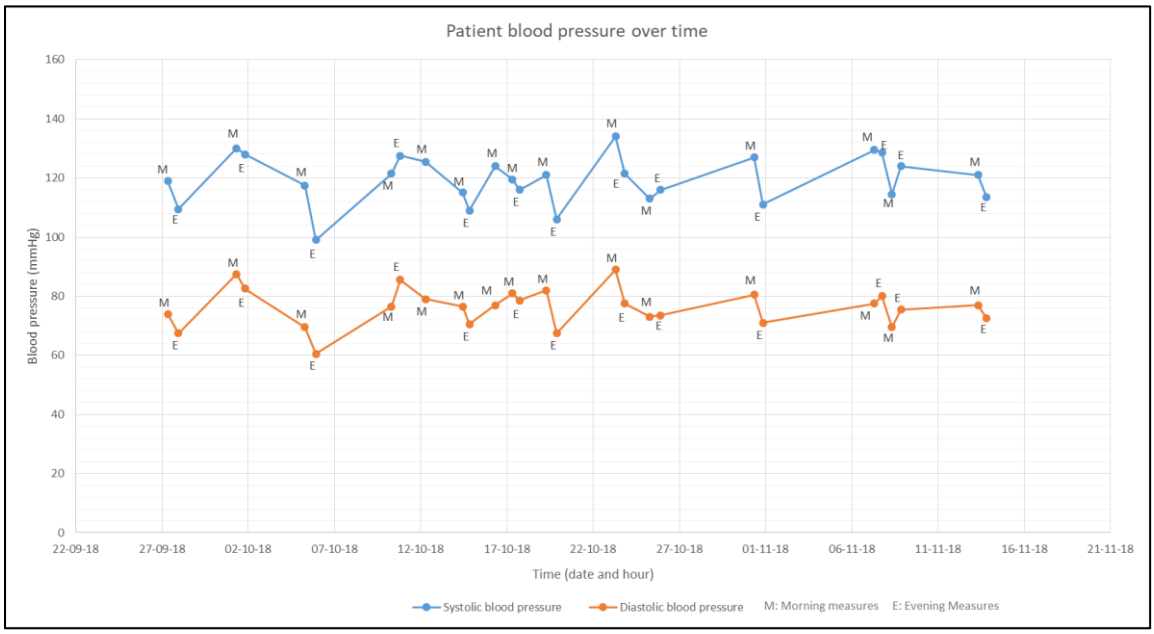
There were 77,5% (62 out of 80) of cases which came from a "compliance issue" (green and yellow cases) but 67,7% (42/62) of these cases were due to patients taking their blood pressure just after the case was created and to the patient who started very late the measurements.

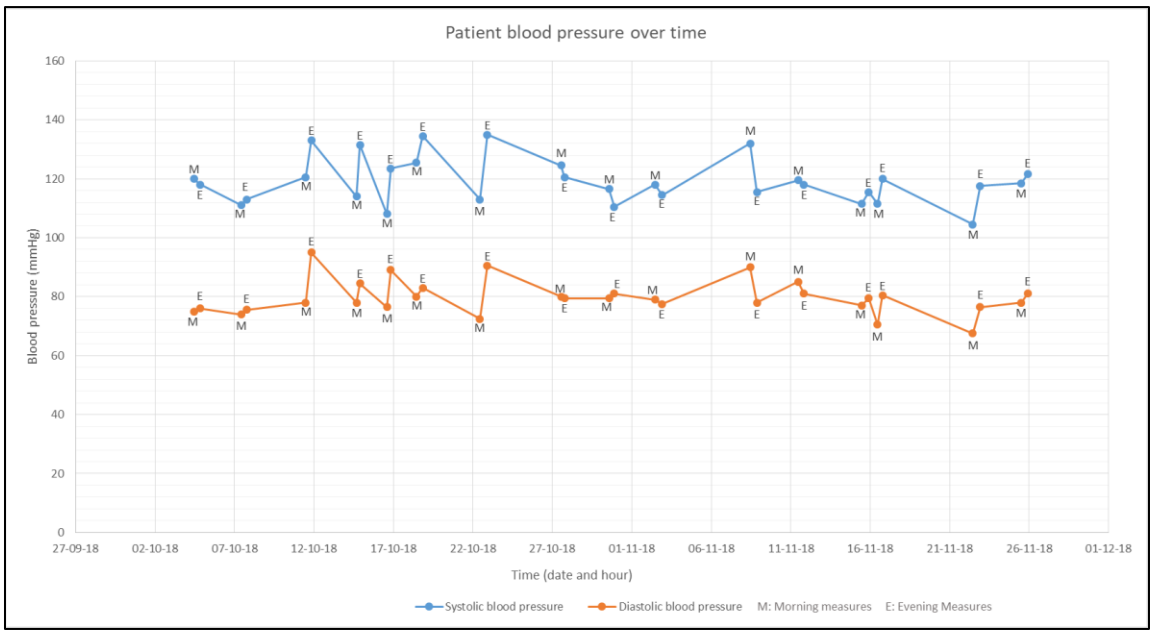
There seems to be no difference in the lack of compliance between the morning and the evening with 12 missing measures in the morning and 11 missing measures in the evening. No differences were seen in the compliance between the first and second month.

d. Blood pressure evolution

Regarding the blood pressure data, four patients (50%) had very often a blood pressure below 135/85mmHg. Three patients (37,5%) often had a systolic blood pressure above 140mmHg and one patient (12,5%) had a blood pressure that varied a lot. There were only 4 times that a third measure was asked (1,79%) which means the measures are concordant (no more than 20mmHg in the systolic blood pressure between the first two measures). This can be translated that self-measurement does not induce stress (otherwise the two measures would be discordant and third measurement would be asked more often) and that the devices are technically reliable.

A slight decrease and normalization can be observed in the diastolic blood pressure of four patients after 1 month (Figure 16).





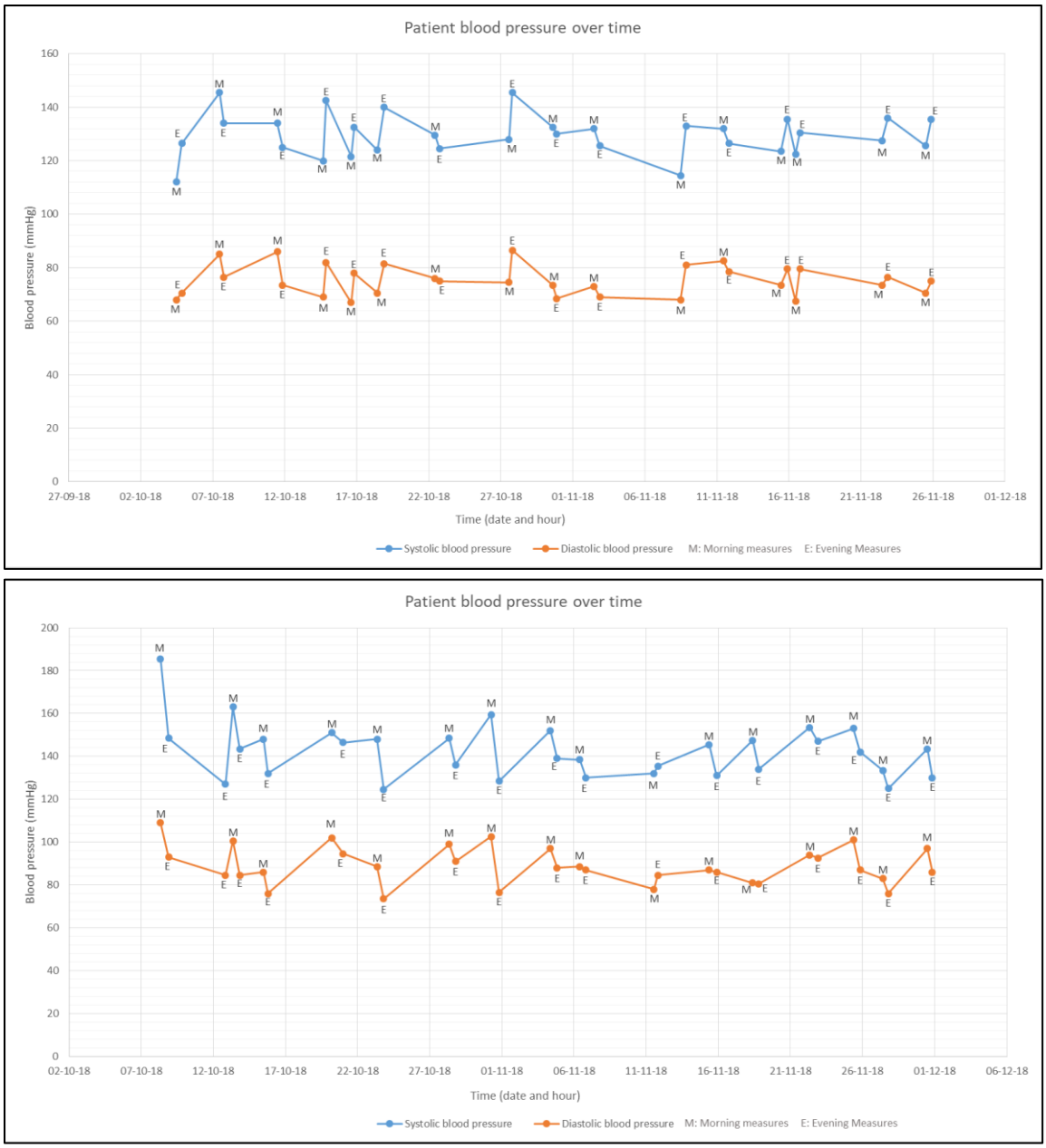


Figure 16. Patient's blood pressure over time.

Some "out of range" cases occurred: one patient with a diastolic blood pressure often below 60mmHg and another patient with sometimes a diastolic blood pressure above 100mmHg. The limits were then change to 90/50mmHg for the upper limit instead of 90/60mmHg and to 200/110mmHg for the lower limit instead of 200/100mmHg. These changes were performed according to the literature [30].

When comparing the measures above the limits for arterial hypertension during the first month versus the measures during the second month, there is a decrease in both systolic and diastolic blood pressure after the first month (37 *vs* 25 measures above the limits for the systolic blood pressure and 40 *vs* 35 measures above the limits for the diastolic blood pressure). However the sample size is too small to determine if it's significant or not. This might also means that the patients' blood pressure is not well controlled under their treatment.

One patient with several co-morbidities (hypercholesterolemia, diabetes and renal impairment) and who does not take her blood pressure before the study, is very compliant (Figure 17A) and had a controlled blood pressure, especially for the second month (Figure 17B). This reflect a potential benefit of the self-measurement for this patient.

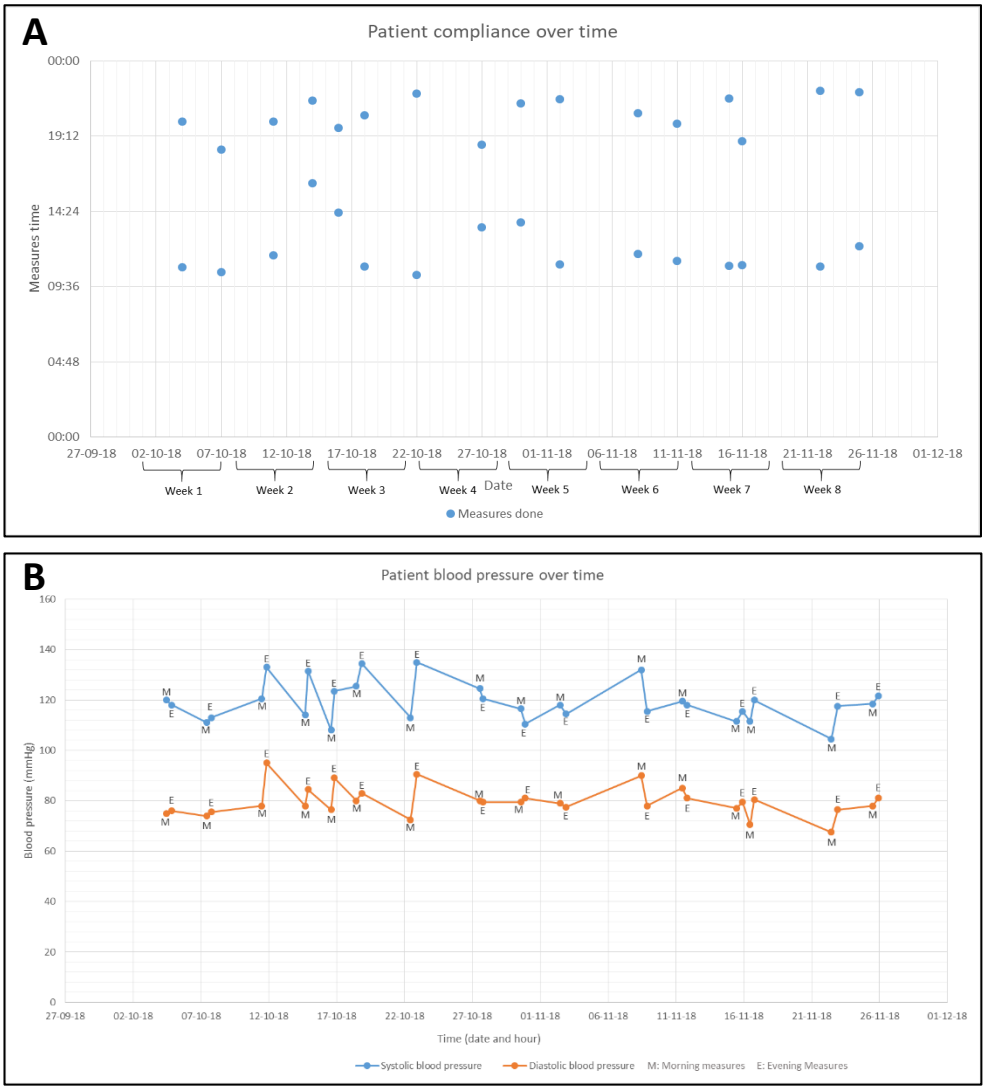


Figure 17. Patient's compliance (A) and blood pressure (B) over time.

One patient had a blood pressure that varied a lot (Figure 18). The blood pressure peaks occurred every time in the evening. This patient is in a polytherapy with a combination of a diuretic, a central anti-hypertensive drug and an ACE inhibitor. All these drugs are taken in the evening. A potential explanation is related to the half-life of the drugs, that are efficient at night and during the day but that the efficiency decrease at the end of the day, which explain the blood pressure peaks in the evening. This means that the information provided by the Suite can help the physician to adapt the treatment remotely for some patients.

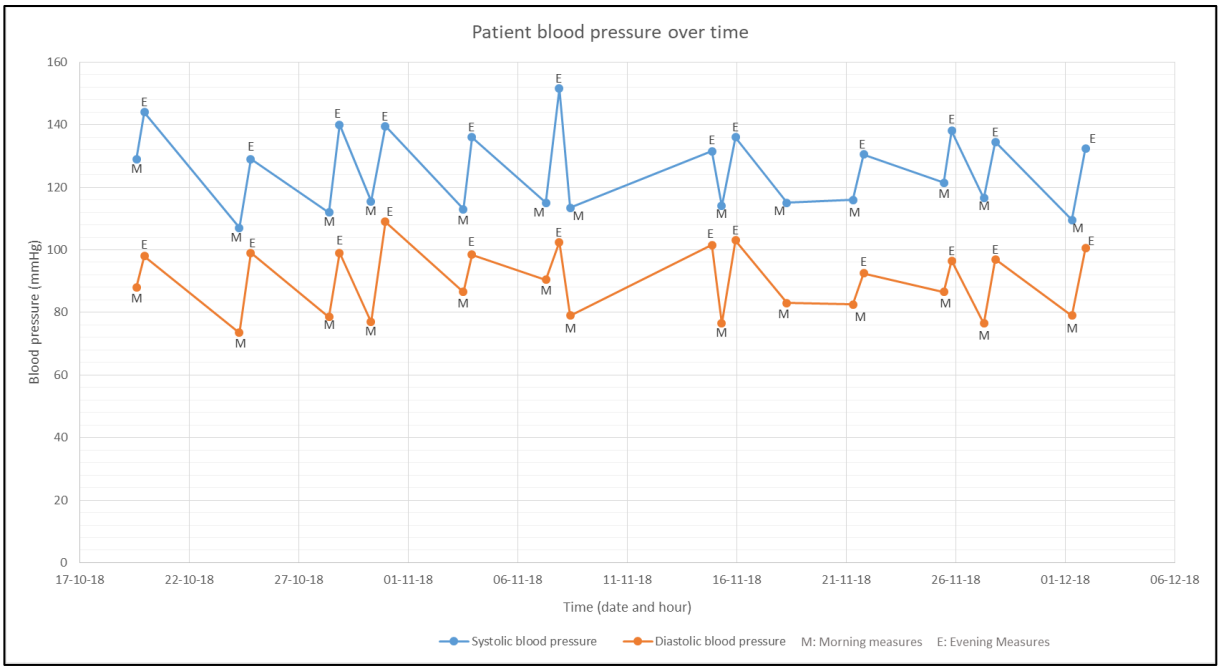


Figure 18. Patient's blood pressure over time in a patient with a not well adapted treatment regimen.

One patient once had a high increase of his blood pressure (185.5/109mmHg) in the morning. The investigator contacted him immediately in order to assess any symptoms resulting from this elevated blood pressure and to know what the circumstances of his blood pressure measurement were. The patient reported no symptoms and stated that he felt healthy but he reported that he was lacking of anti-hypertensive medication since few days. The patient was advised to see his general practitioner and to get a refill of medication later that day. In the evening, his blood pressure was decreased to more acceptable levels (148.5/93mmHg) and has decreased again 4 days later to normal values (127/84.5mmHg) (Figure 19).

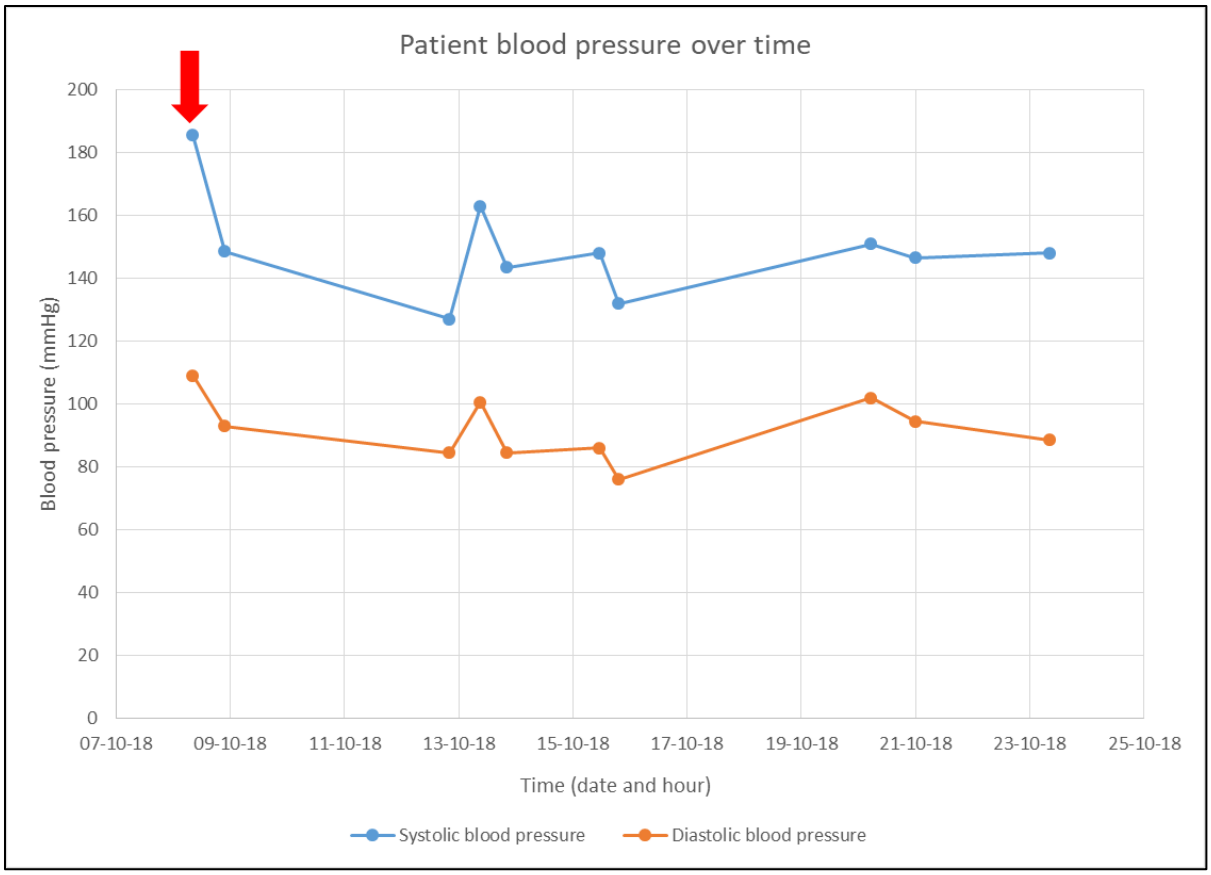


Figure 19. Patient's blood pressure over the time. The red arrow shows the highly elevated blood pressure which triggered a call from the investigator to the patient. The blood pressure decreased afterwards since the patient had taken his medication.

e. Patients' feedback

The patients were seen face to face to answer the feedback questionnaire. 7 out of 8 patients (87,5%) found the study very useful and were also ready to extend this practice. 5 out of 8 of patients (62,5%) were very confident in this system, the three others (37,5%) were moderately confident. The patients found the devices easy to use but two patients reported having difficulties with the cuff that was stiff and two other patients reported that sometimes the device couldn't get their blood pressure and they had to try 3 or 4 more times in order to get a measure. All the patients found the smartphone application convenient.

Four patients (50%) shared their data with their general practitioner and for two of them the practitioner was glad to see that they show a white coat phenomenon but didn't have hypertension at home. Using such an enabling suite might avoid escalation in the treatment of patients presenting with a white coat hypertension. The patients didn't shared the data with their cardiologist neither with their pharmacist. Only one patient had a treatment modification during the study. Four patients (50%) were indifferent to the fact of taking their blood pressure themselves but the four others were reassured while taking it because it would confirm that they only have a white coat effect but no hypertension at home.

Seven patients (87,5%) agreed that the self-measurements with the help of the smartphone application and the platform might help them to have a better control of their blood pressure. All the patients would recommend this system to a relative and five patients (62,5%) were ready to pay to use this system for up to 10€ per month.

As other remarks, one patient found the device bulky and thus difficult to transport if we go on holiday. The patient also stated that the reminders on Wednesday and Sunday are too early in the evening. Another patient reported that some messages received in case of problem might be stressful for the patients and should then be adapted.

VI. Conclusion and perspectives

The primary endpoint of the platform's convenience in terms of functionality, feasibility and performance is achieved. Indeed, beside the first week issue (which was rapidly corrected), a large majority of the data were correctly treated and the patients didn't reported any serious issue. The platform still need some improvements and adaptations to be more robust and to correspond more to the patient's demand.

The patient compliance to the protocol was high during the study. Some patients even made extra measures. The level of compliance is not different between the morning and evening measures. However, the patient didn't take their blood pressure on regular moments, a routine should then be implemented via some adaptations in the schedule of measurements and reminders sent to the patients. No difference were seen in the compliance between the first and second month nor in patients with a different degree of education.

Regarding the blood pressure evolution, some interesting observations and hypothesis can be draw. The significance couldn't be calculate with this small study population but there seems to be a trend. Indeed, the blood pressure seems to be better controlled after 1 month of self-measurement with a slight decrease in systolic and diastolic blood pressure. Moreover, this system allowed the investigator to intervene quickly on a patient with a highly elevated blood pressure and who didn't take his antihypertensive drugs to advise him to take his drugs. The platform also highlighted a patient with an inadequate treatment regimen. These cases can be transposed in real life and reflect the benefits of such system.

The patients found this system very useful and helpful. They were ready to continue this practice and found that this system might help to have a better blood pressure control. Some patients' general practitioners were reassured that their patients presents white coat hypertension but that their blood pressure is controlled at home.

A further study is then envisaged to evaluate the benefit of such system in non or poor adherent hypertensive patients. In parallel, Yatabe et al. (2018) are conducting a study in which they compare traditional care to telemedicine in hypertensive patients using HBPM. They will compare a control group (traditional care with office visit) to a telemonitoring group (HBPM

with office visits) and to a telemedicine group (HBPM without office visits and physician assessment by mail) [31]. If the use of telemedicine and our system is proved to be superior to traditional care, it may have a serious impact on the way to treat hypertensive patients and on the medical costs of such condition.

The pharmacist might also have a role in blood pressure control among hypertensive patients. Indeed, the HyperLink study assessed whether a pharmacist case management in combination with home telemonitoring of blood pressure improves the blood pressure control compared to usual care in uncontrolled hypertensive patients [30]. This study is a two-arm randomized trial. The intervention arm consists in HBPM in combination with a pharmacist case management. The pharmacist will first review the medical history of the patients before teaching them about the arterial hypertension and eventually instruct them on how to use the telemonitoring device. The pharmacist will then receive all the measures from the patients and is allowed to make changes in their medication, to adjust dosage, to order refills or to order lab tests in case of adverse effects from the therapy according to the data received. They will also discuss and set blood pressure goals with the patients. Phone visits are performed by the pharmacist during which they will emphasize on the adherence to therapy and on the patient's lifestyle. The change in medication is only performed when there are less than 75% of blood pressure readings that achieved the goal that was set up. The usual care arm consists on patients managed by their care providers as usual [30].

At the end of the study, the intervention group showed a significant improvement in blood pressure control and a decrease in blood pressure over 12 months. The intervention group also had an increase in medication and a better therapeutic adherence. The benefits persisted for 6 months after the intervention [32]. An economic evaluation was done in this study. The intervention cost 7337$ per person in average with 139$ and 265$ per decreased mmHg for the systolic and diastolic blood pressure respectively. There was a non-statistically significant decrease of the medical care costs in the intervention group but a significant cost reduction might be realised over a long term period. A pharmacist intervention might then be effective and implemented without increasing the overall medical care costs [33].

Another study by Green et al. [34] showed the effectiveness of telemonitoring in combination with pharmacist care on blood pressure control. In this study, patients with uncontrolled hypertension were divided into three groups: usual care, HBPM with web training and HBPM with web training plus a pharmacist care delivered through web communication. The pharmacist had to collect medical data from the patients and then decide an "action plan" with them. The patients were then contacted on a regular basis by the pharmacist in order to discuss about the goals achieved by the patients and their concerns about the treatments. The follow-up lasted twelve months. The results showed no significant difference between the usual care and HBPM with web training but there is a significant improvement in blood pressure control in the intervention group applying the pharmacist care. Indeed, there are 25% and 20% more patients with controlled blood pressure in this intervention group compared to usual care and HBPM with web training respectively [34].

An extension to this study was performed to assess the effectiveness of the intervention one year after the completion [35]. All three groups have a better blood pressure control but the pharmacist care group still have a better blood pressure control than the two others (usual care and HBPM with web training) [35]. The results of these two studies [34, 35] were retranscripted by Omboni et al. (Figure 20) [36].

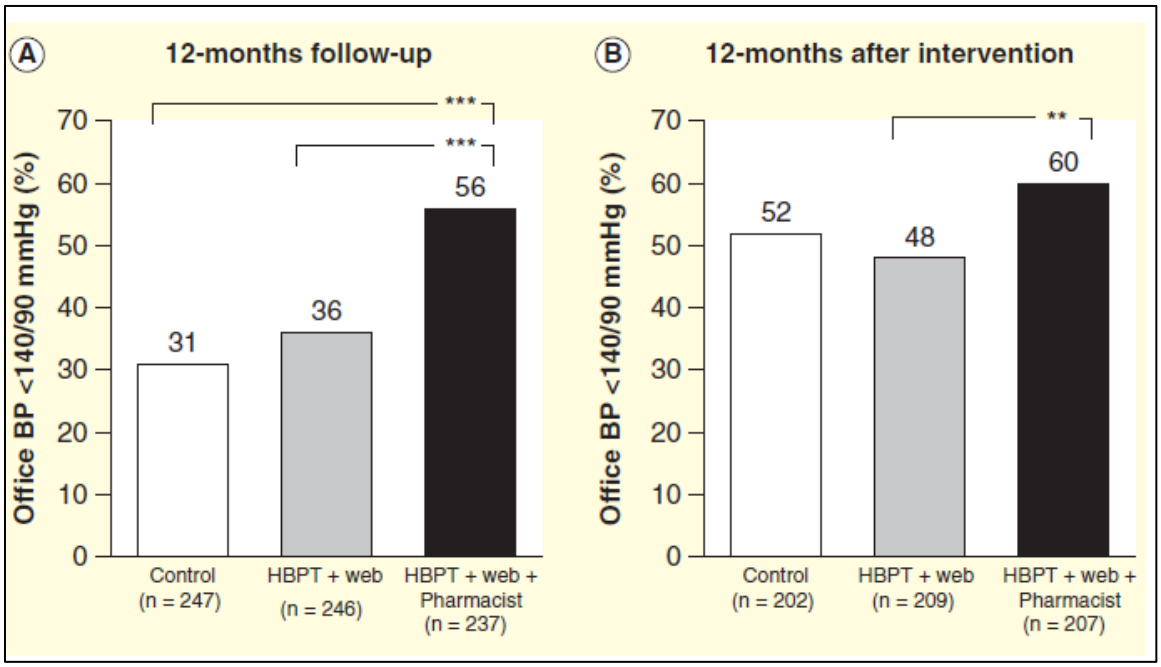


Figure 20. Retranscipted results from Green et al. studies [34, 35] by Omboni et al. [36] showing the percentage of patients with controlled blood pressure (<140/90mmHg) among the three study arms after 12 months follow-up (A) and 12 months after the intervention (B). The pharmacist care group (HBPT + web + Pharmacist) shows a greater percentage of patients with controlled blood pressure

Omboni et al. also emphasized the role of the pharmacist in managing chronic disease such as arterial hypertension [36]. They can bring a useful clinical expertise and recommendations about medications in order to support the physicians. They are involved in long term monitoring of the patients and can help them with adherence issues. This bring an improvement in patients' health and well-being, knowledge and satisfaction. As seen in the HyperLink study, pharmacists can improve the patients' education about arterial hypertension, they can change their medication and manage the refills. The benefits of this relationship between the patients and the pharmacists tended to improve if the pharmacist intervention is performed on a regular basis (at least monthly). The white coat effect was also reduced with successive and regular visits to the pharmacists comparing to the physician's office visits. The collaboration between the pharmacists and physicians seems to be a good approach for a better management of the arterial hypertension and is a way to move to a patient-centered model [36].

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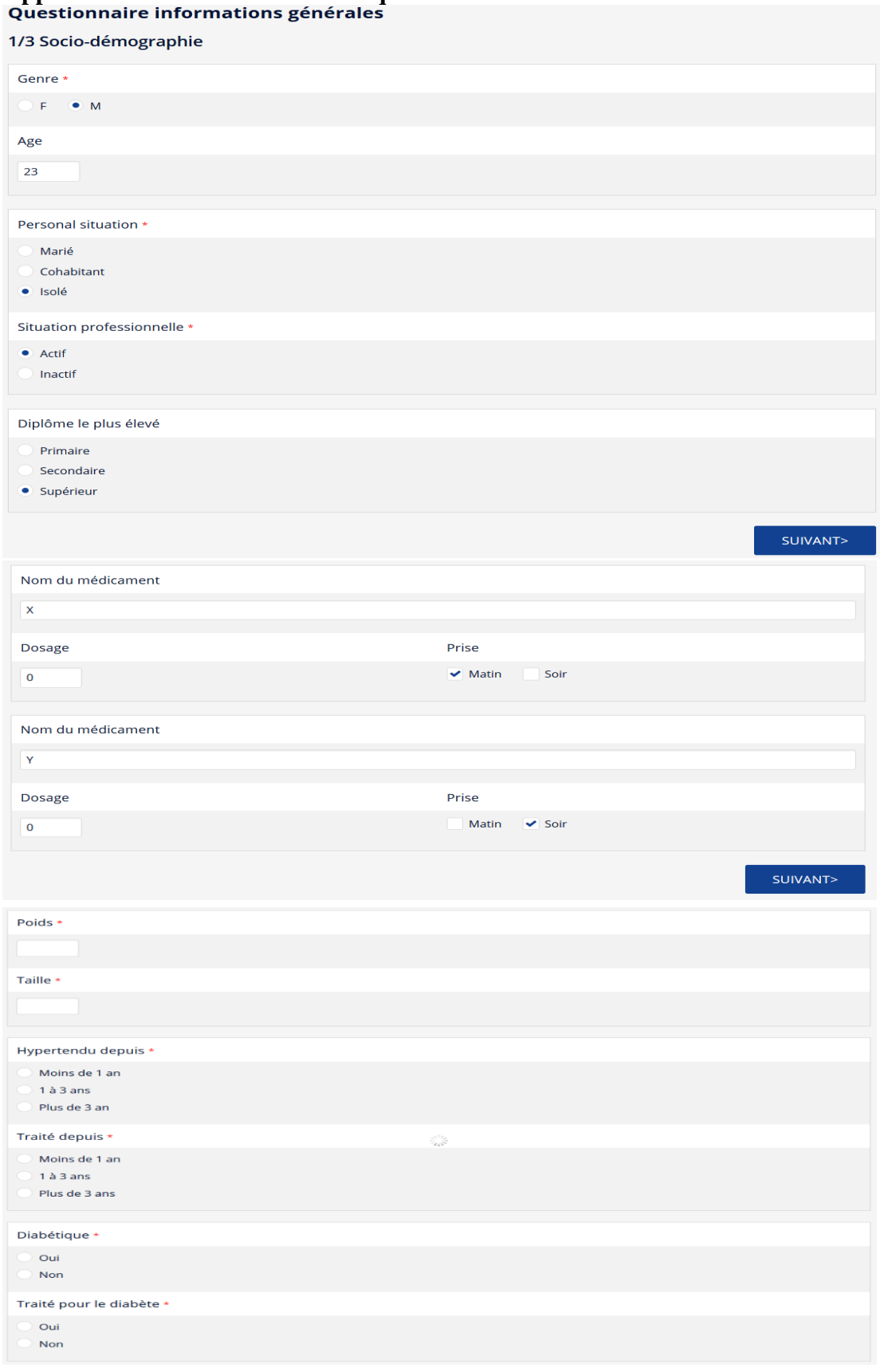
VIII. Appendices

Appendix 1. General information questionnaire



Hypercholestérolémie *

- Oui
- Non

Traité pour l'hypercholestérolémie *

- Oui
- Non

Nombre total de comprimés/gélules pris par jour *

Fréquence de visite chez le médecin généraliste pour l'hypertension artérielle *

- 0 fois/an
- 1 fois/an
- 2 fois/an
- 3 fois/an
- 4 fois/an
- Plus de 4 fois/an

Fréquence de visite chez le spécialiste pour l'hypertension artérielle *

- 0 fois/an
- 1 fois/an
- 2 fois/an
- 3 fois/an
- 4 fois/an
- Plus de 4 fois/an

Avez-vous par le passé fait un infarctus du myocarde ? *

- Oui
- Non

Avez-vous par le passé fait un accident vasculaire cérébral ? *

- Oui
- Non

Votre médecin vous a-t-il dit par le passé que vos reins ne fonctionnaient pas bien ? *

- Oui
- Non

Mesurez-vous déjà vous-même votre tension à domicile ? *

- Oui
- Non

Si oui, quel type d'appareil utilisez-vous ?

- Bras
- Poignet
- Je ne prend pas de mesures moi-même

Si oui, à quel fréquence faites-vous vos mesures ?

- Tous les jours
- Plusieurs fois/semaine
- Quelques fois/mois
- Avant la visite chez votre médecin
- Jamais
- Je ne prend pas de mesures moi-même

Appendix 2. Feedback questionnaire

Questionnaire Jour 60: Feedback du patient

Enquête de satisfaction

D'une manière générale, avez-vous trouvé que cette expérience vous a été utile ? *

- Très utile
- Moyennement utile
- Peu utile
- Pas du tout utile

Seriez-vous prêts à prolonger cette pratique ? *

- Oui
- Non

Avez-vous confiance dans ce système ? *

- Tout à fait d'accord
- Plutôt d'accord
- Plutôt en désaccord
- Pas du tout d'accord

L'utilisation du tensiomètre était-elle facile ? *

- Très facile
- Facile
- Plutôt difficile
- Difficile

L'utilisation de l'application était-elle pratique ? *

- Très pratique
- Plutôt pratique
- Pas pratique
- Pas du tout pratique

Avez-vous partagé les données avec votre médecin généraliste ? *

- Oui
- Non

Avec votre spécialiste si vous en avez-un ? *

- Oui
- Non

Avec votre pharmacien ? *

- Oui
- Non

Votre traitement a-t-il été modifié pendant l'expérience ? *

- Oui
- Non

Les explications données dans l'application étaient : *

- Très utiles
- Moyennement utiles
- Peu utiles
- Pas du tout utiles

Mesurer ma tension moi-même : *

- Me rassure
- M'inquiète
- Ni l'un ni l'autre

La réalisation d'automesures m'aide à mieux contrôler ma tension :

- Tout à fait d'accord
- Plutôt d'accord
- Plutôt en désaccord
- Pas du tout d'accord

L'application m'aide à mieux contrôler ma tension : *

- Tout à fait d'accord
- Plutôt d'accord
- Plutôt en désaccord
- Pas du tout d'accord

Conseilleriez-vous ce système à un proche ? *

- Oui
- Non

Seriez-vous prêt à payer pour obtenir cette application ? *

- Oui
- Non

Si oui, combien seriez-vous prêt à payer ? *

- Je ne suis pas prêt à payer pour ce type de système
- 10€/mois
- 20€/mois
- 30€/mois
- 50€/mois
- Plus de 50€/mois

Appendix 3. Warnings and related messages

'NO_MEASUREMENTS_SESSION_DAY_DURING_FIRST_PART_OF_THIS_WEEK':

SmsText = 'Bonjour, nous n'avons pas enregistré de mesures de votre part en ce début de semaine. Pouvez-vous recommencer à prendre vos mesures de tension matin et soir comme convenu. Si vous rencontrez une difficulté, vous pouvez contacter les responsables de l'étude, Cyril Noel (tél : 0477849823) ou le Pr Marc Tomas (tél : 0496590442). Merci d'avance.'

break

'NO_MEASUREMENTS_SESSION_AT_ALL_DAY_THIS_WEEK':

SmsText = 'Bonjour, nous n'avons pas enregistré de mesures de votre part cette semaine. Pouvez-vous recommencer à prendre vos mesures de tension matin et soir comme convenu. Si vous rencontrez une difficulté, vous pouvez contacter les responsables de l'étude, Cyril Noel (tél : 0477849823) ou le Pr Marc Tomas (tél : 0496590442). Merci d'avance.'

break

'MISSING_ONE_MEASUREMENT_SESSION_DAY_THIS_WEEK':

SmsText = 'Bonjour, il semble que vous n'avez pris qu'une seule fois votre tension cette semaine. Pour pouvoir vous assurer le meilleur suivi, pensez à faire 2 fois par semaine 2 mesures matin et soir comme convenu avec le Dr Delmotte. Merci d'avance. '

break

'BRAVO_GOOD_MEASUREMENTS_FOR_THIS_WEEK':

SmsText = 'Bravo, vous avez bien effectué vos deux mesures cette semaine!'

break

'MEASUREMENT_OUT_OF_RANGE':

SmsText = 'Bonjour, votre tension artérielle semble hors norme. Vous devriez bientôt recevoir un appel du Dr Delmotte afin d'en déterminer la cause.'

break

'PLEASE_DO_A_THIRD_MEASUREMENT':

SmsText = 'Bonjour, vos deux premières mesures ne semblent pas concorder. Veuillez en effectuer une troisième s'il vous plait.'

break

'MEASUREMENT_SESSION_SUCCESSFULL_BRAVO':

SmsText = "Bravo, vous avez bien effectué vos mesures!"

break

'MEASUREMENT_TOO_DIFFERENT__TECHNICAL_PROBLEM_PLEASE_CONTACT_SUPPORT':

SmsText = 'Bonjour, il semble qu'un problème technique se présente à la prise de votre tension artérielle. Vous devriez bientôt recevoir un appel du Dr Delmotte afin d'en déterminer la cause. Le cas échéant, merci de contacter les responsables de l'étude, Cyril Noel (tél : 0477849823) ou le Pr Marc Tomas (tél : 0496590442). Merci d'avance.'

break

'INCOMPLETE_SESSION_DAY_THIS_WEEK_PLEASE_FOLLOW_THE_PROTOCOL':

SmsText = 'Bonjour, il semble que vous ne preniez qu'une seule fois votre tension le matin ou le soir. Pour pouvoir vous assurer le meilleur suivi, pensez à faire 2 mesures matin et soir comme convenu avec le Dr Delmotte. Merci d'avance. '

break

Appendix 4. Informed Consent form given to the patients

Titre de l'étude : Etude E-pertension : Preuve de faisabilité de l'emploi d'une plateforme digitale (« Enablement Suite ») couplée à des auto-mesures de la tension artérielle chez des patients hypertendus.

Promoteur de l'étude : Pr Dr Marc Tomas, Groupe de recherche ACTO, Faculté de Médecine, Université de Namur (Unamur) - Rue de Bruxelles 61 - 5000 Namur +32496590442

Co-promoteur : Cyril Noël – Etudiant Master Sciences biomédicales Unamur + 32477849823

Comité d'Ethique Médicale : CHU Ambroise Paré

Investigateurs locaux :

Dr Philippe Delmotte – CHU Ambroise Paré – 7000 Mons +065970009

Information essentielle à votre décision de participer

Introduction

Vous êtes invité à participer à une étude clinique destinée à tester une application smartphone combinée à un appareil d'auto mesure de la pression artérielle afin d'avoir une meilleure gestion de votre hypertension artérielle.

Le promoteur, le co-promoteur et l'investigateur espèrent que cette méthode peut présenter des avantages chez des patients atteints d'hypertension artérielle comme vous. Néanmoins, il n'y a aucune garantie que vous tirerez un bénéfice immédiat de votre participation à cette étude.

Avant que vous n'acceptiez d'y participer, nous vous invitons à prendre connaissance de ses implications en termes d'organisation, avantages et risques éventuels, afin que vous puissiez prendre une décision en toute connaissance de cause. Ceci s'appelle donner un « consentement éclairé ».

Veuillez lire attentivement ces quelques pages d'information et poser toutes les questions que vous souhaitez à l'investigateur ou à la personne qui le représente. Ce document comprend 3 parties : l'information essentielle à votre prise de décision, votre consentement écrit et des informations complémentaires (annexes) qui détaillent certaines parties de l'information de base.

Si vous participez à cette étude clinique, vous devez savoir que :

- Cette étude clinique est mise en œuvre après évaluation par un ou plusieurs comité(s) d'éthique.
- Votre participation est volontaire et doit rester libre de toute contrainte. Elle nécessite la signature d'un document exprimant votre consentement. Même après l'avoir signé, vous pouvez arrêter de participer en informant l'investigateur. Votre décision de ne pas ou de ne plus participer à l'étude n'aura aucun impact sur la qualité de vos soins ni sur vos relations avec l'investigateur.
- Les données recueillies à cette occasion sont confidentielles et votre anonymat est garanti lors de la publication des résultats.
- Une assurance a été souscrite au cas où vous subiriez un dommage lié à votre participation à cette étude clinique.
- Aucun frais ne vous sera facturé pour les visites / consultations, examens ou traitements spécifiques à cette étude.
- Vous pouvez toujours contacter l'investigateur ou un membre de son équipe si vous avez besoin d'informations complémentaires.

Un complément d'informations sur vos « Droits de participant à une étude clinique » est fourni en annexe.

Objectifs et description du protocole de l'étude

Nous vous proposons de participer à une étude clinique portant sur l'utilisation d'un appareil pour prendre sa tension soi-même, connecté à une application smartphone, qui devrait inclure une douzaine de patients de l'hôpital Ambroise Paré à Mons.

Cette étude vise à tester l'applicabilité de cette application smartphone dans la gestion de votre tension artérielle.

Les critères d'inclusion de cette étude sont les suivants :

- Avoir au moins 18 ans
- Etre traité par au moins 2 classes différentes de médicaments antihypertenseurs
- Posséder un smartphone capable de lancer des applications, ayant accès à internet et être à même de savoir l'utiliser quotidiennement

Déroulement de l'étude

Votre participation à l'étude durera 2 mois.

Elle vous sera proposée par le Dr Delmotte, investigateur, lors de votre consultation à l'hôpital Ambroise Paré. Durant cette session, vous aurez l'occasion de poser toutes les questions que vous voudrez. Après la session, l'appareil vous sera fourni et vous pourrez rentrer chez vous afin de débuter les prises de mesure de votre tension artérielle.

Ces prises de mesures devront s'effectuer 2 fois le matin et 2 fois le soir, 2 jours par semaine durant les 2 mois. Une troisième mesure vous sera éventuellement demandée via l'application si les 2 premières mesures montrent des résultats anormaux. Le tableau ci-dessous reprend le rythme de prise de mesure hebdomadaire :

Lundi ou Mardi	Prise tension 2 fois matin + 2 fois soir
Mercredi	Jour limite pour première prise de tension hebdomadaire
Jeudi, vendredi ou samedi	Prise tension 2 fois matin + 2 fois soir
Dimanche	Jour limite pour seconde prise de tension hebdomadaire

Une séance d'apprentissage vous sera proposée par l'investigateur ou le co-promoteur. Toutes les informations expliquées oralement lors de la session d'apprentissage seront disponibles sur l'application et les coordonnées de l'équipe de recherche seront disponibles également en cas de problèmes. Un document papier vous sera également remis lors de la séance d'information. Par ailleurs l'étudiant co-promoteur en charge de cette étude vous contactera durant la première semaine ainsi qu'à la fin du premier et second mois afin de vérifier que tout se passe bien et que vous ne rencontrez pas de difficultés. A tout moment il vous sera possible de contacter le promoteur ou le co-promoteur pendant les heures normales de bureau. En-dehors de ces heures, il conviendra de contacter votre médecin traitant si nécessaire comme vous le faites habituellement en-dehors de cette étude. Celui-ci sera informé, avec votre accord, par l'investigateur de votre participation à l'étude au démarrage de celle-ci. Il aura accès à vos résultats s'il le souhaite et si vous donnez votre accord préalable.

Au début de l'étude, un questionnaire d'informations générales vous sera soumis par le biais de l'application. Votre avis sur l'étude vous sera demandé lors d'une dernière session à l'hôpital Ambroise Paré à la fin des 2 mois.

Le déroulement complet est repris dans un tableau récapitulatif en annexe 1.

Risques et inconvénients

L'étude porte sur l'utilisation d'appareils diagnostiques et d'aide au suivi de l'hypertension et non sur une prise de médicament. Par conséquent, tout effet indésirable sera dû au traitement que vous prenez déjà et devra donc être rapporté à votre médecin traitant ou spécialiste.

Notification d'informations nouvelles

Il se peut que pendant le déroulement de cette étude clinique, de nouvelles informations importantes sur la méthode étudiée deviennent disponibles. Vous serez informé(e) de tout élément nouveau susceptible d'affecter votre décision de poursuivre votre participation à cette étude.

Dans ce cas, on vous demandera de signer soit un complément au formulaire de consentement, soit un nouveau document d'information et consentement. Si, à la lumière de la nouvelle information, vous décidez de mettre un terme à votre participation à l'étude, votre investigateur veillera à ce que vous continuiez d'être traité(e) de la meilleure façon qui soit.

Bénéfices

Si vous acceptez de participer à cette étude, l'utilisation de l'appareil d'auto mesure et de l'application pourra ou non s'avérer bénéfique pour la gestion de l'hypertension pour d'autres patients.

Les informations obtenues grâce à cette étude peuvent contribuer à une meilleure connaissance de l'utilisation de cette méthode pour le suivi du traitement de l'hypertension chez de futurs patients.

Traitement alternatif : Que se passe-t-il si

D'autres traitements existent pour votre affection. Cependant une modification éventuelle du traitement est du seul ressort du médecin traitant ou du spécialiste qui vous soigne.

Retrait de l'étude

Votre participation est volontaire et vous avez le droit de vous retirer de l'étude pour quelque raison que ce soit, sans devoir vous justifier. Néanmoins, il peut être utile pour l'investigateur et pour le promoteur de l'étude de savoir si vous vous retirez parce que les contraintes sont trop importantes.

Il est aussi possible que ce soit l'investigateur qui vous retire de l'étude parce qu'il pense que c'est le mieux pour votre santé ou qu'il constate que vous ne respectez pas les consignes données aux participants.

Enfin, il arrive parfois que les autorités compétentes nationales ou internationales, le comité d'éthique qui a initialement approuvé l'étude ou le promoteur interrompent l'étude parce que les informations recueillies montrent que la méthode étudiée n'est pas efficace (n'apporte pas assez d'amélioration de la santé des participants).

Traitement après l'arrêt de l'étude

Dans toutes ces situations de retrait de l'étude mais également lorsque le temps de participation prévu est terminé, votre médecin traitant ou spécialiste reste seul responsable de l'évaluation de votre état de santé et de la prescription du meilleur traitement disponible.

Si vous avez participé à l'entièreté de l'étude et si vous le souhaitez, l'investigateur pourra vous proposer de participer à une étude d'extension qui vous permettra d'utiliser l'appareil ainsi que l'application pendant une nouvelle période. L'investigateur vous fera cette proposition s'il estime que cette option vous est favorable et que vous répondez aux critères d'inclusion de l'étude d'extension.

Si vous participez à cette étude clinique, nous vous demandons :

- De collaborer pleinement au bon déroulement de cette recherche.
- De ne masquer aucune information relative à votre état de santé, aux médicaments que vous prenez ou aux symptômes que vous ressentez.
- De ne participer à aucune autre recherche clinique concernant un traitement expérimental, qu'il s'agisse d'un médicament, d'un dispositif médical ou d'une procédure, tant que vous participerez à la présente étude.

Vous devez également savoir que :

- pour votre sécurité, il est souhaitable que votre médecin généraliste si vous en avez un ou d'autres médecins spécialistes en charge de votre santé soient informés de votre participation à cette étude. Nous vous demanderons de confirmer votre accord mais respecterons votre éventuelle volonté de ne pas les informer.

Contact

Si vous avez besoin d'informations complémentaires, mais aussi en cas de problème, d'inquiétude ou d'urgence vous pouvez contacter l'investigateur, le Docteur Philippe Delmotte, le promoteur, Marc Tomas ou le co-promoteur, Cyril Noël aux numéros de téléphone suivants :

Dr Philippe Delmotte +065 97 00 09
Marc Tomas +32 496 59 04 42
Cyril Noël +32 477 84 98 23

En dehors des heures de consultation, adressez-vous à votre médecin traitant ou aux urgences de votre hôpital en leur signalant que vous participez à une étude clinique. Votre dossier contiendra les informations utiles au médecin de garde concernant cette étude clinique.

Si vous avez des questions relatives à vos droits de participant à une étude clinique, vous pouvez contacter le comité d'éthique du centre hospitalier Ambroise Paré - Mons au numéro de téléphone suivant : 065 41 75 18.

Titre de l'étude : Etude E-pertension : Preuve de faisabilité de l'emploi d'une plateforme digitale (« Enablement Suite ») couplée à des auto-mesures de la tension artérielle chez des patients hypertendus.

Consentement éclairé

Participant

Je déclare que j'ai été informé sur la nature de l'étude, son but, sa durée, les éventuels bénéfices et risques et ce que l'on attend de moi. J'ai pris connaissance du document d'information et des annexes à ce document.

J'ai eu suffisamment de temps pour y réfléchir et en parler avec une personne de mon choix comme mon médecin généraliste ou un membre de ma famille.

J'ai eu l'occasion de poser toutes les questions qui me sont venues à l'esprit et j'ai obtenu une réponse satisfaisante à mes questions.

J'ai compris que ma participation à cette étude est volontaire et que je suis libre de mettre fin à ma participation à cette étude sans que cela ne modifie mes relations avec l'équipe thérapeutique en charge de ma santé.

J'ai compris que des données me concernant seront récoltées pendant toute ma participation à cette étude et que l'investigateur et le promoteur de l'étude se portent garant de la confidentialité de ces données.

Je consens au traitement de mes données personnelles selon les modalités décrites dans la rubrique traitant de garanties de confidentialité (annexe 2). Je donne également mon accord au transfert et au traitement de ces données dans d'autres pays que la Belgique.

J'accepte / n'accepte pas (biffer la mention inutile) que les données de recherche récoltées pour les objectifs de la présente étude puissent être traitées ultérieurement pour autant que ce traitement soit limité au contexte de la présente étude pour une meilleure connaissance de la maladie et de son traitement.

J'accepte / n'accepte pas (biffer la mention inutile) que mon médecin généraliste ou d'autres médecins spécialistes en charge de ma santé soient informés de ma participation à cette étude clinique.

J'ai reçu une copie de l'information au participant et du consentement éclairé.

Nom, prénom, date et signature du volontaire.

Investigateur

Je soussigné, **Philippe Delmotte** investigateur, confirme avoir fourni oralement les informations nécessaires sur l'étude et avoir fourni un exemplaire du document d'information au participant.

Je confirme qu'aucune pression n'a été exercée pour que le patient accepte de participer à l'étude et que je suis prêt à répondre à toutes les questions supplémentaires, le cas échéant.

Je confirme travailler en accord avec les principes éthiques énoncés dans la dernière version de la « Déclaration d'Helsinki », des « Bonnes pratiques Cliniques » et de la loi belge du 7 mai 2004, relative aux expérimentations sur la personne humaine.

Nom, prénom, Date et signature du représentant de l'investigateur	Nom, Prénom, Date et signature de l'investigateur

Titre de l'étude : Etude E-pertension : Preuve de faisabilité de l'emploi d'une plateforme digitale (« Enablement Suite ») couplée à des auto-mesures de la tension artérielle chez des patients hypertendus.

Informations complémentaires

1 : Compléments d'informations sur l'organisation de l'étude

Voici un tableau récapitulatif reprenant le déroulement de l'étude :

Période	Evènement	Lieu	Commentaire
Début de l'étude	Session d'information et d'apprentissage	Hôpital Ambroise Paré	Session visant à expliquer l'étude ainsi que le fonctionnement des appareils
1er mois	Prise de la tension au moins 2 fois par semaine, 2 fois le matin et 2 fois le soir	Chez le patient	Le patient sera contacté par l'investigateur ou le co-promoteur durant la première semaine ainsi que fin du mois pour s'assurer du bon déroulement
2e mois	Prise de la tension au moins 2 fois par semaine, 2 fois le matin et 2 fois le soir	Chez le patient	Le patient sera contacté par l'investigateur ou le co-promoteur fin du mois pour s'assurer du bon déroulement
Fin de l'étude	Questionnaire de feedback	Hôpital Ambroise Paré	Le patient recevra un questionnaire dans lequel il exprimera son avis quant à sa participation à l'étude

2 : Complément d'informations sur la protection et les droits du participant à une étude clinique

Comité d'Ethique

Cette étude a été évaluée par un Comité d'Ethique indépendant, à savoir le Comité d'Ethique CHU Ambroise Paré, qui a émis un avis favorable. Les Comités d'Ethique ont pour tâche de protéger les personnes qui participent à un essai clinique. Ils s'assurent que vos droits en tant que patient et en tant que participant à une étude clinique sont respectés, qu'au vu des connaissances actuelles, la balance entre risques et bénéfices reste favorable aux participants, que l'étude est scientifiquement pertinente et éthique.

En aucun cas vous ne devez prendre l'avis favorable du Comité d'Ethique comme une incitation à participer à cette étude.

Participation volontaire

Avant de signer, n'hésitez pas à poser toutes les questions que vous jugez utiles. Prenez le temps d'en parler à une personne de confiance si vous le souhaitez.

Votre participation à l'étude est volontaire et doit rester libre de toute contrainte: ceci signifie que vous avez le droit de ne pas y participer ou de vous retirer sans justification même si vous aviez accepté préalablement d'y participer. Votre décision ne modifiera en rien vos relations avec l'investigateur et la qualité de votre prise en charge thérapeutique future.

Toutefois, il est conseillé pour votre sécurité, de prévenir l'investigateur si vous avez décidé d'arrêter votre participation à l'étude.

Si vous acceptez d'y participer, vous signerez le formulaire de consentement éclairé. L'investigateur signera également ce formulaire et confirmera ainsi qu'il vous a fourni les informations nécessaires sur l'étude. Vous recevrez l'exemplaire qui vous est destiné.

Coûts associés à votre participation

La méthode de suivi de l'hypertension étudiée est à charge du promoteur.

Sachez cependant que si vous décidez de participer à cette étude, tout traitement prescrit ainsi que tout examen complémentaire réclamé par votre médecin traitant et/ou spécialiste restent à votre charge ainsi qu'à celle de votre mutuelle. Le promoteur et l'investigateur n'interviendront donc pas dans l'achat du traitement de votre affection même si celui-ci venait à augmenter suite à l'utilisation de cette méthode de suivi de l'hypertension.

Le promoteur a prévu de vous indemniser raisonnablement pour vos frais de déplacement à raison d'un bon d'achat de 25€ valable à la Fnac. Adressez-vous à l'équipe investigatrice pour les modalités pratiques.

Garantie de confidentialité

Votre participation à l'étude signifie que vous acceptez que l'investigateur recueille des données vous concernant et que le promoteur de l'étude les utilise dans un objectif de recherche et dans le cadre de publications scientifiques et médicales.

Vous avez le droit de demander à l'investigateur quelles sont les données collectées à votre sujet et quelle est leur utilité dans le cadre de l'étude. Ces données concernent votre situation clinique actuelle mais aussi certains de vos antécédents, les résultats des examens réalisés dans le cadre d'une prise en charge selon les standards actuels de votre santé et bien entendu les résultats des examens requis par le protocole. Vous disposez d'un droit de regard sur ces données et le droit d'y apporter des rectifications au cas où elles seraient incorrectes[1].

L'investigateur a un devoir de confidentialité vis à vis des données collectées.

Ceci veut dire qu'il s'engage non seulement à ne jamais divulguer votre nom dans le cadre d'une publication ou d'une conférence mais aussi qu'il codera (que votre identité sera remplacée par un code d'identification dans l'étude) vos données avant de les transmettre à un éventuel gestionnaire de la base des données collectées.

[1] Ces droits vous sont garantis par la loi du 8 décembre 1992 relative à la protection de la vie privée à l'égard des traitements de données à caractère personnel et par la loi du 22 août 2002 relative aux droits du patient.

L'investigateur et son équipe seront donc les seuls à pouvoir faire le lien entre les données transmises pendant toute la durée de l'étude et votre dossier médical[2].

Les données personnelles transmises ne contiendront pas d'association d'éléments qui permettraient de vous identifier[3].

Pour le gestionnaire des données de recherche désigné par le promoteur, les données transmises ne permettent pas de vous identifier. Ce dernier est responsable de la collecte des données recueillies par tous les investigateurs participant à la recherche, de leur traitement et de leur protection en conformité avec les impératifs de la loi belge relative à la protection de la vie privée.

Pour vérifier la qualité de l'étude, il est possible que votre dossier médical soit examiné par des personnes soumises au secret professionnel et désignées par le comité d'éthique, le promoteur de l'étude ou un organisme d'audit indépendant. En tout état de cause, cet examen de votre dossier médical ne peut avoir lieu que sous la responsabilité de l'investigateur et sous la supervision d'un des collaborateurs qu'il aura désigné.

Les données de recherche (codées) pourront être transmises aux autorités réglementaires belges ou autres, aux comités d'éthique concernés, à d'autres médecins et/ou à des organismes travaillant en collaboration avec le promoteur.

Elles pourront également être transmises à d'autres sites du promoteur en Belgique et dans d'autres pays où les normes en matière de protection des données personnelles peuvent être différentes ou moins contraignantes. Comme expliqué plus haut, les données transmises sont codées[4].

Votre consentement à participer à cette étude implique donc aussi votre consentement à l'utilisation de vos données médicales codées aux fins décrites dans ce document d'information et à leur transmission aux personnes et instances susmentionnées.

Le promoteur s'engage à utiliser les données collectées uniquement dans le cadre de l'étude à laquelle vous participez.

Le promoteur utilisera les données collectées dans le cadre de l'étude à laquelle vous participez mais souhaite également pouvoir les utiliser dans le cadre d'autres recherches concernant la même maladie que la vôtre. Toute utilisation de vos données en dehors du contexte décrit dans le présent document ne pourrait être menée qu'après approbation du comité d'éthique.

Si vous retirez votre consentement à participer à l'étude, afin de garantir la validité de la recherche, les données codées jusqu'au moment de votre interruption seront conservées. Aucune nouvelle donnée ne pourra être transmise au promoteur.

Assurance

Toute participation à une étude clinique comprend un risque aussi petit soit-il. Le promoteur assume, même en l'absence de faute, la responsabilité du dommage causé au participant (ou en cas de décès, à ses ayants-droit) et lié de manière directe ou indirecte à sa participation à la recherche. Le promoteur a souscrit un contrat d'assurance de cette responsabilité[5]. Ce contrat a été souscrit auprès de la compagnie d'assurance AMLIN INSURANCE SE avec le numéro de police suivant : LXX072113.

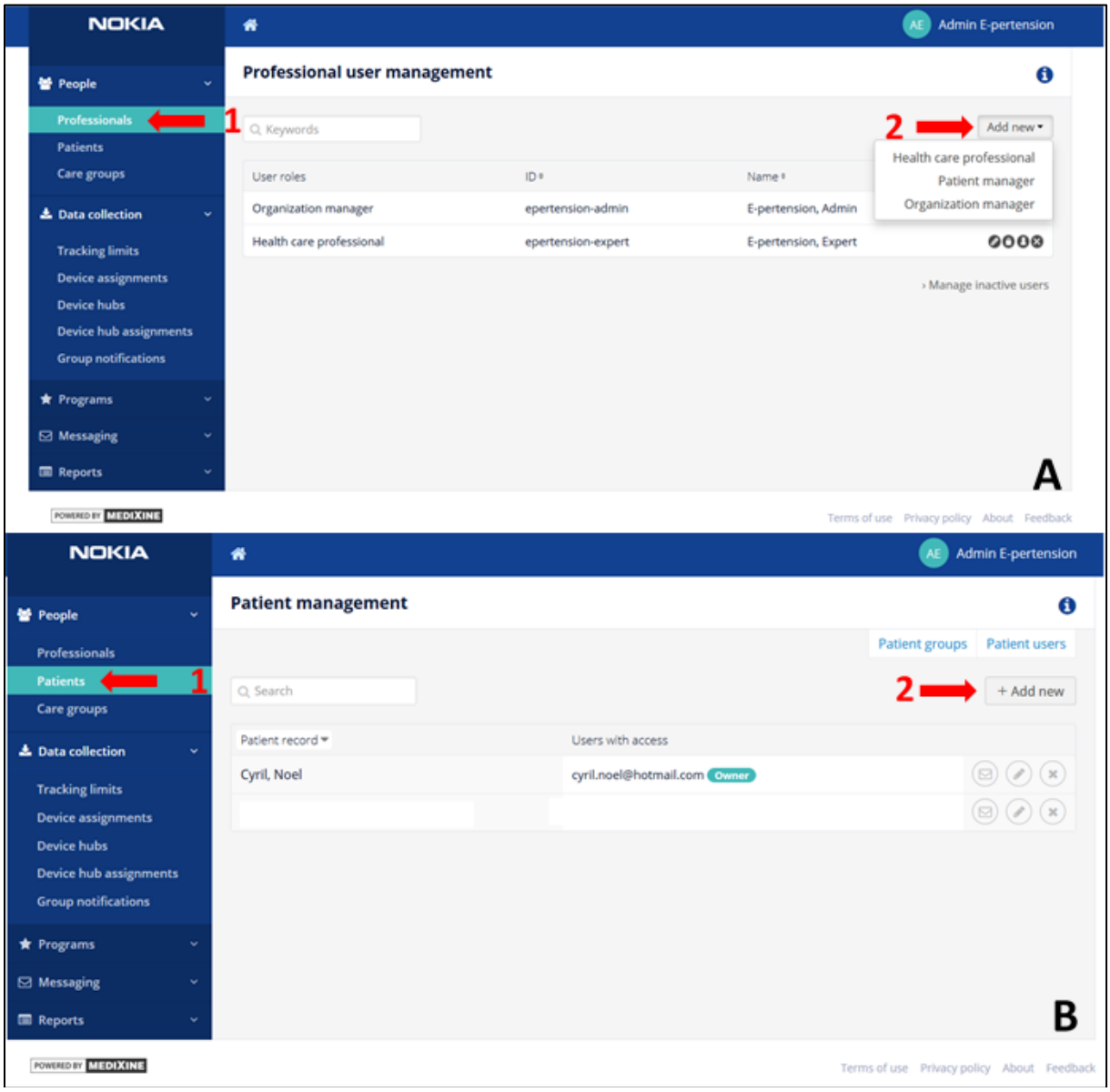
Si l'investigateur estime qu'un lien avec l'étude est possible (l'assurance ne couvrant pas l'évolution naturelle de votre maladie ni les effets secondaires connus de votre traitement habituel), il se chargera d'informer le promoteur de l'étude qui se chargera d'initier la procédure de déclaration à l'assurance. Celle-ci nommera - si elle l'estime nécessaire - un expert pour juger du lien entre vos nouveaux problèmes de santé et l'étude.

En cas de désaccord soit avec l'investigateur, soit avec l'expert nommé par la compagnie d'assurances ainsi que chaque fois que vous l'estimeriez utile, vous ou - en cas de décès - vos ayants droit pouvez assigner l'assureur directement en Belgique (nom assurance, N° police, contact).

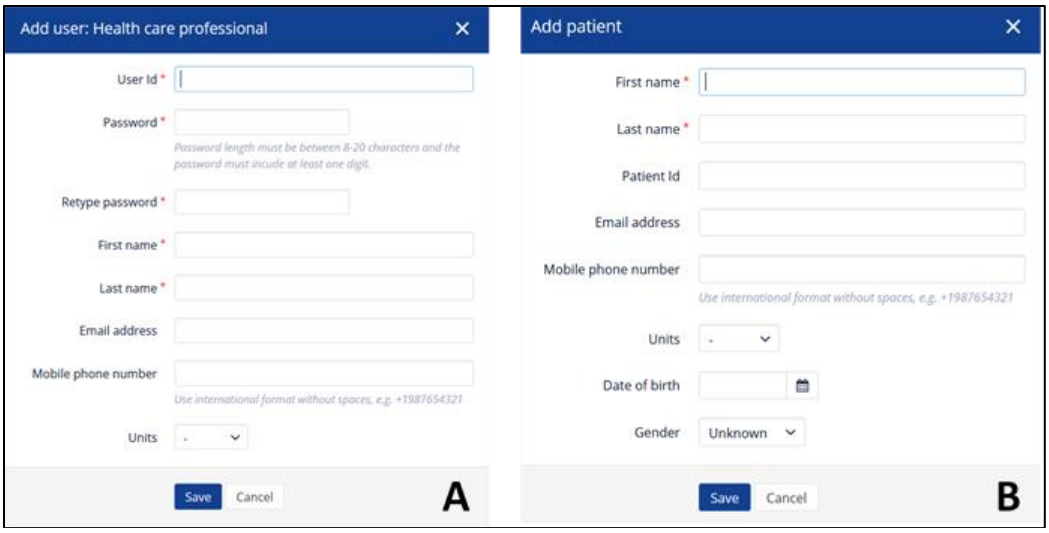
[2] Pour les essais cliniques, la loi oblige à conserver ce lien avec votre dossier durant 20. Dans le cas d'un médicament de thérapie innovante utilisant du matériel corporel humain, cette durée sera de minimum 30 ans et maximum 50 ans en accord avec la loi belge du 19 décembre 2008 sur l'utilisation du matériel corporel humain et les arrêtés royaux d'application.
[3] La base de données contenant les résultats de l'étude ne contiendra donc pas d'association d'éléments comme vos initiales, votre sexe et votre date de naissance complète (j/mm/aaaa).
[4] Le promoteur s'engage alors à respecter les contraintes de la directive européenne et de la législation belge en matière de protection de la vie privée.
[5] Conformément à l'article 29 de la loi belge relative aux expérimentations sur la personne humaine (7 mai 2004)

La loi prévoit que la citation de l'assureur puisse se faire soit devant le juge du lieu où s'est produit le fait générateur du dommage, soit devant le juge de votre domicile, soit devant le juge du siège de l'assureur.

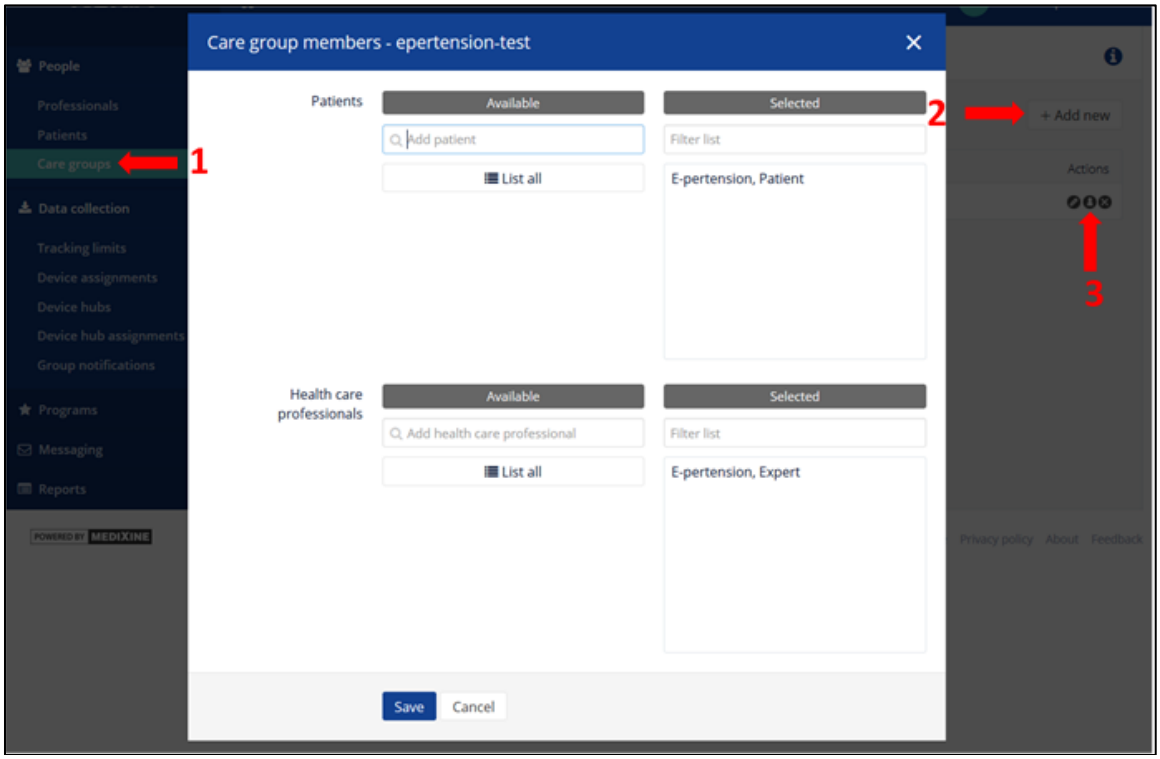
Appendix 5. Screenshots from the platform



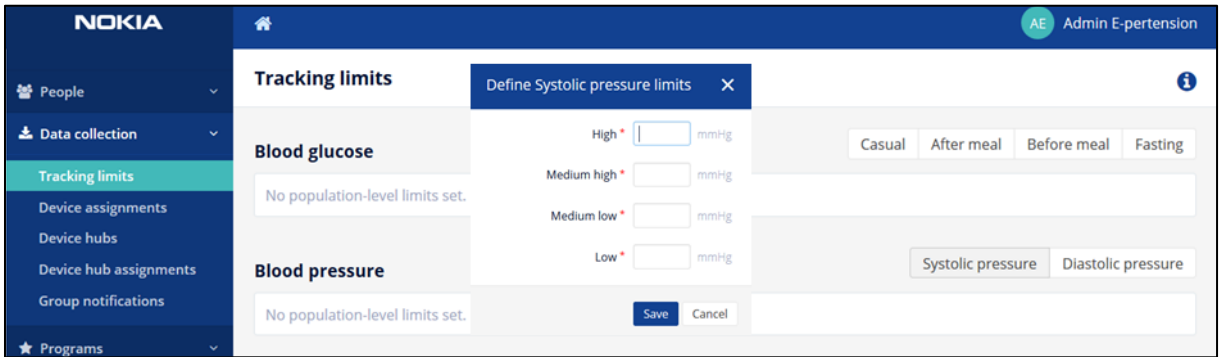
(A) Webpage allowing the addition of a healthcare professional in the system. (B) Webpage allowing the addition of a patient in the system. The red arrows represent which buttons to click to get to that page and in which order.



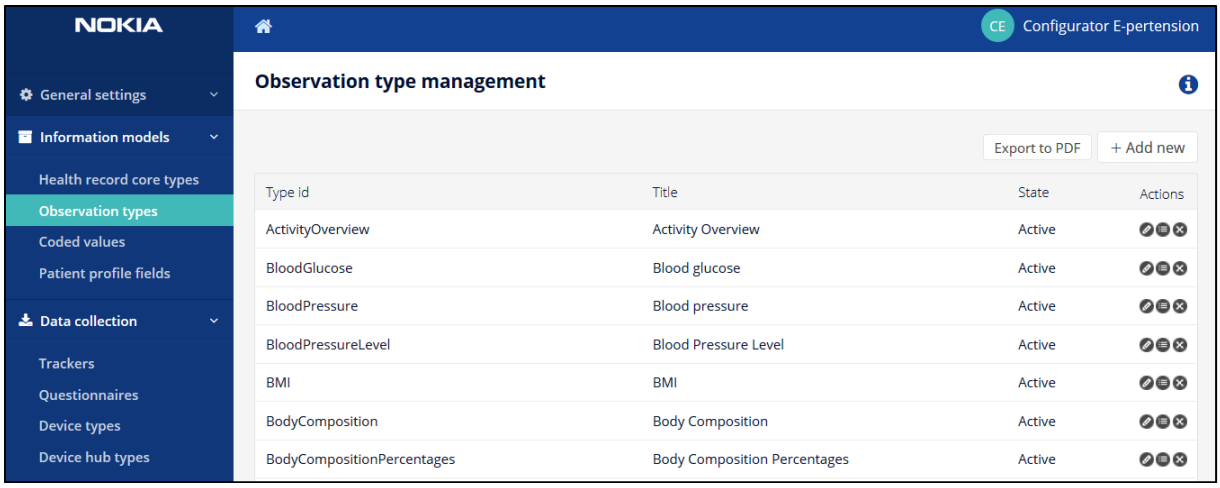
(A) Information asked when adding a healthcare professional in the system. (B) Information asked when adding a patient in the system



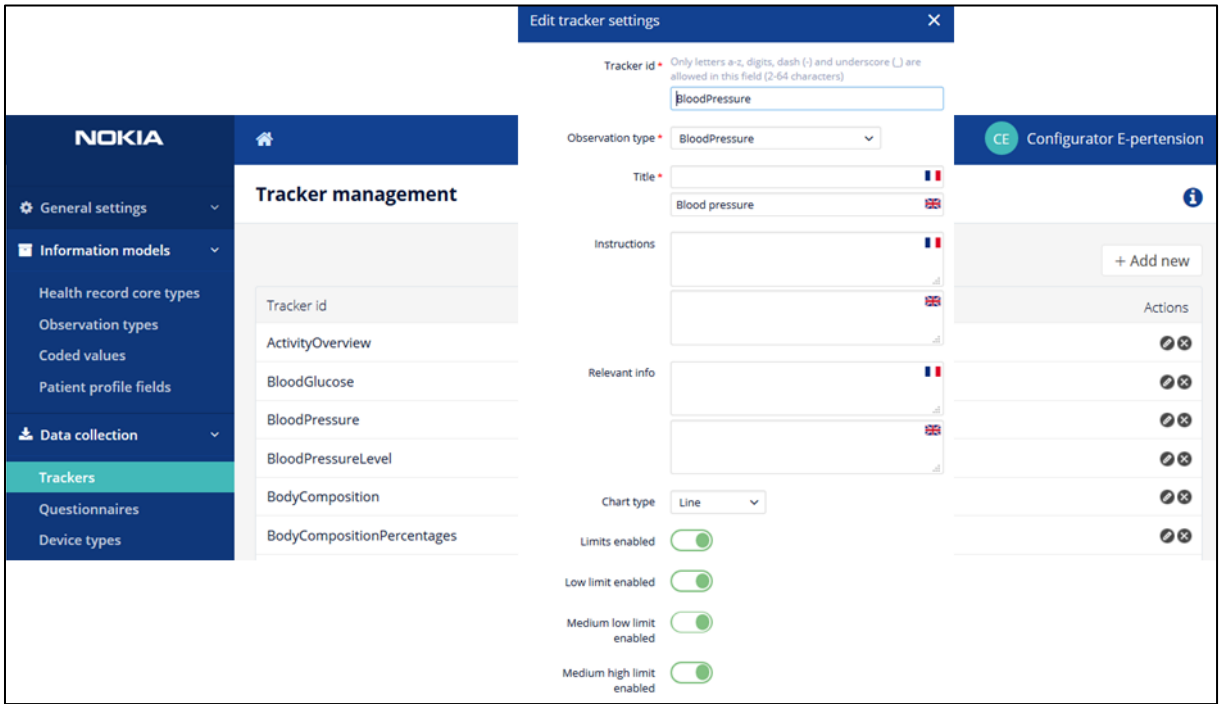
Care group webpage. The red arrows represent which buttons to click to get to that page and in which order



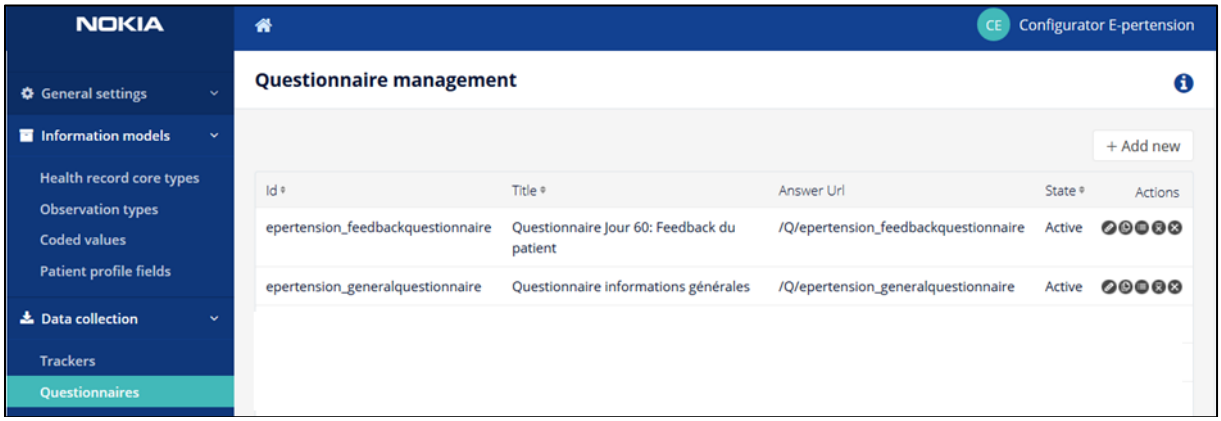
Tracking limits tool in "epertension-admin" account



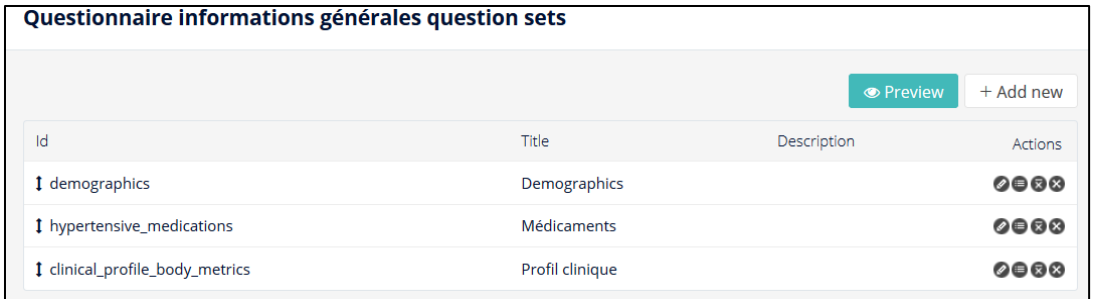
Tool allowing the creation of different types of trackers in the "epertension-config" account



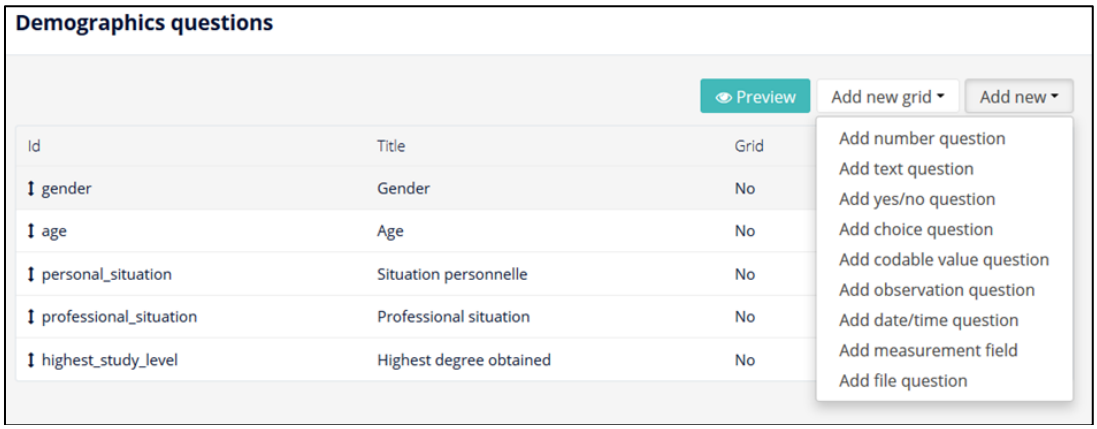
Trackers settings' edition



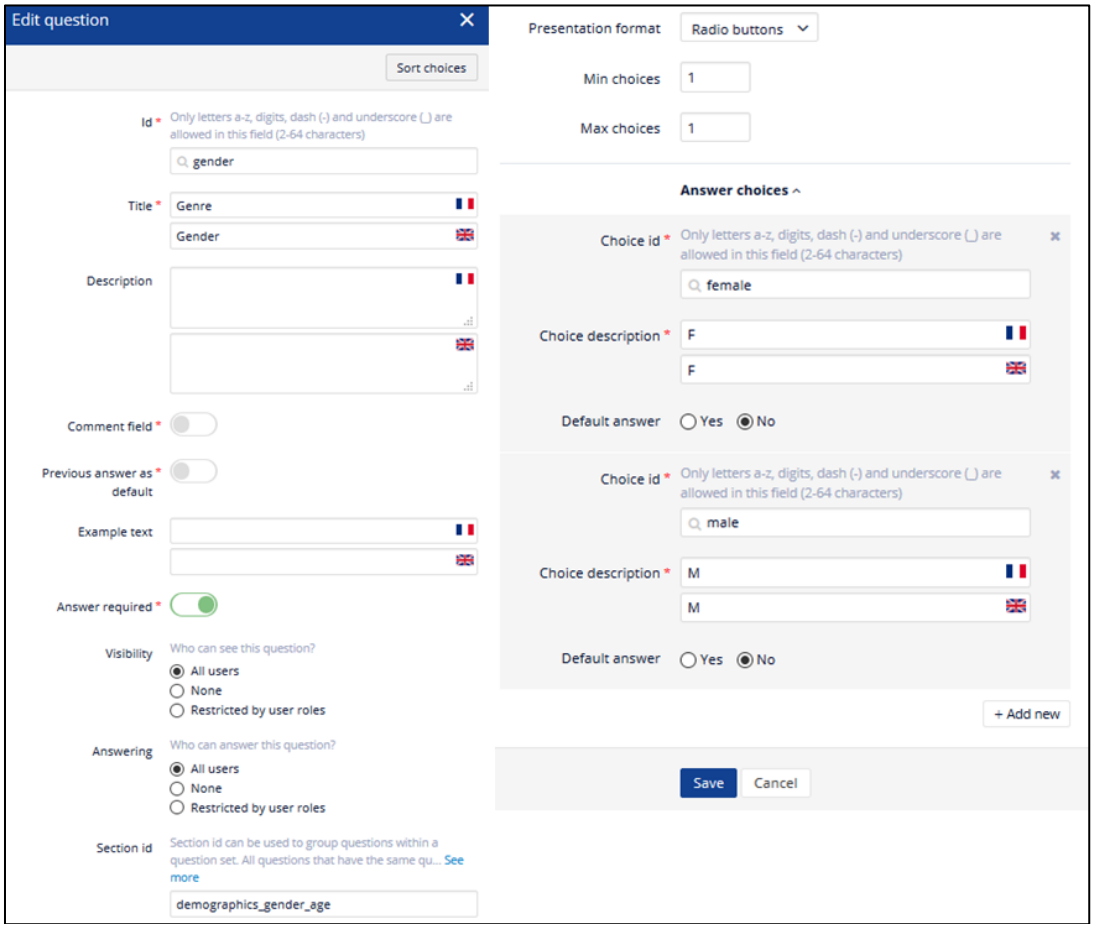
Questionnaire creation tool. General information and feedback questionnaires can be seen



Questions sets for the General information questionnaire



Questions from the "demographic" questions set in the General information questionnaire. Different types of questions are available

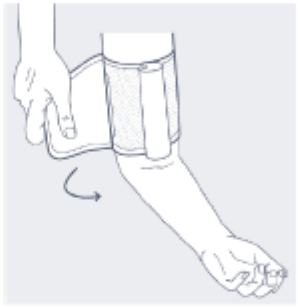


Question edition menu

Appendix 6. Patient's leaflet

Auto mesure de la tension artérielle

- Avant de prendre la 1ère mesure, lisez le mode d'emploi de votre tensiomètre et de l'application.
- Asseyez-vous en position confortable , remontez votre manche gauche si nécessaire.
- Détendez-vous 5 minutes environ.
- Enfilez le brassard au niveau de votre bras, 2 cm au-dessus du coude avec le tube en métal dans le creux du bras et le bouton d'alimentation vers le dessus (comme indiqué sur le dessin).
- Placez votre bras sur la table à la hauteur de votre cœur (au niveau de votre poitrine, à la hauteur de votre sein). Il doit être légèrement fléchi comme sur le dessin.



Nokia BPM User Guide

- Démarrez l'application, activez votre brassard (via le bouton sur le dessus) et lancez une mesure pour gonfler le brassard (pendant le gonflage et le dégonflage ne bougez pas, restez détendu et évitez de parler).

Mesurez votre tension, matin et soir, 2 jours sur la semaine :

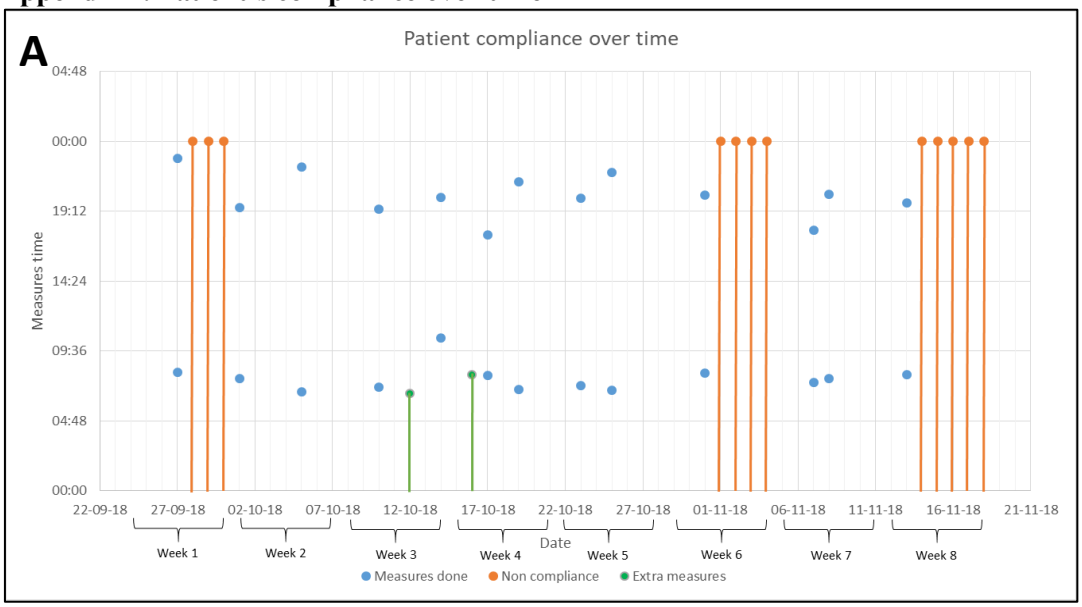
- Le matin, avant le petit-déjeuner, avant de prendre vos médicaments.
- Le soir, avant de vous coucher.
- Le matin et le soir, répétez la manœuvre 2 fois de suite, à 1 ou 2 minutes d'intervalle. Une 3eme mesure vous sera demandée par l'application en cas de résultats anormaux.

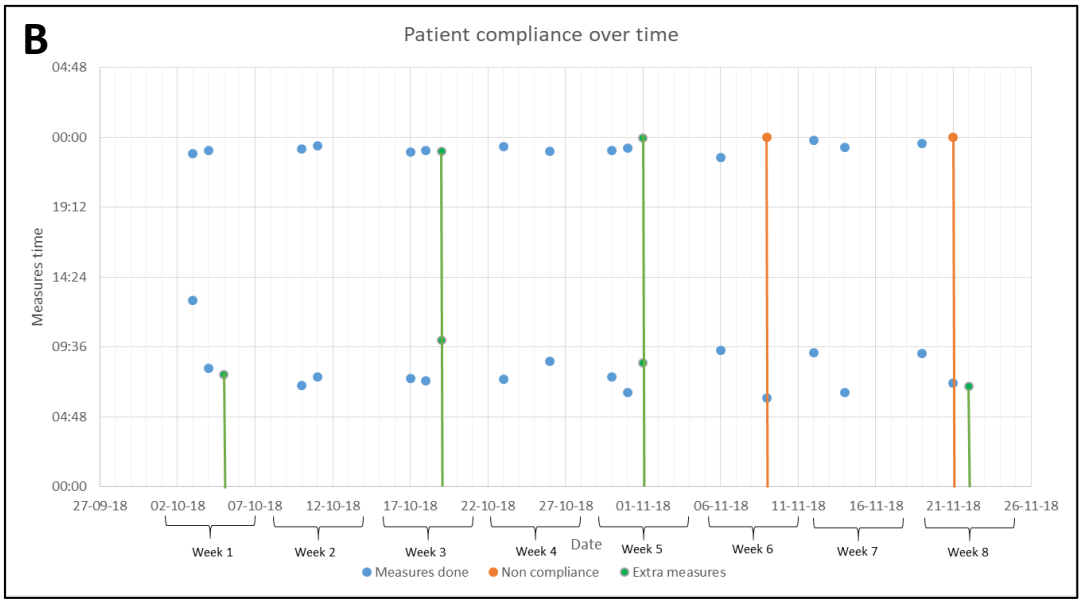
En cas de problèmes ou pour plus d'informations, veuillez nous contacter aux coordonnées suivantes :

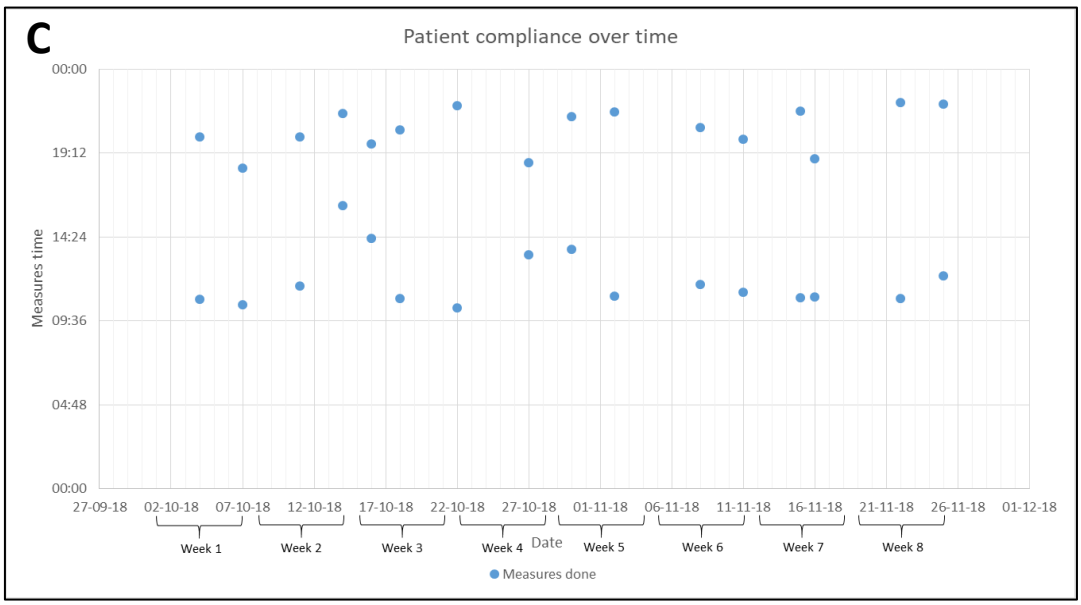
TOMAS Marc
Tél : +32 496 59 04 42

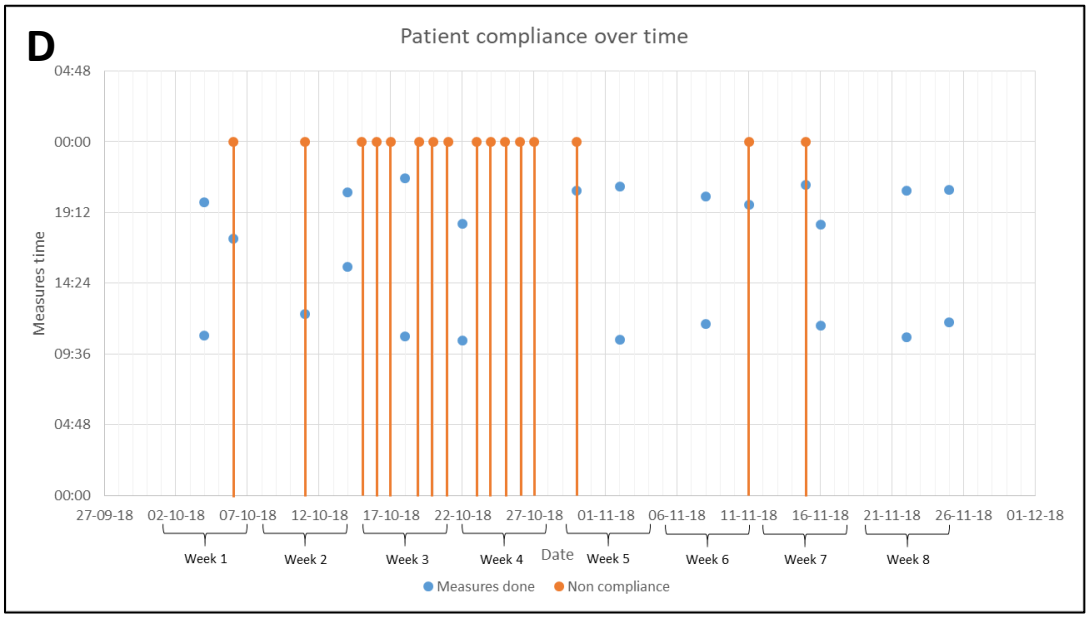
NOËL Cyril
Tél : +32 477 84 98 23

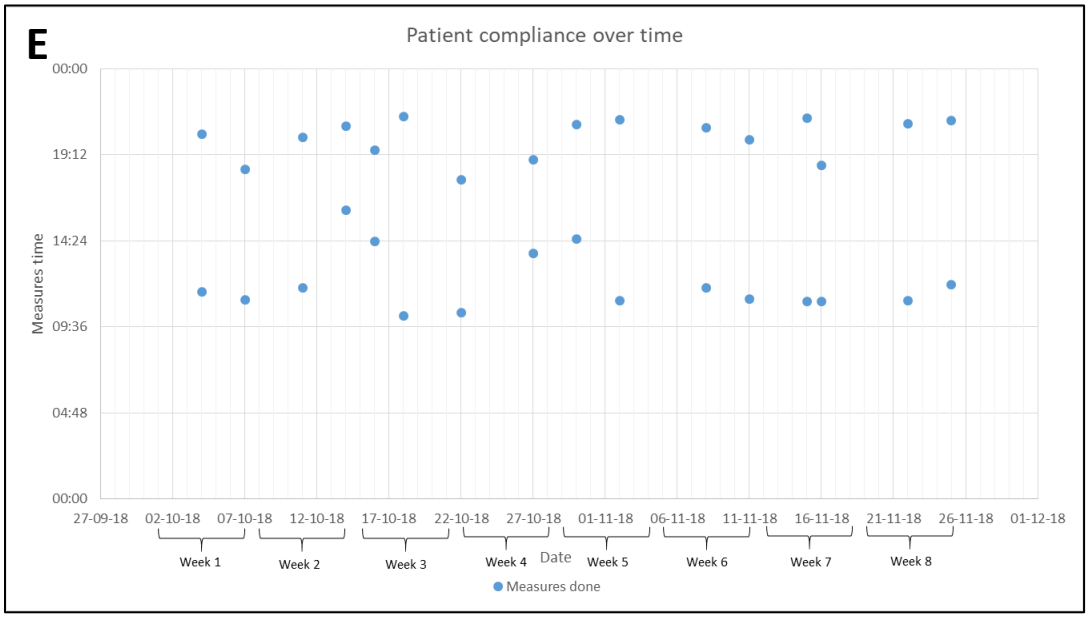
Appendix 7. Patient's compliance over time

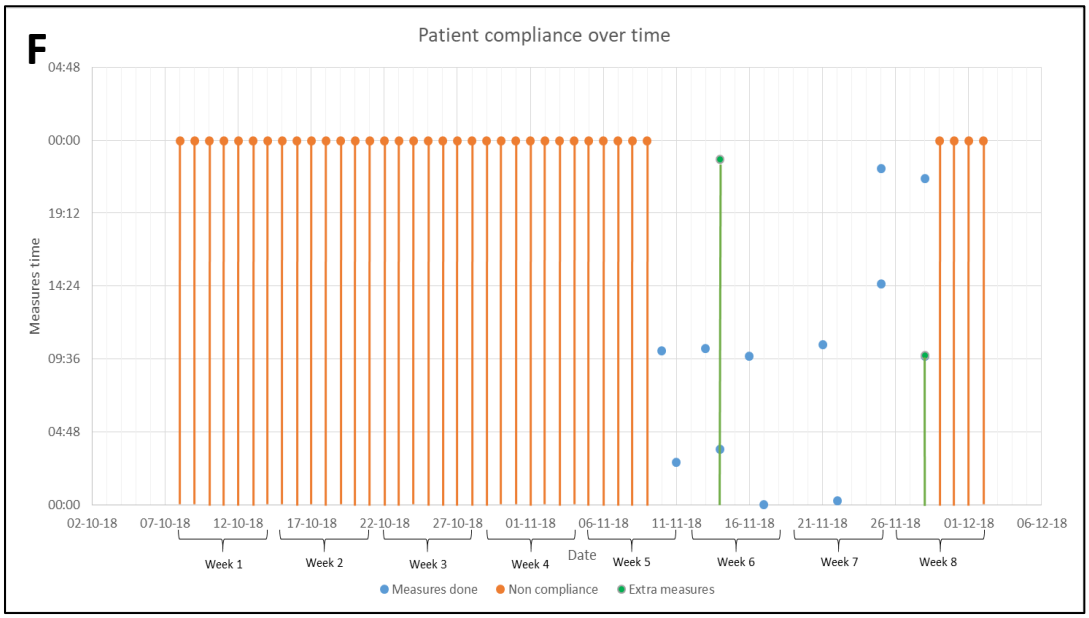


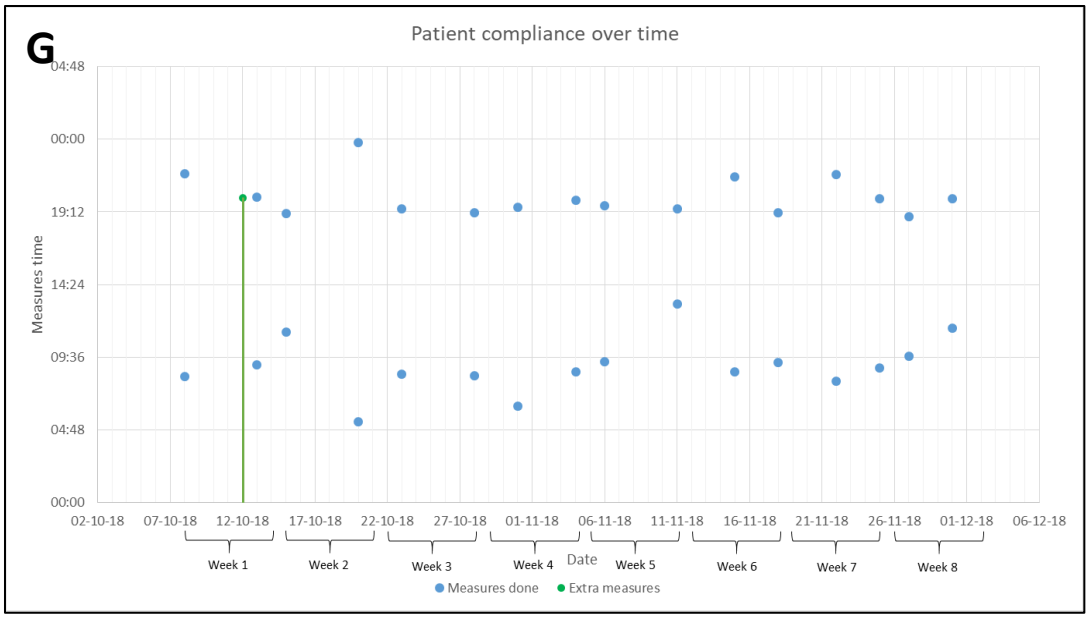


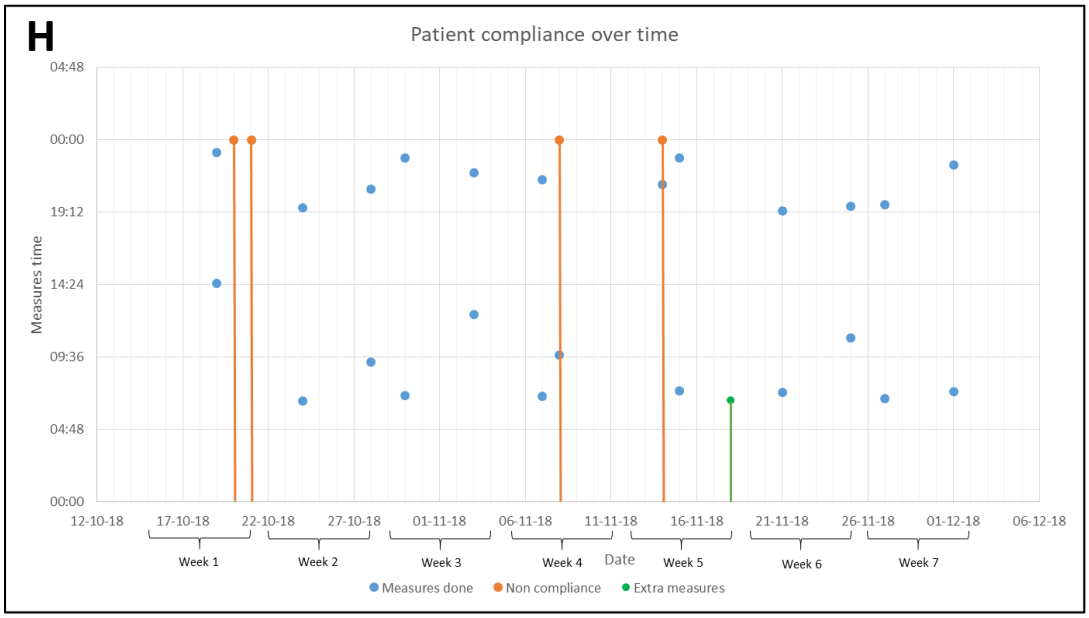



D
Patient compliance over time
04:48
00:00
19:12
14:24
09:36
04:48
00:00
Measures time
27-09-18
02-10-18
07-10-18
12-10-18
17-10-18
22-10-18
27-10-18
01-11-18
06-11-18
11-11-18
16-11-18
21-11-18
26-11-18
01-12-18
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Date
Measures done
Non compliance


E
Patient compliance over time
00:00
19:12
14:24
09:36
04:48
00:00
Measures time
27-09-18
02-10-18
07-10-18
12-10-18
17-10-18
22-10-18
27-10-18
01-11-18
06-11-18
11-11-18
16-11-18
21-11-18
26-11-18
01-12-18
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Date
Measures done

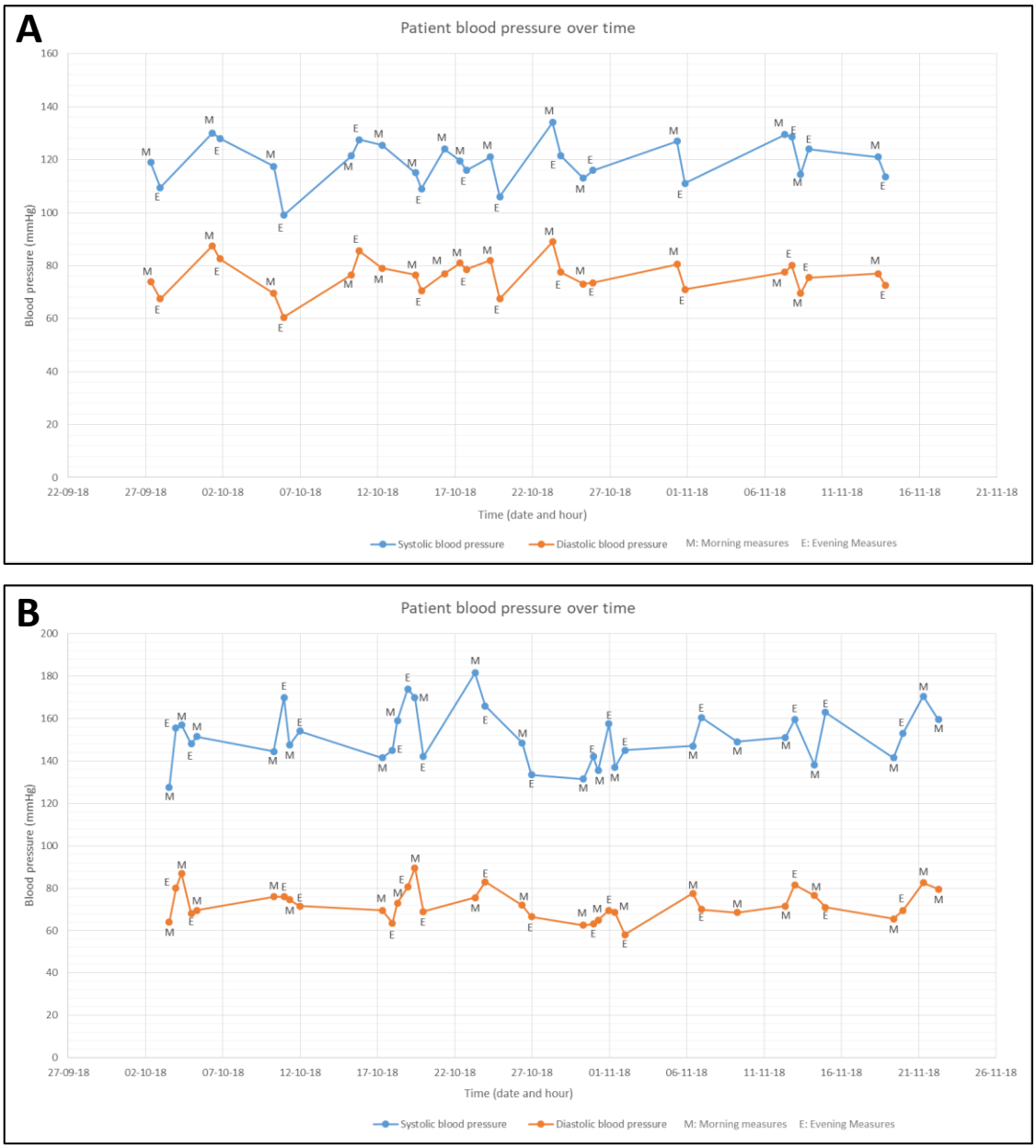

F
Patient compliance over time
04:48
00:00
19:12
14:24
09:36
04:48
00:00
Measures time
02-10-18
07-10-18
12-10-18
17-10-18
22-10-18
27-10-18
01-11-18
06-11-18
11-11-18
16-11-18
21-11-18
26-11-18
01-12-18
06-12-18
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Date
Measures done
Non compliance
Extra measures

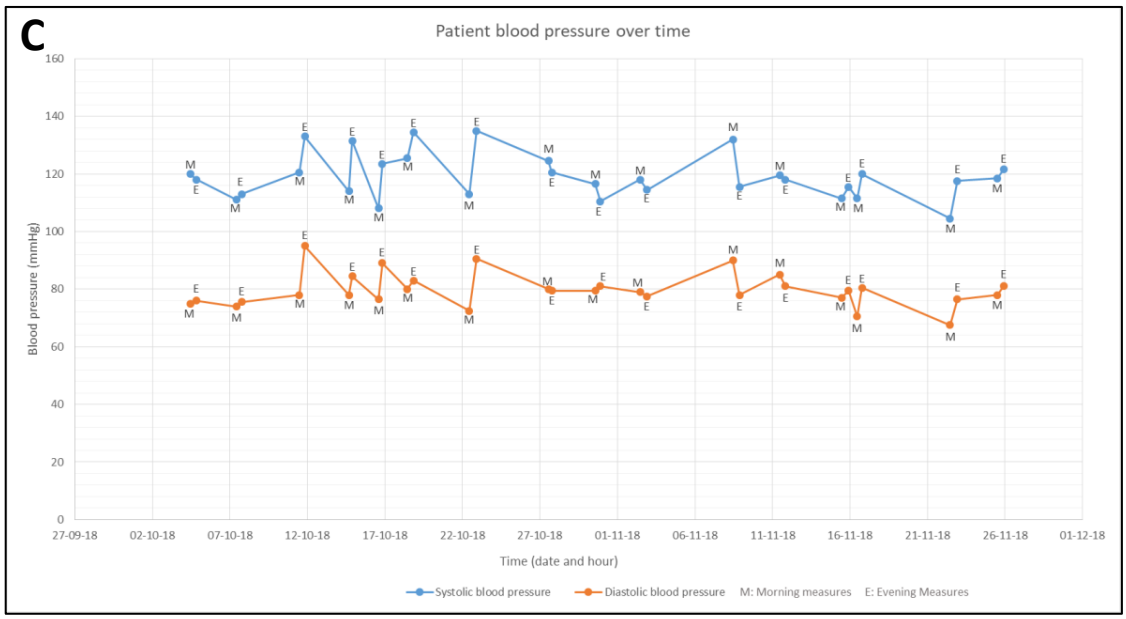


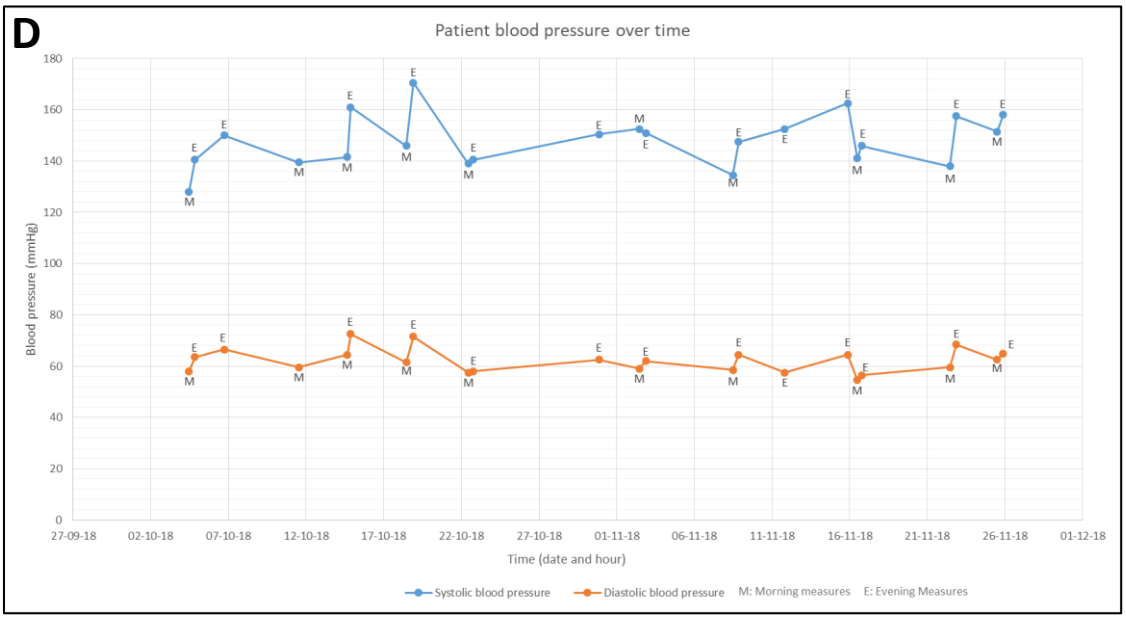


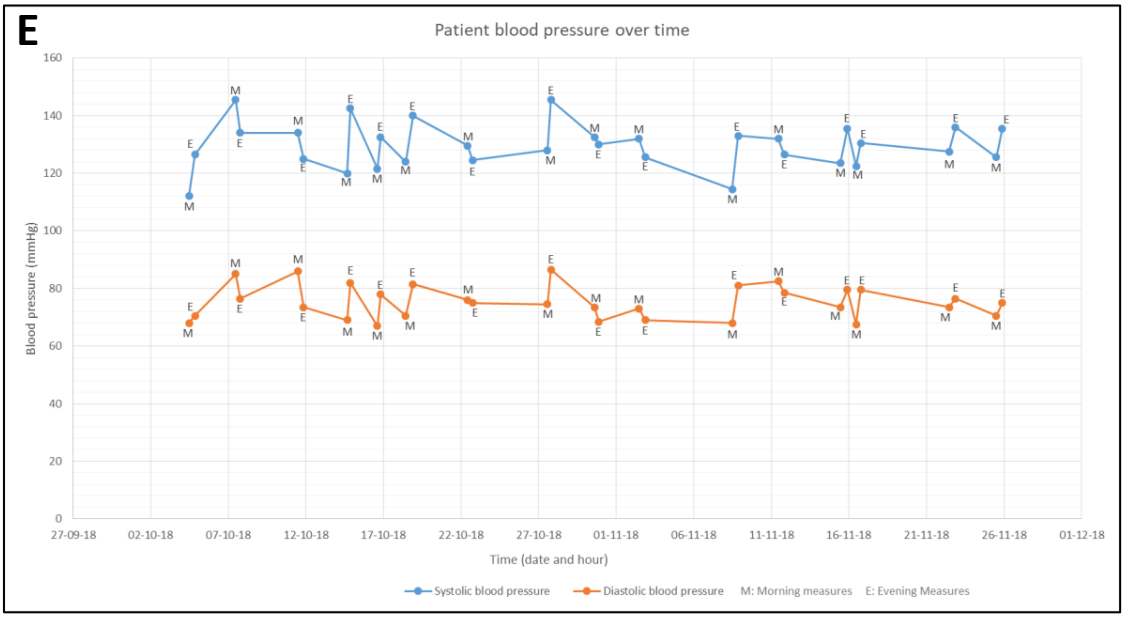
The blue dots represent each measure at which time and date. The orange lines represent the lack of compliance. A lack of compliance is considered when there is no measures at all in a week, only one measure done in a day or when there is only one day of measurement in a week. The green lines represent the extra days of measurement

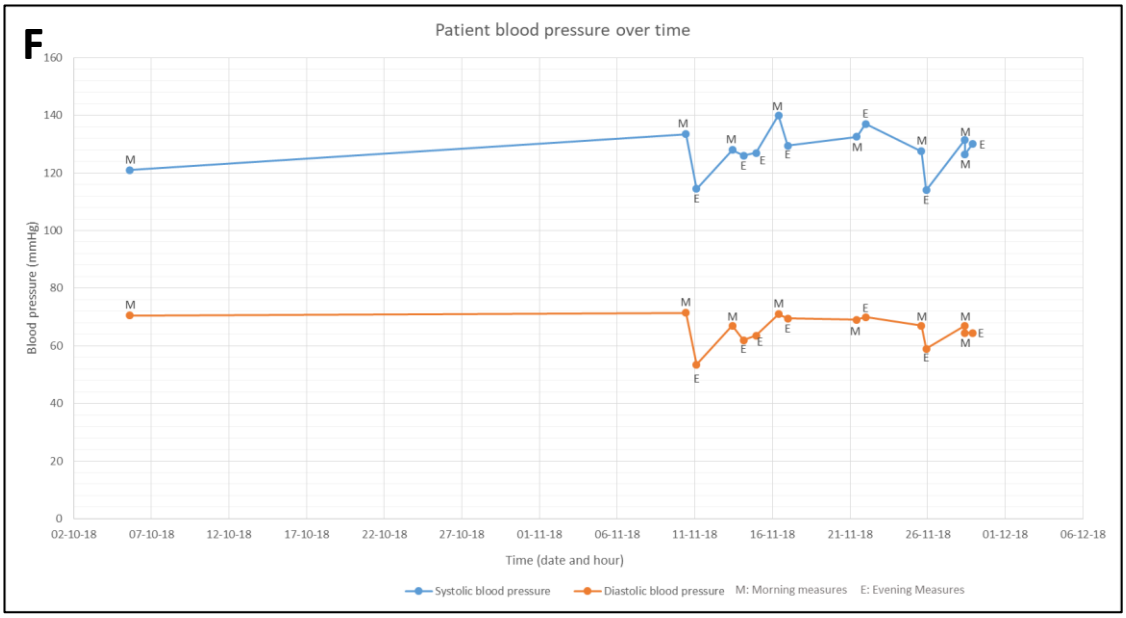
Appendix 8. Patient's blood pressure over time

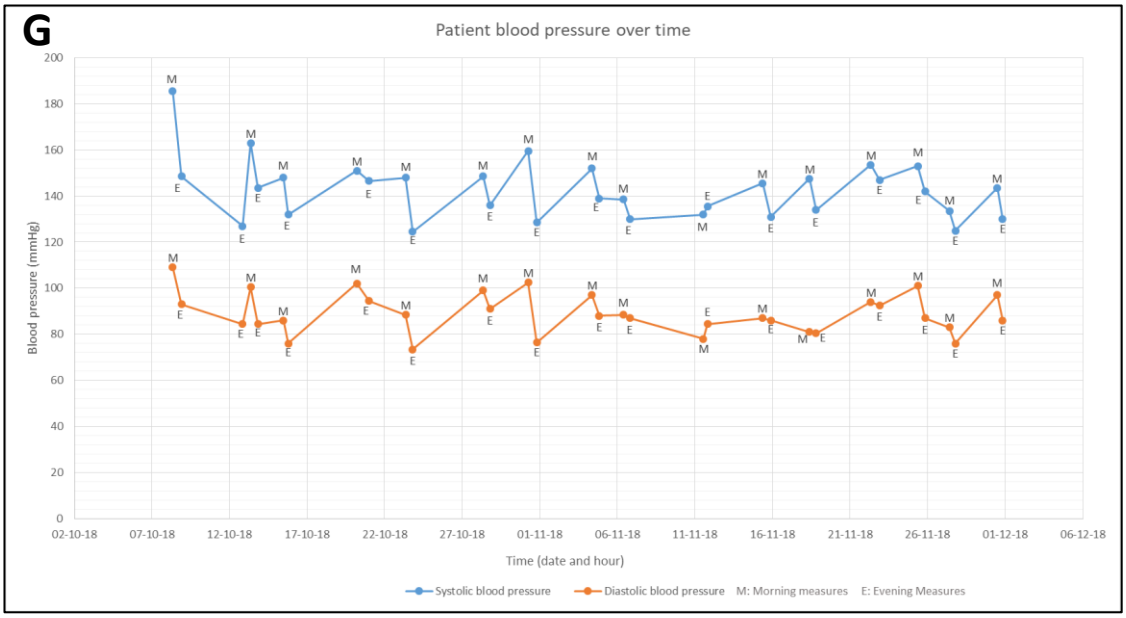


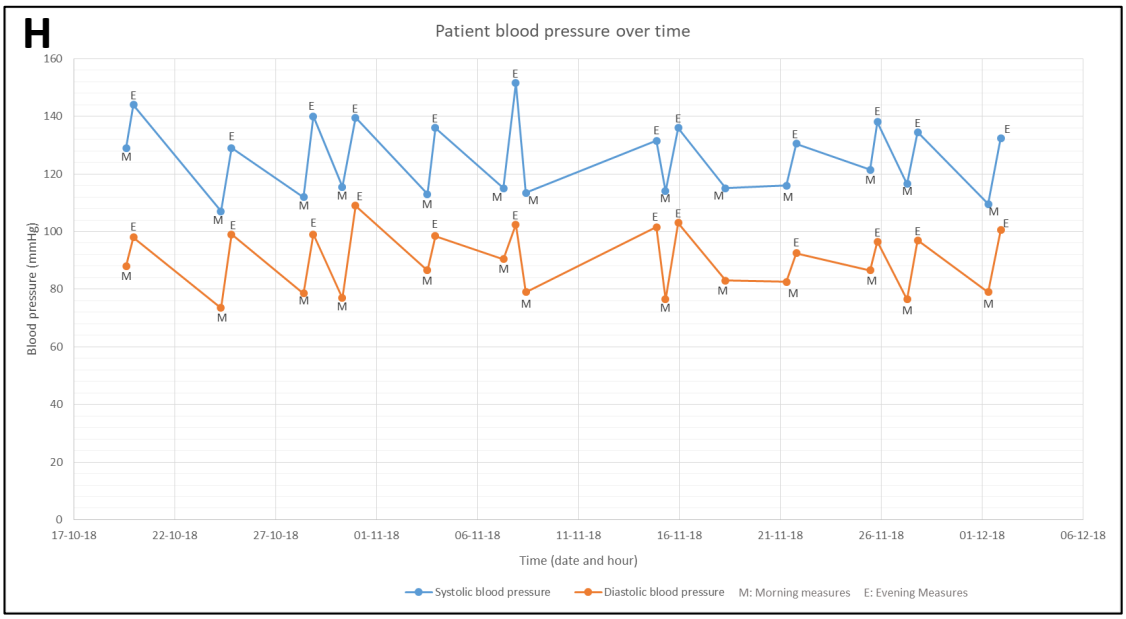

C
Patient blood pressure over time
Blood pressure (mmHg)
Time (date and hour)
Systolic blood pressure
Diastolic blood pressure
M: Morning measures
E: Evening Measures


D
Patient blood pressure over time
Blood pressure (mmHg)
Time (date and hour)
Systolic blood pressure
Diastolic blood pressure
M: Morning measures
E: Evening Measures


E
Patient blood pressure over time
Blood pressure (mmHg)
Time (date and hour)
Systolic blood pressure
Diastolic blood pressure
M: Morning measures
E: Evening Measures


F
Patient blood pressure over time
Blood pressure (mmHg)
Time (date and hour)
Systolic blood pressure
Diastolic blood pressure
M: Morning measures
E: Evening Measures


G
Patient blood pressure over time
Blood pressure (mmHg)
Time (date and hour)
Systolic blood pressure
Diastolic blood pressure
M: Morning measures
E: Evening Measures


H
Patient blood pressure over time
Blood pressure (mmHg)
Time (date and hour)
Systolic blood pressure
Diastolic blood pressure
M: Morning measures
E: Evening Measures