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Multicentre, randomized, single-blind, parallel group trial to compare the effectiveness of a Holter for Parkinson's symptoms against other clinical monitoring methods

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ABSTRACT

Introduction

In recent years, multiple studies have aimed to develop and validate portable technological devices capable of monitoring the motor complications of Parkinson's disease patients (Parkinson's Holter). The effectiveness of these monitoring devices for improving clinical control is not known.

Methods and analysis

This is a single-blind, cluster-randomized controlled clinical trial. Neurologists from Spanish health centres will be randomly assigned to one of three study arms (1:1:1): A) therapeutic adjustment using information from a Parkinson's Holter that will be worn by their patients for 7 days; B) therapeutic adjustment using information from a diary of motor fluctuations that will be completed by their patients for 7 days; and C) therapeutic adjustment using clinical information collected during consultation. It is expected that 162 consecutive patients will be included over a period of 6 months.

The primary outcome is the efficiency of the Parkinson's Holter compared to traditional clinical practice in terms of Off time reduction with respect to the baseline (recorded through a diary of motor fluctuations, which will be completed by all patients). As secondary outcomes, changes in variables related to other motor complications (dyskinesia and freezing of gait), quality of life, autonomy in activities of daily living, adherence to the monitoring system and number of doctor-patient contacts will be analysed. The noninferiority of the Parkinson's Holter against the diary of motor fluctuations in terms of Off time reduction will be studied as the exploratory objective.

Ethics and dissemination

thical approval for this study has been obtained from the Hospital Universitari de Bellvitge Ethics Committee. The results of this study will inform the practical utility of the objective information provided by a Parkinson's Holter and therefore the convenience of adopting this technology in clinical practice and in future clinical trials. We expect public dissemination of the results in 2022.

Trial registration: NCT04176302 Registered 18 November 2019,

https://clinicaltrials.gov/show/NCT04176302

Keywords

Parkinson's, wearable, Parkinson's diary, motor complications, dyskinesia, Off

ARTICLE SUMMARY

- This is the first study to examine the efficacy, in terms of clinical control, of a Parkinson's Holter.

- The study will also evaluate neurologists' and patients' satisfaction with the device.

- The results will provide information on the convenience of adopting this technology in clinical practice, in future clinical trials and in various studies on PD.

- The major limitation of the trial is that, by design, neurologists cannot be blind to the branch of study, which could affect their behaviour.

INTRODUCTION

Parkinson's disease (PD) is the most common form of chronic and progressive hypokinetic syndrome among the elderly population and is the second most common neurodegenerative disease after Alzheimer's disease[1]. In early stages, PD responds well to dopaminergic therapy; however, as the disease progresses, the duration of the effect decreases and motor complications develop due to “wearing off” effects (end-of-dose deterioration) or due to a delayed or no response to medication, which requires frequent therapeutic adjustments to achieve good symptom control throughout the day[2]. Despite all therapeutic adjustment efforts, 90% of patients have motor complications or fluctuations after 10 years[3]. These fluctuations consist of changes between periods called Off, in which the medication has no effect and mobility is difficult, and periods called On, in which patients can move fluidly because the medication is having its best effect[4]. In addition, in the transition between these two states (On and Off) or during the period of maximum medication effect, patients may present with dyskinesias, i.e. involuntary movements of the head, torso or extremities, which may interfere with the patient’s activity[5].

Motor complications in patients with advanced disease are not easy to control; they can have a variable character, fluctuating, as mentioned, throughout the day and between different days. The chronology of symptoms throughout the day and between different days is of great value for the precise adjustment of the medication dosage, adapting the scheduled doses to the most prevalent symptoms in the post-dose period. However, neurologists do not currently have detailed information on their patients’ symptom chronology; therefore, they have serious difficulties in obtaining good results with medication adjustments. Currently, the information available to neurologists on the hourly course of symptoms comes from the patient’s self-report during consultation, or

in the best case, from diaries kept by the patient at home noting their motor state (On or Off) periodically (e.g., every hour)[6]. Although the latter method continues to be the reference standard in research and care, it has serious limitations, as patients often forget to make notes (especially when they are Off), many do not recognize their motor state well, and few can adhere to such a laborious system beyond a few days[7]. Thus, a system for measuring motor fluctuations that is objective, does not require intervention on the part of the patient and can therefore be part of their day-to-day for the long-term, if necessary, can be of great utility in clinical practice to help optimize medication regimens and improve disease control.[8]

During the last decade, our research group has developed a system for monitoring patients with PD based on accelerometry that can be comfortably worn at the waist during daily activities. This system is capable of detecting various motor symptoms, including bradykinesia, freezing of gait and dyskinesia[9–11], establishing the chronology of motor fluctuations (On and Off periods) and detecting falls[12,13]. This system, which henceforth will be generically referred to as Parkinson's Holter, is possibly the only such system that is easy to carry, is validated under real conditions of use and provides sufficient information to improve the medication regimen. However, it remains a hypothesis that detailed knowledge of the motor symptoms of patients leads to better disease control, thanks to optimization of the therapeutic regimen. To confirm or refute this hypothesis, we propose a clinical trial in which the clinical effectiveness of this device will be analysed in patients with moderate PD and motor fluctuations.

The primary objective of this trial is to compare the clinical outcomes in Parkinson's Disease patients, measured as changes from baseline to last visit in daily Off time, in three different arms according to different sources of information in regards of motor fluctuations: 1) Parkinson's Holter, 2) patient's diary and 3) no information (the only information that the patient can provide at the visit).

As secondary objectives, besides security issues and user satisfaction with the Parkinson's Holter, the following efficacy results will be measured: number of medical contacts, adherence to monitoring system, severity of motor complications, severity of Freezing of Gait, quality of live and performance in activities of daily living performance.

METHODS AND ANALYSIS

Study design

A single-blind, cluster-randomized controlled clinical trial with three arms (1:1:1): Group A (therapeutic adjustment using information from a Parkinson's Holter); Group B (therapeutic adjustment using information from a diary of motor fluctuations); and Group C (The therapeutic adjustment is not supported by additional information, other than the clinical information collected during consultation).

Study setting and duration

The fieldwork will last 9 months in total (3 months of recruitment + 6 months of follow-up) and will be carried out between 2019 and 2020. Neurologists from at least 40 hospitals in Spain will participate in the study.

Participants

The target population is patients with PD and difficult-to-control motor fluctuations. It is planned that 162 patients with idiopathic PD according to the clinical criteria of the Brain Bank of the United Kingdom[14] will be included in the study. Patients will have moderate to severe disease (Hoehn & Yahr ≥ 2, in the Off state)[15] and motor fluctuations, with at least 2 hours per day in the Off state. To be included in the study, previously informed patients will agree to participate voluntarily and sign a written consent form.

Patients who are unable to walk independently or with Hoehn & Yahr = 5, patients participating in another clinical trial, patients with acute intercurrent disease, patients with psychiatric or cognitive disorders preventing collaboration (Mini-Mental Status Examination <24)[16] and patients with difficulty understanding the study procedures will be excluded.

The neurologists will be professionals who care for patients with PD and who recognize the potential of recruiting five patients with difficult-to-control motor fluctuations at the time of recruitment foreseen in the study.

Interventions and randomization

Prior to each visit with their neurologist, all patients participating in the study will keep a diary of motor fluctuations for 7 days at home and will be monitored using a Parkinson's Holter during the same period of time (the Holter and the diary will be delivered and collected by courier). The neurologists participating in the study will be randomly assigned to one of the following three groups:

- Group A: For therapeutic adjustment, neurologists will have access to the information from the Parkinson's Holter (study device) and to the information collected during consultation.

- Group B: For therapeutic adjustment, neurologists will have access to the information from the diary of motor fluctuations (reference standard) and to the information collected during consultation.

- Group C: For therapeutic adjustment, neurologists will only have access to the information collected during a typical consultation, without information from the Holter's Parkinson or diary of motor symptoms (traditional clinical practice).

The staff responsible for implementing the randomization sequence will receive the patient's clinical information by courier: 1.- Holter with data stored on the memory card and 2.- Patient's diary of motor fluctuations. This staff will be responsible for sending this information to the patient' neurologist by encrypted email and before the next appointment that has been randomly assigned to them: information from the Parkinson's Holter, diary of motor fluctuations or no additional information. The randomization sequence will have been performed by independent staff with the help of a table of random numbers and following a balanced blocks model, whose size and composition will not be revealed to the researchers or to the staff responsible for implementing the sequence.[17]

Procedures

All patients will keep a diary of motor fluctuations and will be monitored with a Parkinson's Holter for 7 days prior to the consultation with the neurologist. However, according to the randomization arm, the information available to the neurologist at the time of consultation will be only that from the Holter, that from the diary or none.

The Parkinson's Holter is a commercial device (STAT-ON®) manufactured by Sense4Care (www.sense4care.com) that records motor fluctuations (On and Off periods) during daily activities[18], in addition to dyskinesias, bradykinesia and freezing of gait episodes[9–11] (Figure 1).

The Parkinson's Holter will be delivered to patients by courier along with the user manual and a quick start guide. There will be a technical assistance telephone line at their disposal to answer questions on how to handle the device. The device will have been previously configured so that patients only have to turn it on the first time it is taken out of the box by pressing the only button on the device. From that time on, the device will

turn on and off autonomously depending on the movement detected by its sensors, so patients do not have to perform any other operation. The device will have a charged battery and autonomy longer than 7 days, so no charger will be provided nor will patients have to worry about recharging the batteries. After the last day of use, the device will be picked up by courier and transported to the centre that manages the deliveries (which is a centre independent of the sponsoring entity) to download the collected data.

Simultaneously, patients will fill out a diary of motor fluctuations at home. The motor fluctuations diary was designed by the researchers (supplementary file), and the neurologists participating in the study will explain to the patients how to fill it out. To do this, the neurologists will follow a common procedure that involves showing instructional videos to patients that provide examples of the different phases (On/Off) and motor complications. The diary of motor fluctuations will be collected by courier on the same day as the Holter device.

The results of the measurements taken at home (Holter or diary of motor fluctuations) will be sent to the corresponding neurologists by encrypted email before their next consultation with the patient.

The home monitoring procedure will be repeated systematically before each appointment with the neurologist. The study's first appointment will take place in week 12 (± 2 weeks) after patient inclusion. The study's last evaluation will be carried out by week 26 (± 2 weeks). The neurologist is free to schedule intermediate appointments if necessary, before which the home monitoring process will also be repeated. The efficacy variables described in the next section will be recorded at each study evaluation and at the last appointment, usability and satisfaction questionnaires will also be administered to both the patients and neurologists (Table 1).

At the end of the study, the neurologists will receive the complete information from the records of all their patients (regardless of the study group to which they belong) by email, including the diaries of motor fluctuations filled out at home and the complete information from the Parkinson's Holter.

In this study there are no concomitant treatments prohibited, although information systems or patient monitoring systems, other than those tested, cannot be used.

Outcome variables and measurement instruments

The efficacy of clinical control will be measured using the following variables.

Primary:

- Daily Off time: through a diary of motor fluctuations (On/Off)[19,20]

Secondary:

- Number of medical visits and telephone contacts for medication adjustment
- Record of therapeutic changes
- Adherence to the motor fluctuations recording system (On/Off diary and Parkinson's Holter)
- Motor complications (Unified Parkinson's Disease Rating Scale [UPDRS] part IV[21], administered by the neurologist)
- Daily On time: through a diary of motor fluctuations (patient's diary)[19]
- Presence and severity of freezing of gait episodes: Freezing of Gait Questionnaire (FOG-Q, administered to the patient by phone)[22]
- Quality of life: using the 39-item Parkinson's Disease Questionnaire (PDQ-39, self-administered by the patient)[23]
- Autonomy in activities of daily living: UPDRS part II[21] (administered by the neurologist)

In addition, a record of adverse effects during the study period will be kept and the usability of and user satisfaction with the Parkinson's Holter will be evaluated using the System Usability Scale (SUS)[24] and the Quebec User Evaluation of Satisfaction with Assistive Technologies scale (QUEST) [25], respectively.

Other PD-related data will be recorded as control variables (year of PD diagnosis, stage according to the Hoehn & Yahr scale in the Off state[15]), patient sociodemographic data (age, sex, educational level) and neurologist data: age, sex, years of practice, type of activity (consultation, ward, etc.) and number of patients treated per year at each care level.

Monitoring

All study data and procedures will be supervised by an independent monitor. The supervision will be carried out in accordance with Best Clinical Practices, ISO 14155:2011

Blinding

The participating patients are responsible for recording the main variable (Off time) in their diary of motor fluctuations. Patients will be blinded to the neurologist's randomization arm, who will not disclose what information is available to adjust the therapeutic regimen. Patients are also responsible for recording the On time (diary of motor fluctuations) and the variables related to freezing of gait events (FOG-Q) and quality of life (PDQ-39); therefore, there is blinding to these data. The neurologists are responsible for collecting the UPDRS data and recording the therapeutic changes and adverse effects; therefore, there is no blinding to these secondary variables. The data analysts will also be blinded to the type of intervention in each group.

Blinding could be broken in the event the patient's physician deems it vital to access any of the study information (especially the patient's diary filled out at home) because the

patient's clinical situation requires it. This fact will be recorded for later exclusion from all analyses potentially affected by the infringement of the protocol

Sample size

Assuming a mean reduction from baseline of 75 min of OFF time daily (SD 130) [43] between Arm A and C, a sample size of 49 patients per group would provide 80% power to show superiority at a significance level alpha of 5% (two-sided).

Unassessable patients will be those that signed the informed consent form (inclusion visit) but are lost to follow-up before the baseline visit. The rest of the subjects will be assessable even if they are not adherent to the motor fluctuation measurement systems. To cover loss to follow-up and unassessable patients, the sample size will be increased by 10% so that, in principle, 162 patients will be necessary (54 per arm). A standard method to handle missing data (Last Observation Carried Forward) will be used.

The inclusion of 40 physicians is proposed, assuming that, each physician will be assigned four or five patients in the study.

Data analysis plan

In the patient's diary (main outcome variable), lost data will be imputed, by interpolation between equal data, provided that the period without data does not exceed the hour of duration. No other lost data of the study will be imputed.

A fixed effects ANOVA with the baseline Off time as a covariate will be used to test the superiority of Group A vs. Group C in the overall analysis and the noninferiority of group B in the per-protocol analysis.

A descriptive analysis of all the variables included in the study will be performed. For the quantitative variables, robust estimators of central tendency (mean, winsorized mean, trimmed mean, Huber estimator) and of sample variability (standard deviation, standardised median absolute deviation, sample quasi-α-Winsorised-standard deviation, weighted root mean variance and the adjusted percentage root mean variance) will be used. Confidence intervals will be calculated by applying bootstrap or resampling methods. The maximum, minimum, skewness and kurtosis of the distributions will be calculated. For comparison of two related means, the Wilcoxon test or the robust generalization of repeated measures ANOVA will be used.

For qualitative variables, the frequency of the distributions will be calculated with percentages. For comparisons, Pearson's chi-squared or McNemar's test will be used as appropriate.

The total score on the usability and user satisfaction scales (SUS and QUEST) will be calculated according to the instructions of each instrument, and a descriptive analysis of these results will be performed for the overall sample. The results for the usability of and the physician satisfaction with the device will be analysed for the overall sample

Lastly, a descriptive analysis of the frequency and severity of the adverse effects and device-related adverse effects will be performed.

Patients lost to follow-up will be included in the analysis if at least one therapeutic adjustment was made before dropout. The baseline data of the patients lost before this point, will be also analysed in order to study the potential impact of these dropouts in the balance between groups, regarding the main confounding factors.

The analysts will be blinded to the type of diagnostic intervention in each group.

Patient Involvement

Patients were not involved in the design, recruitment or choice of outcome measures of this research protocol. However, patients played a central role the in the development of the Parkinson's Holter, carried out by the research team in previous research projects. Selected groups of patients, wo were involved from first stages, contributed to identify needs and use cases, provided information on their symptoms and feedback on design and usability, which have served to improve the product in various iterations. Parkinson's patient associations will be involved in development the dissemination plan of the results.

ETHICS AND DISSEMINATION

This protocol and the informed consent form were approved by the Ethics Committee of Hospital Universitari de Bellvitge (code AC012/19). Any protocol change that may increase the risk or present new risks for the patient, or that may affect the validity of the study, must be approved by the sponsor in writing before being implemented. All study participants will sign the written consent form, after being properly informed by a study local investigator.

In all of the reports and communications related to the study subjects, the subjects will be identified only by their case numbers. Data will be handled strictly in accordance with the professional standards of confidentiality, under the terms stipulated in Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on Information Protection (GDPR).

The sponsor has a civil liability insurance policy that covers the potential damages for participants that could derive from the application of this protocol.

The results will be disseminated to the scientific community in the form of a publication, preferably in an open access journal, and to the general population, by press release for the national media. Various Spanish and European patient associations will receive direct communication of the results.

DISCUSSION

This study will evaluate the efficacy of a PD symptom monitoring device for improving the clinical control of patients. This improvement will be measured in the form of a reduction in the daily Off time and according to other health outcomes, as well as the neurologists' and patients' satisfaction with the device.

Although multiple studies have explored the validity of various devices for monitoring PD symptoms, currently there is no evidence of the therapeutic efficacy of monitoring by such means[26]. That the developed devices correctly monitor motor symptoms does not necessarily imply that this monitoring improves clinical control. This is the first study to examine the efficacy, in terms of clinical control, of these new sensors. Additionally, the same data may be used to test the efficacy of motor fluctuation diaries, considered a reference standard, which have been previously validated but for which there are also no available clinical efficacy studies[19]. The results of this study will provide information on the practical utility of the objective information that these devices provide and therefore on the convenience of adopting this technology in clinical practice, in future clinical trials and in various studies on PD.

This study has some limitations, such as the lack of blinding of the neurologists, which is inherent to the objective of the study: neurologists must necessarily know the monitoring information that has been assigned to them by chance. This could lead to a greater effort to optimize the medication regimen by neurologists with access to Holter data and by neurologists with access to the diary. While this phenomenon is not due to a Hawthorne effect (neurologists try harder because they know they are being observed in the study), it is not necessarily a negative phenomenon, since it is possible that part of the improvement potentially produced by these means of monitoring is due to the neurologist's increased attention to the case. That is, it is possible that the diary or Holter produce better clinical results not only because of the information they produce but also because they encourage neurologists to better adjust medication, which is one of the positive effects that should be included in the observation.

In contrast, neurologists may in fact be subject to the aforementioned Hawthorne effect[27]. Given that the protocol is identical in all arms of the study, if the Hawthorne effect is symmetrical, that is, if it has the same consequences in all arms, it will not affect the relative comparisons between arms. However, if the effect is more marked in any of the arms (for example, in the case of neurologists who do not have additional information but who particularly strive due to being observed in the study), then the differences observed in the study may vary with respect to the real ones in clinical practice.

In addition, observer bias may occur in this study because the neurologists, who know the information they have managed, are also responsible for applying some instruments to measure the secondary outcomes[28]. That is, knowledge of the study arm can lead to changes in the way the UPDRS is applied or interpreted, for example. This bias has been reduced as much as possible by removing the responsibility of applying the scales from the participating neurologists: the scales will be self-applied or applied by telephone by a blinded evaluator, except for the UPDRS, which requires a physical examination by

the neurologist. In any case, the results to which the neurologists were not blinded will be analysed with techniques that attempt to determine the presence of this bias: observer bias tends to more strongly affect less severe patients; therefore, if the intervention is effective only in less severe patients, the possible presence of this bias will be reported[29].

In conclusion, this clinical trial has been designed to determine whether automated symptom monitoring systems (Parkinson's Holter) improve the clinical control of patients with motor fluctuations. We expect the first results in 2021.

DECLARATIONS

Authors' contributions

ARM conceived and designed the study, and drafted this paper.

JHV, AB, JMC and DAP contributed to the study design.

CPL contributed to study logistics preparation, including software for managing Parkinson's Holter data during the trial.

AM contributed to the statistical analysis plan.

All authors have read and approved the manuscript.

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Role of the funders: none

Competing interests

ARM is a shareholder of Sense4Care, the company that will market the tested device in the short term. A.R.M. participated with other authors in obtaining funding for the study and in the protocol design. Given his conflict of interest, he will manage the project as the sponsoring centre's coordinator but will not participate in the data collection, study monitoring, statistical analysis or interpretation of results.

The remaining declare that they have no competing interests.

Acknowledgments

Acknowledgments are pending acceptance by the mentioned persons

Table 1. Schedule of the study evaluations.

	Inclusion	Baseline evaluation	Visit week 12 ± 2	Unscheduled visit	Visit week 26 ± 2
Inclusion criteria	X				
Informed consent	X				
Sociodemographic data	X				
Year of diagnosis	X				
Hoehn & Yahr Scale	X				
Baseline treatment	X				
Freezing of Gait Questionnaire		X	X	X	X
Unified Parkinson's Disease Rating Scale		X	X	X	X
39-item Parkinson's Disease Questionnaire		X	X	X	X
Diary of motor fluctuations			X	X	X
Parkinson's Holter			X	X	X
Record of health visits and contacts			X	X	X
Record of therapeutic changes			X	X	X
Adherence			X	X	X
Record of adverse effects			X	X	X
Usability and satisfaction					X

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FIGURE LEGENDS

Figure 1. Parkinson's Holter.

Figure 1
Parkinson's Holter.

135x50mm (300 x 300 DPI)

(Anverso)

Fecha (día / mes / año): ____ /____ /_____ ID sujeto_____
(a rellenar por los investigadores)

Haga una sola marca en cada línea

HORA	DORMIDO / A	OFF	**ON** sin discinesia	**ON** con **discinesia** no problemática	**ON** con **discinesia problemática**
00:00-00:30					
00:30-01:00					
01:00-01:30					
01:30-02:00					
02:00-02:30					
02:30-03:00					
03:00-03:30					
03:30-04:00					
04:00-04:30					
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07:00-07:30					
07:30-08:00					
08:00-08:30					
08:30-09:00					
09:00-09:30					
09:30-10:00					
10:00-10:30					
10:30-11:00					
11:00-11:30					
11:30-12:00					

ON: Periodo en el que la medicación es eficaz y le ayuda a mejorar la movilidad, la lentitud y la rigidez.

OFF: periodo en el que han desaparecido los efectos de la medicación y no le ayuda a mejorar la movilidad, la lentitud y la rigidez.

Discinesia: movimientos involuntarios de giro y torsión. Estos movimientos son un efecto de los medicamentos y se producen durante los periodos ON. Estos movimientos son más amplios y lentos que el temblor, que no se considera discinesa.

Discinesia no problmemática: no interfiere en su actividad ni le causa molestias significativas

Discinesia problemática: interfiere en las actividades normales o causa molestias significativas

(Reverso)

Haga una sola marca en cada línea

HORA	DORMIDO / A	OFF	**ON** sin discinesia	**ON** con **discinesia** no problemática	**ON** con **discinesia problemática**
12:00-12:30					
12:30-13:00					
13:00-13:30					
13:30-14:00					
14:00-14:30					
14:30-15:00					
15:00-15:30					
15:30-16:00					
16:00-16:30					
16:30-17:00					
17:00-17:30					
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21:00-21:30					
21:30-22:00					
22:00-22:30					
22:30-23:00					
23:00-23:30					
23:30-00:00					

ANOTE la hora en la que comenzó a usar el sensor hoy: ____:____

ANOTE la hora en la que dejó de usar el sensor hoy: ____:____

ON: Periodo en el que la medicación es eficaz y le ayuda a mejorar la movilidad, la lentitud y la rigidez.

OFF: periodo en el que han desaparecido los efectos de la medicación y no le ayuda a mejorar la movilidad, la lentitud y la rigidez.

Discinesia: movimientos involuntarios de giro y torsión. Estos movimientos son un efecto de los medicamentos y se producen durante los periodos ON. Estos movimientos son más amplios y lentos que el temblor, que no se considera discinesa.

Discinesia no problmemática: no interfiere en su actividad ni le causa molestias significativas

Discinesia problemática: interfiere en las actividades normales o causa molestias significativas

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym See title page (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry See after abstract (page 3)
	2b	All items from the World Health Organization Trial Registration Data Set See after abstract (page 3)
Protocol version	3	Date and version identifier N/A
Funding	4	Sources and types of financial, material, and other support See “funding” section (page 19)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors See title page and “Authors contributions” section (page 19)
	5b	Name and contact information for the trial sponsor See title page (page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities See “funding” section, paragraph 1 (page 19)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) See “Ethics" section, paragraph 1 (page 15)
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention See “introduction” section, paragraphs 1-4 (page 5)
	6b	Explanation for choice of comparators N/A
Objectives	7	Specific objectives or hypotheses See the last two paragraphs of the introduction. (page 6)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) See “Study Design” section, paragraph 1
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained See “study setting and duration” section paragraph 1 (page 7)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) See “Participants” section paragraphs 1-3 (page 7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered See “Interventions” section, paragraph 1 (page 8)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Please, see last paragraph of “Procedures” (page 9)

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended See "Outcome variables and measurement instruments", all section (page 11-12).
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) See fifth paragraph of "Procedures" (page 10) and Table 1 (page 20)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations See "Sample Size" section, paragraphs 1-3 (page 13)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size N/A

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions See last paragraph of "Interventions and randomization" (page 9)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned See last paragraph of "Interventions and randomization" (page 9)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions See last paragraph of "Interventions and randomization" (page 9)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how See "Blinding" (page 12)

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial See "Blinding" paragraph 1-2 (page 12)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol See "Outcome variables and measurement instruments", all section (page 11)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols See second to last paragraph of the "data analysis plan" section. (page 13)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol See "Ethics and dissemination" (page 15)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol See "data analysis plan", paragraphs 1-5 (page 13)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) See "data analysis plan" paragraphs 6-9 (page 14)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) See the first paragraph and the second to last paragraph of the "data analysis plan" section. (page 13)
Methods: Monitoring		

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed See "Monitoring" section, paragraph 1 (page 12)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Please see "Outcome variables and measurement instruments", "Data analysis plan" and Table 1
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor See "Monitoring" section, paragraph 1 (page 12)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval See Ethics and dissemination, paragraph 1 (page 15)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) This item is included the original protocol, but we have not considered it of interest for the article. If necessary we will introduce it upon request of the editor.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) See the first paragraph of "Ethics and dissemination", paragraph 1 (page 15)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial See "Ethics and dissemination", paragraph 2 (page 15)

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site See “Declarations” section (page 19)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators To be included upon editor’s request
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation See “Ethics and dissemination” section (page 16)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions See last paragraph of “Ethics and dissemination” section (page 16)
	31b	Authorship eligibility guidelines and any intended use of professional writers This is in accordance to BMJ authorship criteria.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code No plans yet. Not decided.
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates To be included upon editor’s request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

BMJ Open

Multicentre, randomized, single-blind, parallel group trial to compare the effectiveness of a Holter for Parkinson's symptoms against other clinical monitoring methods: study protocol

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Multicentre, randomized, single-blind, parallel group trial to compare the effectiveness of a Holter for Parkinson's symptoms against other clinical monitoring methods: study protocol.

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ABSTRACT

Introduction

In recent years, multiple studies have aimed to develop and validate portable technological devices capable of monitoring the motor complications of Parkinson's disease patients (Parkinson's Holter). The effectiveness of these monitoring devices for improving clinical control is not known.

Methods and analysis

This is a single-blind, cluster-randomized controlled clinical trial. Neurologists from Spanish health centres will be randomly assigned to one of three study arms (1:1:1): A) therapeutic adjustment using information from a Parkinson's Holter that will be worn by their patients for 7 days; B) therapeutic adjustment using information from a diary of motor fluctuations that will be completed by their patients for 7 days; and C) therapeutic adjustment using clinical information collected during consultation. It is expected that 162 consecutive patients will be included over a period of 6 months.

The primary outcome is the efficiency of the Parkinson's Holter compared to traditional clinical practice in terms of Off time reduction with respect to the baseline (recorded through a diary of motor fluctuations, which will be completed by all patients). As secondary outcomes, changes in variables related to other motor complications (dyskinesia and freezing of gait), quality of life, autonomy in activities of daily living, adherence to the monitoring system and number of doctor-patient contacts will be analysed. The noninferiority of the Parkinson's Holter against the diary of motor fluctuations in terms of Off time reduction will be studied as the exploratory objective.

Ethics and dissemination

thical approval for this study has been obtained from the Hospital Universitari de Bellvitge Ethics Committee. The results of this study will inform the practical utility of the objective information provided by a Parkinson's Holter and therefore the convenience of adopting this technology in clinical practice and in future clinical trials. We expect public dissemination of the results in 2022.

Trial registration: NCT04176302 Registered 18 November 2019,

https://clinicaltrials.gov/show/NCT04176302

Keywords

Parkinson's, wearable, Parkinson's diary, motor complications, dyskinesia, Off

STRENGTHS AND LIMITATIONS

- First clinical trial to assess efficacy of a Parkinson's Holter to improve patients' motor symptoms.
- Three-arm trial comparing the symptomatic control of patients monitored with a Parkinson's Holter, monitored with a patient's diary or not monitored.
- Patients are blind to the study arm.
- Neurologists are not blind to the study arm
- Observer bias could happen in some secondary outcomes which are measured by the neurologists

INTRODUCTION

Parkinson's disease (PD) is the most common form of chronic and progressive hypokinetic syndrome among the elderly population and is the second most common neurodegenerative disease after Alzheimer's disease[1]. In early stages, PD responds well to dopaminergic therapy; however, as the disease progresses, the duration of the effect decreases and motor complications develop due to “wearing off” effects (end-of-dose deterioration) or due to a delayed or no response to medication, which requires frequent therapeutic adjustments to achieve good symptom control throughout the day[2]. Despite all therapeutic adjustment efforts, 90% of patients have motor complications or fluctuations after 10 years[3]. These fluctuations consist of changes between periods called Off, in which the medication has no effect and mobility is difficult, and periods called On, in which patients can move fluidly because the medication is having its best effect[4]. In addition, in the transition between these two states (On and Off) or during the period of maximum medication effect, patients may present with dyskinesias, i.e. involuntary movements of the head, torso or extremities, which may interfere with the patient’s activity[5].

Motor complications in patients with advanced disease are not easy to control; they can have a variable character, fluctuating, as mentioned, throughout the day and between different days. The chronology of symptoms throughout the day and between different days is of great value for the precise adjustment of the medication dosage, adapting the scheduled doses to the most prevalent symptoms in the post-dose period. However, neurologists do not currently have detailed information on their patients’ symptom chronology; therefore, they have serious difficulties in obtaining good results with medication adjustments. Currently, the information available to neurologists on the hourly course of symptoms comes from the patient’s self-report during consultation, or

in the best case, from diaries kept by the patient at home noting their motor state (On or Off) periodically (e.g., every hour)[6]. Although the latter method continues to be the reference standard in research and care, it has serious limitations, as patients often forget to make notes (especially when they are Off), many do not recognize their motor state well, and few can adhere to such a laborious system beyond a few days[7]. Thus, a system for measuring motor fluctuations that is objective, does not require intervention on the part of the patient and can therefore be part of their day-to-day for the long-term, if necessary, can be of great utility in clinical practice to help optimize medication regimens and improve disease control.[8]

During the last decade, our research group has developed a system for monitoring patients with PD based on accelerometry that can be comfortably worn at the waist during daily activities. This system is capable of detecting various motor symptoms, including bradykinesia, freezing of gait and dyskinesia[9–11], establishing the chronology of motor fluctuations (On and Off periods) and detecting falls[12,13]. This system, which henceforth will be generically referred to as Parkinson's Holter, is possibly the only such system that is easy to carry, is validated under real conditions of use and provides sufficient information to improve the medication regimen. However, it remains a hypothesis that detailed knowledge of the motor symptoms of patients leads to better disease control, thanks to optimization of the therapeutic regimen. To confirm or refute this hypothesis, we propose a clinical trial in which the clinical effectiveness of this device will be analysed in patients with moderate PD and motor fluctuations.

The primary objective of this trial is to compare the clinical outcomes in Parkinson's Disease patients, measured as changes from baseline to last visit in daily Off time, in three different arms according to different sources of information in regards of motor fluctuations: 1) Parkinson's Holter, 2) patient's diary and 3) no information (the only information that the patient can provide at the visit).

As secondary objectives, besides security issues and user satisfaction with the Parkinson's Holter, the following efficacy results will be measured: number of medical contacts, adherence to monitoring system, severity of motor complications, severity of Freezing of Gait, quality of live and performance in activities of daily living performance.

METHODS AND ANALYSIS

Study design

A single-blind, cluster-randomized controlled clinical trial with three arms (1:1:1): Group A (therapeutic adjustment using information from a Parkinson's Holter); Group B (therapeutic adjustment using information from a diary of motor fluctuations); and Group C (The therapeutic adjustment is not supported by additional information, other than the clinical information collected during consultation).

Study setting and duration

The study will last a maximum of 9 months for each patients (3 months from inclusion to basal visit at maximum, plus 6 months of follow-up period) The first patient was included in November 2019; the estimated last visit for the last patient is march 2022. Neurologists from at least 40 hospitals in Spain will participate in the study.

Investigational device

The Parkinson's Holter is a commercial product (STAT-ON®) manufactured by Sense4Care SL (www.sense4care.com). This medical device is intended to ambulatory monitor motor manifestations and activity of Parkinson's patients. The Holter records motor fluctuations (On and Off periods) during daily activities[14], in addition to dyskinesias, bradykinesia and freezing of gait episodes[9–11] (Figure 1). Holter's data are stored in its internal memory, and can be downloaded by users (patients or neurologists) to any

mobile phone that has the application provided by the manufacturer installed. This application produces reports in PDF, like the ones shown in figures 2 and 3

The sensor must be used a minimum of 3 days, for calibration reasons and has no upper temporary limit of use (it can be used indefinitely). The manufacturer recommends using it for 7 days to capture the specific changes in motor manifestations and patient's routines, which often occur on the weekend.

Participants

The target population is patients with PD and difficult-to-control motor fluctuations.

The neurologists participating in the study will select patients from among those undergoing follow-up in their outpatient clinic. In line with the clinical use envisaged for Parkinson's Holter, neurologists are advised to offer the study to those patients who could benefit from daily monitoring of their motor symptoms, in order to better control them. It is planned to include 162 patients who meet all the following inclusion criteria: 1.- Idiopathic PD according to the clinical criteria of the Brain Bank of the United Kingdom[15] ; 2.- moderate to severe disease (Hoehn & Yahr ≥ 2, in the Off state) [16]; 3.- motor fluctuations present, with at least 2 hours per day in the Off state. The time in off will estimated by the neurologist in a first stage (according to the clinical information available) and will be later confirmed by means of a patient's diary, which all candidates will fill in at home before the baseline study visit (see Procedures section). To be included in the study, previously informed patients will agree to participate voluntarily and sign a written consent form.

Patients who are unable to walk independently or with Hoehn & Yahr = 5, patients participating in another clinical trial, patients with acute intercurrent disease, patients with psychiatric or cognitive disorders preventing collaboration (Mini-Mental Status

Examination <24) [17] and patients with difficulty understanding the study procedures will be excluded.

The neurologists will be professionals who care for patients with PD and who recognize the potential of recruiting five patients with difficult-to-control motor fluctuations at the time of recruitment foreseen in the study.

Interventions and randomization

Prior to each visit with their neurologist, all patients participating in the study will be monitored using a Parkinson's Holter during 7 days at home. In addition, all patients of the study will keep a diary of motor fluctuations for 7 days at home, prior to the first and last study visit to the neurologist. The Holter and the diary will be delivered and collected by courier

The neurologists participating in the study will be randomly assigned to one of the following three groups:

- Group A: For therapeutic adjustment, neurologists will have access to the information from the Parkinson's Holter (study device) and to the information collected during consultation.

- Group B: For therapeutic adjustment, neurologists will have access to the information from the diary of motor fluctuations (reference standard) and to the information collected during consultation. In this specific group, patients will fill a motor fluctuations diary, prior to every scheduled visit (not only in the first and last visit).

- Group C: For therapeutic adjustment, neurologists will only have access to the information collected during a typical consultation, without information from the Holter's Parkinson or diary of motor symptoms (traditional clinical practice).

The staff responsible for implementing the randomization sequence will receive the patient's clinical information by courier: 1.- Holter with data stored on the memory card and 2.- Patient's diary of motor fluctuations. This staff will be responsible for sending this information to the patient' neurologist by encrypted email and before the next appointment that has been randomly assigned to them: information from the Parkinson's Holter, diary of motor fluctuations or no additional information. The randomization sequence will have been performed by independent staff with the help of a table of random numbers and following a balanced blocks model, whose size and composition will not be revealed to the researchers or to the staff responsible for implementing the sequence. [18]

Procedures

All study patients will wear the sensor 7 days before prior consultation with the neurologist, although this information will not be shown to the neurologist if they are not expected to see it by randomization arm (group A). Similarly, all patients will keep a diary of motor fluctuations prior to the first and last consultation with the neurologist, although the information will not be shown to the neurologists, unless they belongs to group B. Patients whose neurologist has been assigned to group B, will also fill in the diary in the intermediate visits of the study.

The Parkinson's Holter will be delivered to patients by courier along with the user manual and a quick start guide. There will be a technical assistance telephone line at their disposal to answer questions on how to handle the device. The device will have been previously configured so that patients only have to turn it on the first time it is taken out

of the box by pressing the only button on the device. From that time on, the device will turn on and off autonomously depending on the movement detected by its sensors, so patients do not have to perform any other operation. The device will have a charged battery and autonomy longer than 7 days, so no charger will be provided nor will patients have to worry about recharging the batteries. After the last day of use, the device will be picked up by courier and transported to the centre that manages the deliveries (which is a centre independent of the sponsoring entity) to download the collected data.

Simultaneously, patients will fill out a diary of motor fluctuations at home. The motor fluctuations diary was designed by the researchers (Figure 4), and the neurologists participating in the study will explain to the patients how to fill it out. To do this, the neurologists will follow a common procedure that involves showing instructional videos to patients that provide examples of the different phases (On/Off) and motor complications. The diary of motor fluctuations will be collected by courier on the same day as the Holter device. All patients' diaries will be reviewed by a devoted team at baseline. Those diaries with completeness problems, duplicates (simultaneous On and Off entries), or mayor inconsistencies, will be dismissed, and the investigator will be contacted to make a decision on the convenience of repeating the diary, after retraining the patient, or excluding the patient. Patients who have less than 2 hours Off in the first study diary (before the baseline visit) will be considered screening failures and will not be able to continue the study.

The results of the measurements taken at home (Holter or diary of motor fluctuations) will be sent to the corresponding neurologists by encrypted email before their next consultation with the patient. All the neurologists will receive specific training in interpreting the Parkinson's Holter data and will have a manual and an explanatory video available during the study time.

The home monitoring procedure will be repeated systematically before each appointment with the neurologist. The study's first appointment will take place in week 12 (± 2 weeks) after patient inclusion. The study's last evaluation will be carried out by week 26 (± 2 weeks). The neurologist is free to schedule intermediate appointments if necessary, before which the home monitoring process will also be repeated. The efficacy variables described in the next section will be recorded at each study evaluation and at the last appointment, usability and satisfaction questionnaires will also be administered to both the patients and neurologists (Table 1).

At the end of the study, the neurologists will receive the complete information from the records of all their patients (regardless of the study group to which they belong) by email, including the diaries of motor fluctuations filled out at home and the complete information from the Parkinson's Holter.

In this study there are no concomitant treatments prohibited, although information systems or patient monitoring systems, other than those tested, cannot be used.

Outcome variables and measurement instruments

The efficacy of clinical control will be measured using the following variables.

Primary:

- Daily Off time: through a diary of motor fluctuations (On/Off)[19,20]

Secondary:

- Number of medical visits and telephone contacts for medication adjustment
- Record of therapeutic changes
- Record of prescribed exercise programs
- Adherence to the motor fluctuations recording system (On/Off diary and Parkinson's Holter)

- Motor complications (Unified Parkinson's Disease Rating Scale [UPDRS] part IV[21], administered by the neurologist)
- Daily On time: through a diary of motor fluctuations (patient's diary)[19]
- Presence and severity of freezing of gait episodes: Freezing of Gait Questionnaire (FOG-Q, administered to the patient by phone)[22]
- Quality of life: using the 39-item Parkinson's Disease Questionnaire (PDQ-39, self-administered by the patient)[23]
- Autonomy in activities of daily living: UPDRS part II[21] (administered by the neurologist)

In addition, a record of adverse effects during the study period will be kept and the usability of and user satisfaction with the Parkinson's Holter will be evaluated using the System Usability Scale (SUS)[24] and the Quebec User Evaluation of Satisfaction with Assistive Technologies scale (QUEST) [25], respectively.

Other PD-related data will be recorded as control variables (year of PD diagnosis, stage according to the Hoehn & Yahr scale in the Off state[15]), patient sociodemographic data (age, sex, educational level) and neurologist data: age, sex, years of practice, type of activity (consultation, ward, etc.) and number of patients treated per year at each care level.

Monitoring

All study data and procedures will be supervised by an independent monitor. The supervision will be carried out in accordance with Best Clinical Practices, ISO 14155:2011

Blinding

The participating patients are responsible for recording the main variable (Off time) in their diary of motor fluctuations. Patients will be blinded to the neurologist's randomization arm, who will not disclose what information is available to adjust the therapeutic regimen. Patients are also responsible for recording the On time (diary of motor fluctuations) and the variables related to freezing of gait events (FOG-Q) and quality of life (PDQ-39); therefore, there is blinding to these data. The neurologists are responsible for collecting the UPDRS data and recording the therapeutic changes and adverse effects; therefore, there is no blinding to these secondary variables. The data analysts will also be blinded to the type of intervention in each group.

Blinding could be broken in the event the patient's physician deems it vital to access any of the study information (especially the patient's diary filled out at home) because the patient's clinical situation requires it. This fact will be recorded for later exclusion from all analyses potentially affected by the infringement of the protocol

Sample size

Assuming a mean reduction from baseline of 75 min of OFF time daily (SD 130) [43] between Arm A and C, a sample size of 49 patients per group would provide 80% power to show superiority at a significance level alpha of 5% (two-sided).

Unassessable patients will be those that signed the informed consent form (inclusion visit) but are lost to follow-up before the baseline visit. The rest of the subjects will be assessable even if they are not adherent to the motor fluctuation measurement systems. To cover loss to follow-up and unassessable patients, the sample size will be increased by 10% so that, in principle, 162 patients will be necessary (54 per arm). A standard method to handle missing data (Last Observation Carried Forward) will be used.

The inclusion of 40 physicians is proposed, assuming that, each physician will be assigned four or five patients in the study.

Data analysis plan

In the patient's diary (main outcome variable), lost data will be imputed, by interpolation between equal data, provided that the period without data does not exceed the hour of duration. No other lost data of the study will be imputed.

A fixed effects ANOVA with the baseline Off time as a covariate will be used to test the superiority of Group A vs. Group C in the overall analysis and the noninferiority of group B in the per-protocol analysis.

A descriptive analysis of all the variables included in the study will be performed. For the quantitative variables, robust estimators of central tendency (mean, winsorized mean, trimmed mean, Huber estimator) and of sample variability (standard deviation, standardised median absolute deviation, sample quasi-α-Winsorised-standard deviation, weighted root mean variance and the adjusted percentage root mean variance) will be used. Confidence intervals will be calculated by applying bootstrap or resampling methods. The maximum, minimum, skewness and kurtosis of the distributions will be calculated. For comparison of two related means, the Wilcoxon test or the robust generalization of repeated measures ANOVA will be used.

For qualitative variables, the frequency of the distributions will be calculated with percentages. For comparisons, Pearson’s chi-squared or McNemar’s test will be used as appropriate.

The total score on the usability and user satisfaction scales (SUS and QUEST) will be calculated according to the instructions of each instrument, and a descriptive analysis of these results will be performed for the overall sample. The results for the usability of and the physician satisfaction with the device will be analysed for the overall sample

Lastly, a descriptive analysis of the frequency and severity of the adverse effects and device-related adverse effects will be performed.

Patients lost to follow-up will be included in the analysis if at least one therapeutic adjustment was made before dropout. The baseline data of the patients lost before this point, will be also analysed in order to study the potential impact of these dropouts in the balance between groups, regarding the main confounding factors.

The analysts will be blinded to the type of diagnostic intervention in each group.

Patient Involvement

Patients were not involved in the design, recruitment or choice of outcome measures of this research protocol. However, patients played a central role the in the development of the Parkinson's Holter, carried out by the research team in previous research projects. Selected groups of patients, wo were involved from first stages, contributed to identify needs and use cases, provided information on their symptoms and feedback on design and usability, which have served to improve the product in various iterations. Parkinson's patient associations will be involved in development the dissemination plan of the results.

ETHICAS AND DISSEMINATION

This protocol and the informed consent form were approved by the Ethics Committee of Hospital Universitari de Bellvitge (code AC012/19). Any protocol change that may increase the risk or present new risks for the patient, or that may affect the validity of the study, must be approved by the sponsor in writing before being implemented. All study participants will sign the written consent form, after being properly informed by a study local investigator.

In all of the reports and communications related to the study subjects, the subjects will be identified only by their case numbers. Data will be handled strictly in accordance with the professional standards of confidentiality, under the terms stipulated in Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on Information Protection (GDPR).

The sponsor has a civil liability insurance policy that covers the potential damages for participants that could derive from the application of this protocol.

The results will be disseminated to the scientific community in the form of a publication, preferably in an open access journal, and to the general population, by press release for the national media. Various Spanish and European patient associations will receive direct communication of the results.

DISCUSSION

This study will evaluate the efficacy of a PD symptom monitoring device for improving the clinical control of patients. This improvement will be measured in the form of a reduction in the daily Off time and according to other health outcomes, as well as the neurologists' and patients' satisfaction with the device.

Although multiple studies have explored the validity of various devices for monitoring PD symptoms, currently there is no evidence of the therapeutic efficacy of monitoring by such means[26]. That the developed devices correctly monitor motor symptoms does not necessarily imply that this monitoring improves clinical control. This is the first study to examine the efficacy, in terms of clinical control, of these new sensors. Additionally, the same data may be used to test the efficacy of motor fluctuation diaries, considered a reference standard, which have been previously validated but for which there are also no available clinical efficacy studies[19]. The results of this study will provide information on the practical utility of the objective information that these devices provide and therefore on the convenience of adopting this technology in clinical practice, in future clinical trials and in various studies on PD.

It is important to clarify that, although the Parkinson's Holter has a fall detection functionality, it has not been fully implemented in the study (the verification step by the user was omitted), so the information related to falls will not be analysed.

This study has some limitations, such as the lack of blinding of the neurologists, which is inherent to the objective of the study: neurologists must necessarily know the monitoring information that has been assigned to them by chance. This could lead to a greater effort to optimize the medication regimen by neurologists with access to Holter data and by neurologists with access to the diary. While this phenomenon is not due to a Hawthorne effect (neurologists try harder because they know they are being observed in the study), it is not necessarily a negative phenomenon, since it is possible that part of the improvement potentially produced by these means of monitoring is due to the neurologist's increased attention to the case. That is, it is possible that the diary or Holter produce better clinical results not only because of the information they produce but also because they encourage neurologists to better adjust medication, which is one of the positive effects that should be included in the observation.

In contrast, neurologists may in fact be subject to the aforementioned Hawthorne effect[27]. Given that the protocol is identical in all arms of the study, if the Hawthorne effect is symmetrical, that is, if it has the same consequences in all arms, it will not affect the relative comparisons between arms. However, if the effect is more marked in any of the arms (for example, in the case of neurologists who do not have additional information but who particularly strive due to being observed in the study), then the differences observed in the study may vary with respect to the real ones in clinical practice.

In addition, observer bias may occur in this study because the neurologists, who know the information they have managed, are also responsible for applying some instruments to measure the secondary outcomes[28]. That is, knowledge of the study arm can lead to changes in the way the UPDRS is applied or interpreted, for example. This bias has been reduced as much as possible by removing the responsibility of applying the scales from the participating neurologists: the scales will be self-applied or applied by telephone by a blinded evaluator, except for the UPDRS, which requires a physical examination by the neurologist. In any case, the results to which the neurologists were not blinded will be analysed with techniques that attempt to determine the presence of this bias: observer bias tends to more strongly affect less severe patients; therefore, if the intervention is effective only in less severe patients, the possible presence of this bias will be reported[29].

Lastly, the duration of the clinical review has not been considered as a variable, thus, there will not be possible to draw conclusions on the time consumed in patient attention in the different study arms.

In conclusion, this clinical trial has been designed to determine whether automated symptom monitoring systems (Parkinson's Holter) improve the clinical control of patients with motor fluctuations. We expect the first results in 2021.

DECLARATIONS

Authors' contributions

ARM conceived and designed the study, and drafted this paper.

JHV, AB, JMC and DAP contributed to the study design.

CPL contributed to study logistics preparation, including software for managing Parkinson's Holter data during the trial.

AM contributed to the statistical analysis plan.

All authors have read and approved the manuscript.

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Role of the funders: none

Competing interests

ARM is a shareholder of Sense4Care, the company that will market the tested device in the short term. A.R.M. participated with other authors in obtaining funding for the study and in the protocol design. Given his conflict of interest, he will manage the project as the sponsoring centre's coordinator but will not participate in the data collection, study monitoring, statistical analysis or interpretation of results.

The remaining declare that they have no competing interests.

Acknowledgments

Acknowledgments are pending acceptance by the mentioned persons

Table 1. Schedule of the study evaluations.

	Inclusion	Baseline evaluation	Visit week 12 ± 2	Unscheduled visit	Visit week 26 ± 2
Inclusion criteria	X				
Informed consent	X				
Sociodemographic data	X				
Year of diagnosis	X				
Hoehn & Yahr Scale	X				
Baseline treatment	X				
Freezing of Gait Questionnaire		X	X	X	X
Unified Parkinson's Disease Rating Scale		X	X	X	X
39-item Parkinson's Disease Questionnaire		X	X	X	X
Diary of motor fluctuations			X	X	X
Parkinson's Holter			X	X	X
Record of health visits and contacts			X	X	X
Record of therapeutic changes / Exercise programs			X	X	X
Adherence			X	X	X
Record of adverse effects			X	X	X
Usability and satisfaction					X

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FIGURE LEGENDS

Figure 1. Parkinson's Holter.

Figure 2. Parkinson's Holter summary data table.

Figure 3. Parkinson's Holter weekly record.

Figure 4. Page 1 of the diary of motor fluctuations.

Figure 1
Parkinson's Holter.

135x50mm (300 x 300 DPI)

User ID:	33
Age:	48
Hoehn & Yahr:	2.5
Study start:	16/05/2019
Study end:	30/05/2019
Days monitored:	10
Time Monitored:	73 hours

N° FoG Episodes:	39
Average FoG Episodes/day:	5.6±2.8
Average minutes walking/day:	31±23.9
Average number of steps/day:	2879.2±2375.5
N° falls:	2
Total Time in OFF (% time monitored):	2.2 hours (3 %)
Total Time in Intermediate (% time monitored):	1.5 hours (2.1 %)
Total Time in ON (% time monitored):	19.1 hours (26.2 %)
Total Time with dyskinesias (% time monitored):	0 hours (0 %)

Parkinson's Holter summary data table.

202x160mm (96 x 96 DPI)

- **Green**: The patient is in ON motor state.
- **Red**: The patient is in OFF motor state.
- **Yellow**: The patient is in Intermediate motor state.
- **Purple**: Dyskinesia detection.
- **Grey**: Motor states can't be detected.
- FoG : A Freezing of Gait episode has been detected.

Parkinson's Holter weekly record.

148x126mm (170 x 170 DPI)

Date (day / month / year): ____ /____ /_____ Subject ID_____

TIME	ASLEEP	OFF	**ON** without dyskinesia	**ON** with no troublesome dyskinesia	**ON** with troublesome dyskinesia
00:00-00:30					
00:30-01:00					
01:00-01:30					
01:30-02:00					
02:00-02:30					
02:30-03:00					
03:00-03:30					
03:30-04:00					
04:00-04:30					
04:30-05:00					
05:00-05:30					
05:30-06:00					
06:00-06:30					
06:30-07:00					
07:00-07:30					
07:30-08:00					
08:00-08:30					
08:30-09:00					
09:00-09:30					
09:30-10:00					
10:00-10:30					
10:30-11:00					
11:00-11:30					
11:30-12:00					

Page 1 of the diary of motor fluctuations.

62x80mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym See title page (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry See after abstract (page 3)
	2b	All items from the World Health Organization Trial Registration Data Set See after abstract (page 3)
Protocol version	3	Date and version identifier N/A
Funding	4	Sources and types of financial, material, and other support See “funding” section (page 19)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors See title page and “Authors contributions” section (page 19)
	5b	Name and contact information for the trial sponsor See title page (page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities See “funding” section, paragraph 1 (page 19)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) See “Ethics" section, paragraph 1 (page 15)
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention See “introduction” section, paragraphs 1-4 (page 5)
	6b	Explanation for choice of comparators N/A
Objectives	7	Specific objectives or hypotheses See the last two paragraphs of the introduction. (page 6)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) See “Study Design” section, paragraph 1
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained See “study setting and duration” section paragraph 1 (page 7)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) See “Participants” section paragraphs 1-3 (page 7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered See “Interventions” section, paragraph 1 (page 8)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Please, see last paragraph of “Procedures” (page 9)

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended See "Outcome variables and measurement instruments", all section (page 11-12).
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) See fifth paragraph of "Procedures" (page 10) and Table 1 (page 20)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations See "Sample Size" section, paragraphs 1-3 (page 13)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size N/A

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions See last paragraph of "Interventions and randomization" (page 9)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned See last paragraph of "Interventions and randomization" (page 9)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions See last paragraph of "Interventions and randomization" (page 9)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how See "Blinding" (page 12)

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial See "Blinding" paragraph 1-2 (page 12)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol See "Outcome variables and measurement instruments", all section (page 11)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols See second to last paragraph of the "data analysis plan" section. (page 13)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol See "Ethics and dissemination" (page 15)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol See "data analysis plan", paragraphs 1-5 (page 13)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) See "data analysis plan" paragraphs 6-9 (page 14)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) See the first paragraph and the second to last paragraph of the "data analysis plan" section. (page 13)
Methods: Monitoring		

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed See "Monitoring" section, paragraph 1 (page 12)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Please see "Outcome variables and measurement instruments", "Data analysis plan" and Table 1
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor See "Monitoring" section, paragraph 1 (page 12)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval See Ethics and dissemination, paragraph 1 (page 15)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) This item is included the original protocol, but we have not considered it of interest for the article. If necessary we will introduce it upon request of the editor.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) See the first paragraph of "Ethics and dissemination", paragraph 1 (page 15)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial See "Ethics and dissemination", paragraph 2 (page 15)

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site See “Declarations” section (page 19)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators To be included upon editor’s request
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation See “Ethics and dissemination” section (page 16)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions See last paragraph of “Ethics and dissemination” section (page 16)
	31b	Authorship eligibility guidelines and any intended use of professional writers This is in accordance to BMJ authorship criteria.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code No plans yet. Not decided.
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates To be included upon editor’s request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.

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Multicentre, randomized, single-blind, parallel group trial to compare the effectiveness of a Holter for Parkinson's symptoms against other clinical monitoring methods: study protocol

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Multicentre, randomized, single-blind, parallel group trial to compare the effectiveness of a Holter for Parkinson's symptoms against other clinical monitoring methods: study protocol.

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ABSTRACT

Introduction

In recent years, multiple studies have aimed to develop and validate portable technological devices capable of monitoring the motor complications of Parkinson's disease patients (Parkinson's Holter). The effectiveness of these monitoring devices for improving clinical control is not known.

Methods and analysis

This is a single-blind, cluster-randomized controlled clinical trial. Neurologists from Spanish health centres will be randomly assigned to one of three study arms (1:1:1): A) therapeutic adjustment using information from a Parkinson's Holter that will be worn by their patients for 7 days; B) therapeutic adjustment using information from a diary of motor fluctuations that will be completed by their patients for 7 days; and C) therapeutic adjustment using clinical information collected during consultation. It is expected that 162 consecutive patients will be included over a period of 6 months.

The primary outcome is the efficiency of the Parkinson's Holter compared to traditional clinical practice in terms of Off time reduction with respect to the baseline (recorded through a diary of motor fluctuations, which will be completed by all patients). As secondary outcomes, changes in variables related to other motor complications (dyskinesia and freezing of gait), quality of life, autonomy in activities of daily living, adherence to the monitoring system and number of doctor-patient contacts will be analysed. The noninferiority of the Parkinson's Holter against the diary of motor fluctuations in terms of Off time reduction will be studied as the exploratory objective.

Ethics and dissemination

thical approval for this study has been obtained from the Hospital Universitari de Bellvitge Ethics Committee. The results of this study will inform the practical utility of the objective information provided by a Parkinson's Holter and therefore the convenience of adopting this technology in clinical practice and in future clinical trials. We expect public dissemination of the results in 2022.

Trial registration: NCT04176302 Registered 18 November 2019,

https://clinicaltrials.gov/show/NCT04176302

Keywords

Parkinson's, wearable, Parkinson's diary, motor complications, dyskinesia, Off

STRENGTHS AND LIMITATIONS

- First clinical trial to assess efficacy of a Parkinson's Holter to improve patients' motor symptoms.
- Three-arm trial comparing the symptomatic control of patients monitored with a Parkinson's Holter, monitored with a patient's diary or not monitored.
- Patients are blind to the study arm.
- Neurologists are not blind to the study arm
- Observer bias could happen in some secondary outcomes which are measured by the neurologists

INTRODUCTION

Parkinson's disease (PD) is the most common form of chronic and progressive hypokinetic syndrome among the elderly population and is the second most common neurodegenerative disease after Alzheimer's disease[1]. In early stages, PD responds well to dopaminergic therapy; however, as the disease progresses, the duration of the effect decreases and motor complications develop due to “wearing off” effects (end-of-dose deterioration) or due to a delayed or no response to medication, which requires frequent therapeutic adjustments to achieve good symptom control throughout the day[2]. Despite all therapeutic adjustment efforts, 90% of patients have motor complications or fluctuations after 10 years[3]. These fluctuations consist of changes between periods called Off, in which the medication has no effect and mobility is difficult, and periods called On, in which patients can move fluidly because the medication is having its best effect[4]. In addition, in the transition between these two states (On and Off) or during the period of maximum medication effect, patients may present with dyskinesias, i.e. involuntary movements of the head, torso or extremities, which may interfere with the patient’s activity[5].

Motor complications in patients with advanced disease are not easy to control; they can have a variable character, fluctuating, as mentioned, throughout the day and between different days. The chronology of symptoms throughout the day and between different days is of great value for the precise adjustment of the medication dosage, adapting the scheduled doses to the most prevalent symptoms in the post-dose period. However, neurologists do not currently have detailed information on their patients’ symptom chronology; therefore, they have serious difficulties in obtaining good results with medication adjustments. Currently, the information available to neurologists on the hourly course of symptoms comes from the patient’s self-report during consultation, or

in the best case, from diaries kept by the patient at home noting their motor state (On or Off) periodically (e.g., every hour)[6]. Although the latter method continues to be the reference standard in research and care, it has serious limitations, as patients often forget to make notes (especially when they are Off), many do not recognize their motor state well, and few can adhere to such a laborious system beyond a few days[7]. Thus, a system for measuring motor fluctuations that is objective, does not require intervention on the part of the patient and can therefore be part of their day-to-day for the long-term, if necessary, can be of great utility in clinical practice to help optimize medication regimens and improve disease control.[8]

During the last decade, our research group has developed a system for monitoring patients with PD based on accelerometry that can be comfortably worn at the waist during daily activities. This system is capable of detecting various motor symptoms, including bradykinesia, freezing of gait and dyskinesia[9–11], establishing the chronology of motor fluctuations (On and Off periods) and detecting falls[12,13]. This system, which henceforth will be generically referred to as Parkinson's Holter, is possibly the only such system that is easy to carry, is validated under real conditions of use and provides sufficient information to improve the medication regimen. However, it remains a hypothesis that detailed knowledge of the motor symptoms of patients leads to better disease control, thanks to optimization of the therapeutic regimen. To confirm or refute this hypothesis, we propose a clinical trial in which the clinical effectiveness of this device will be analysed in patients with moderate PD and motor fluctuations.

The primary objective of this trial is to compare the clinical outcomes in Parkinson's Disease patients, measured as changes from baseline to last visit in daily Off time, in three different arms according to different sources of information in regards of motor fluctuations: 1) Parkinson's Holter, 2) patient's diary and 3) no information (the only information that the patient can provide at the visit).

As secondary objectives, besides security issues and user satisfaction with the Parkinson's Holter, the following efficacy results will be measured: number of medical contacts, adherence to monitoring system, severity of motor complications, severity of Freezing of Gait, quality of live and performance in activities of daily living performance.

METHODS AND ANALYSIS

Study design

A single-blind, cluster-randomized controlled clinical trial with three arms (1:1:1): Group A (therapeutic adjustment using information from a Parkinson's Holter); Group B (therapeutic adjustment using information from a diary of motor fluctuations); and Group C (The therapeutic adjustment is not supported by additional information, other than the clinical information collected during consultation).

Study setting and duration

The study will last a maximum of 9 months for each patients (3 months from inclusion to basal visit at maximum, plus 6 months of follow-up period) The first patient was included in November 2019; the estimated last visit for the last patient is march 2022. Neurologists from at least 40 hospitals in Spain will participate in the study.

Investigational device

The Parkinson's Holter is a commercial product (STAT-ON®) manufactured by Sense4Care SL (www.sense4care.com). This medical device is intended to ambulatory monitor motor manifestations and activity of Parkinson's patients. The Holter records motor fluctuations (On and Off periods) during daily activities[14], in addition to dyskinesias, bradykinesia and freezing of gait episodes[9–11] (Figure 1). Holter's data are stored in its internal memory, and can be downloaded by users (patients or neurologists) to any

mobile phone that has the application provided by the manufacturer installed. This application produces reports in PDF, like the ones shown in figures 2 and 3

The first report (figure 2) shows a summary of the data obtained from the patient during the time monitored, including the number of freezing of gait episodes detected and the percentage of time in On, in Off and in status intermediate between the two. The graph shown in Figure 3 is the most important for clinicians, since it shows the time course of the different motor symptoms, over a week of time. It needs to be taken into account that a proportion of the time monitored cannot be classified in any of these three motor states (On, Off or intermediate state). As a result, the sum of the time in each motor state does not reach 100%. Time without classification (represented in gray in Figure 3) corresponds to the time in which there is not enough data for the device algorithms to reach a conclusion, which occurs frequently in prolonged periods of rest of the patient (in some patients this happens in Off, but this information must be confirmed by the neurologist, through an interview with the patient).

The Parkinson's Holter must be used a minimum of 3 days, for calibration reasons and has no upper temporary limit of use (it can be used indefinitely). The manufacturer recommends using it for 7 days to capture the specific changes in motor manifestations and patient's routines, which often occur on the weekend. The Parkinson's Holter user manual is available as Supplemental material.

Participants

The target population is patients with PD and difficult-to-control motor fluctuations.

The neurologists participating in the study will select patients from among those undergoing follow-up in their outpatient clinic. In line with the clinical use envisaged for Parkinson's Holter, neurologists are advised to offer the study to those patients who could benefit from daily monitoring of their motor symptoms, in order to better control

them. It is planned to include 162 patients who meet all the following inclusion criteria: 1.- Idiopathic PD according to the clinical criteria of the Brain Bank of the United Kingdom[15] ; 2.- moderate to severe disease (Hoehn & Yahr ≥ 2, in the Off state) [16]; 3.- motor fluctuations present, with at least 2 hours per day in the Off state. The time in off will estimated by the neurologist in a first stage (according to the clinical information available) and will be later confirmed by means of a patient's diary, which all candidates will fill in at home before the baseline study visit (see Procedures section). To be included in the study, previously informed patients will agree to participate voluntarily and sign a written consent form.

Patients who are unable to walk independently or with Hoehn & Yahr = 5, patients participating in another clinical trial, patients with acute intercurrent disease, patients with psychiatric or cognitive disorders preventing collaboration (Mini-Mental Status Examination <24) [17] and patients with difficulty understanding the study procedures will be excluded.

The neurologists will be professionals who care for patients with PD and who recognize the potential of recruiting five patients with difficult-to-control motor fluctuations at the time of recruitment foreseen in the study.

Interventions and randomization

Prior to each visit with their neurologist, all patients participating in the study will be monitored using a Parkinson's Holter during 7 days at home. In addition, all patients of the study will keep a diary of motor fluctuations for 7 days at home, prior to the first and last study visit to the neurologist. The Holter and the diary will be delivered and collected by courier

The neurologists participating in the study will be randomly assigned to one of the following three groups:

- Group A: For therapeutic adjustment, neurologists will have access to the information from the Parkinson's Holter (study device) and to the information collected during consultation.

- Group B: For therapeutic adjustment, neurologists will have access to the information from the diary of motor fluctuations (reference standard) and to the information collected during consultation. In this specific group, patients will fill a motor fluctuations diary, prior to every scheduled visit (not only in the first and last visit).

- Group C: For therapeutic adjustment, neurologists will only have access to the information collected during a typical consultation, without information from the Holter's Parkinson or diary of motor symptoms (traditional clinical practice).

The staff responsible for implementing the randomization sequence will receive the patient's clinical information by courier: 1.- Holter with data stored on the memory card and 2.- Patient's diary of motor fluctuations. This staff will be responsible for sending this information to the patient' neurologist by encrypted email and before the next appointment that has been randomly assigned to them: information from the Parkinson's Holter, diary of motor fluctuations or no additional information. The randomization sequence will have been performed by independent staff with the help of a table of random numbers and following a balanced blocks model, whose size and composition will not be revealed to the researchers or to the staff responsible for implementing the sequence. [18]

Procedures

All study patients will wear the sensor 7 days before prior consultation with the neurologist, although this information will not be shown to the neurologist if they are not expected to see it by randomization arm (group A). Similarly, all patients will keep a diary of motor fluctuations prior to the first and last consultation with the neurologist, although the information will not be shown to the neurologists, unless they belongs to group B. Patients whose neurologist has been assigned to group B, will also fill in the diary in the intermediate visits of the study.

The Parkinson's Holter will be delivered to patients by courier along with the user manual and a quick start guide. There will be a technical assistance telephone line at their disposal to answer questions on how to handle the device. The device will have been previously configured so that patients only have to turn it on the first time it is taken out of the box by pressing the only button on the device. From that time on, the device will turn on and off autonomously depending on the movement detected by its sensors, so patients do not have to perform any other operation. The device will have a charged battery and autonomy longer than 7 days, so no charger will be provided nor will patients have to worry about recharging the batteries. After the last day of use, the device will be picked up by courier and transported to the centre that manages the deliveries (which is a centre independent of the sponsoring entity) to download the collected data.

Simultaneously, patients will fill out a diary of motor fluctuations at home. The motor fluctuations diary was designed by the researchers (Figure 4), and the neurologists participating in the study will explain to the patients how to fill it out. To do this, the neurologists will follow a common procedure that involves showing instructional videos to patients that provide examples of the different phases (On/Off) and motor complications. The diary of motor fluctuations will be collected by courier on the same

day as the Holter device. All patients' diaries will be reviewed by a devoted team at baseline. Those diaries with completeness problems, duplicates (simultaneous On and Off entries), or mayor inconsistencies, will be dismissed, and the investigator will be contacted to make a decision on the convenience of repeating the diary, after retraining the patient, or excluding the patient. Patients who have less than 2 hours Off in the first study diary (before the baseline visit) will be considered screening failures and will not be able to continue the study.

The results of the measurements taken at home (Holter or diary of motor fluctuations) will be sent to the corresponding neurologists by encrypted email before their next consultation with the patient. All the neurologists will receive specific training in interpreting the Parkinson's Holter data and will have a manual and an explanatory video available during the study time.

The home monitoring procedure will be repeated systematically before each appointment with the neurologist. The study's first appointment will take place in week 12 (± 2 weeks) after patient inclusion. The study's last evaluation will be carried out by week 26 (± 2 weeks). The neurologist is free to schedule intermediate appointments if necessary, before which the home monitoring process will also be repeated. The efficacy variables described in the next section will be recorded at each study evaluation and at the last appointment, usability and satisfaction questionnaires will also be administered to both the patients and neurologists (Table 1).

At the end of the study, the neurologists will receive the complete information from the records of all their patients (regardless of the study group to which they belong) by email, including the diaries of motor fluctuations filled out at home and the complete information from the Parkinson's Holter.

In this study there are no concomitant treatments prohibited, although information systems or patient monitoring systems, other than those tested, cannot be used.

Outcome variables and measurement instruments

The efficacy of clinical control will be measured using the following variables.

Primary:

- Daily Off time: through a diary of motor fluctuations (On/Off)[19,20]

Secondary:

- Number of medical visits and telephone contacts for medication adjustment
- Record of therapeutic changes
- Record of prescribed exercise programs
- Adherence to the motor fluctuations recording system (On/Off diary and Parkinson's Holter)
- Motor complications (Unified Parkinson's Disease Rating Scale [UPDRS] part IV[21], administered by the neurologist)
- Daily On time: through a diary of motor fluctuations (patient's diary)[19]
- Presence and severity of freezing of gait episodes: Freezing of Gait Questionnaire (FOG-Q, administered to the patient by phone)[22]
- Quality of life: using the 39-item Parkinson's Disease Questionnaire (PDQ-39, self-administered by the patient)[23]
- Autonomy in activities of daily living: UPDRS part II[21] (administered by the neurologist)

In addition, a record of adverse effects during the study period will be kept and the usability of and user satisfaction with the Parkinson's Holter will be evaluated using the System Usability Scale (SUS)[24] and the Quebec User Evaluation of Satisfaction with Assistive Technologies scale (QUEST) [25], respectively.

Other PD-related data will be recorded as control variables (year of PD diagnosis, stage according to the Hoehn & Yahr scale in the Off state[15]), patient sociodemographic data (age, sex, educational level) and neurologist data: age, sex, years of practice, type of activity (consultation, ward, etc.) and number of patients treated per year at each care level.

Monitoring

All study data and procedures will be supervised by an independent monitor. The supervision will be carried out in accordance with Best Clinical Practices, ISO 14155:2011

Blinding

The participating patients are responsible for recording the main variable (Off time) in their diary of motor fluctuations. Patients will be blinded to the neurologist's randomization arm, who will not disclose what information is available to adjust the therapeutic regimen. Patients are also responsible for recording the On time (diary of motor fluctuations) and the variables related to freezing of gait events (FOG-Q) and quality of life (PDQ-39); therefore, there is blinding to these data. The neurologists are responsible for collecting the UPDRS data and recording the therapeutic changes and adverse effects; therefore, there is no blinding to these secondary variables. The data analysts will also be blinded to the type of intervention in each group.

Blinding could be broken in the event the patient's physician deems it vital to access any of the study information (especially the patient's diary filled out at home) because the patient's clinical situation requires it. This fact will be recorded for later exclusion from all analyses potentially affected by the infringement of the protocol

Sample size

Assuming a mean reduction from baseline of 75 min of OFF time daily (SD 130) [43] between Arm A and C, a sample size of 49 patients per group would provide 80% power to show superiority at a significance level alpha of 5% (two-sided).

Unassessable patients will be those that signed the informed consent form (inclusion visit) but are lost to follow-up before the baseline visit. The rest of the subjects will be assessable even if they are not adherent to the motor fluctuation measurement systems. To cover loss to follow-up and unassessable patients, the sample size will be increased by 10% so that, in principle, 162 patients will be necessary (54 per arm). A standard method to handle missing data (Last Observation Carried Forward) will be used.

The inclusion of 40 physicians is proposed, assuming that, each physician will be assigned four or five patients in the study.

Data analysis plan

In the patient's diary (main outcome variable), lost data will be imputed, by interpolation between equal data, provided that the period without data does not exceed the hour of duration. No other lost data of the study will be imputed.

A fixed effects ANOVA with the baseline Off time as a covariate will be used to test the superiority of Group A vs. Group C in the overall analysis and the noninferiority of group B in the per-protocol analysis.

A descriptive analysis of all the variables included in the study will be performed. For the quantitative variables, robust estimators of central tendency (mean, winsorized mean, trimmed mean, Huber estimator) and of sample variability (standard deviation,

standardised median absolute deviation, sample quasi-α-Winsorised-standard deviation, weighted root mean variance and the adjusted percentage root mean variance) will be used. Confidence intervals will be calculated by applying bootstrap or resampling methods. The maximum, minimum, skewness and kurtosis of the distributions will be calculated. For comparison of two related means, the Wilcoxon test or the robust generalization of repeated measures ANOVA will be used.

For qualitative variables, the frequency of the distributions will be calculated with percentages. For comparisons, Pearson's chi-squared or McNemar's test will be used as appropriate.

The total score on the usability and user satisfaction scales (SUS and QUEST) will be calculated according to the instructions of each instrument, and a descriptive analysis of these results will be performed for the overall sample. The results for the usability of and the physician satisfaction with the device will be analysed for the overall sample

Lastly, a descriptive analysis of the frequency and severity of the adverse effects and device-related adverse effects will be performed.

Patients lost to follow-up will be included in the analysis if at least one therapeutic adjustment was made before dropout. The baseline data of the patients lost before this point, will be also analysed in order to study the potential impact of these dropouts in the balance between groups, regarding the main confounding factors.

The analysts will be blinded to the type of diagnostic intervention in each group.

Patient Involvement

Patients were not involved in the design, recruitment or choice of outcome measures of this research protocol. However, patients played a central role the in the development of the Parkinson's Holter, carried out by the research team in previous research projects. Selected groups of patients, wo were involved from first stages, contributed to identify needs and use cases, provided information on their symptoms and feedback on design and usability, which have served to improve the product in various iterations. Parkinson's patient associations will be involved in development the dissemination plan of the results.

ETHICAS AND DISSEMINATION

This protocol and the informed consent form were approved by the Ethics Committee of Hospital Universitari de Bellvitge (code AC012/19). Any protocol change that may increase the risk or present new risks for the patient, or that may affect the validity of the study, must be approved by the sponsor in writing before being implemented. All study participants will sign the written consent form, after being properly informed by a study local investigator.

In all of the reports and communications related to the study subjects, the subjects will be identified only by their case numbers. Data will be handled strictly in accordance with the professional standards of confidentiality, under the terms stipulated in Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on Information Protection (GDPR).

The sponsor has a civil liability insurance policy that covers the potential damages for participants that could derive from the application of this protocol.

The results will be disseminated to the scientific community in the form of a publication, preferably in an open access journal, and to the general population, by press release for

the national media. Various Spanish and European patient associations will receive direct communication of the results.

DISCUSSION

This study will evaluate the efficacy of a PD symptom monitoring device for improving the clinical control of patients. This improvement will be measured in the form of a reduction in the daily Off time and according to other health outcomes, as well as the neurologists' and patients' satisfaction with the device.

Although multiple studies have explored the validity of various devices for monitoring PD symptoms, currently there is no evidence of the therapeutic efficacy of monitoring by such means[26]. That the developed devices correctly monitor motor symptoms does not necessarily imply that this monitoring improves clinical control. This is the first study to examine the efficacy, in terms of clinical control, of these new sensors. Additionally, the same data may be used to test the efficacy of motor fluctuation diaries, considered a reference standard, which have been previously validated but for which there are also no available clinical efficacy studies[19]. The results of this study will provide information on the practical utility of the objective information that these devices provide and therefore on the convenience of adopting this technology in clinical practice, in future clinical trials and in various studies on PD.

It is important to clarify that, although the Parkinson's Holter has a fall detection functionality, it has not been fully implemented in the study (the verification step by the user was omitted), so the information related to falls will not be analysed.

This study has some limitations, such as the lack of blinding of the neurologists, which is inherent to the objective of the study: neurologists must necessarily know the

monitoring information that has been assigned to them by chance. This could lead to a greater effort to optimize the medication regimen by neurologists with access to Holter data and by neurologists with access to the diary. While this phenomenon is not due to a Hawthorne effect (neurologists try harder because they know they are being observed in the study), it is not necessarily a negative phenomenon, since it is possible that part of the improvement potentially produced by these means of monitoring is due to the neurologist's increased attention to the case. That is, it is possible that the diary or Holter produce better clinical results not only because of the information they produce but also because they encourage neurologists to better adjust medication, which is one of the positive effects that should be included in the observation.

In contrast, neurologists may in fact be subject to the aforementioned Hawthorne effect[27]. Given that the protocol is identical in all arms of the study, if the Hawthorne effect is symmetrical, that is, if it has the same consequences in all arms, it will not affect the relative comparisons between arms. However, if the effect is more marked in any of the arms (for example, in the case of neurologists who do not have additional information but who particularly strive due to being observed in the study), then the differences observed in the study may vary with respect to the real ones in clinical practice.

In addition, observer bias may occur in this study because the neurologists, who know the information they have managed, are also responsible for applying some instruments to measure the secondary outcomes[28]. That is, knowledge of the study arm can lead to changes in the way the UPDRS is applied or interpreted, for example. This bias has been reduced as much as possible by removing the responsibility of applying the scales from the participating neurologists: the scales will be self-applied or applied by telephone by a blinded evaluator, except for the UPDRS, which requires a physical examination by the neurologist. In any case, the results to which the neurologists were not blinded will be analysed with techniques that attempt to determine the presence of this bias: observer

bias tends to more strongly affect less severe patients; therefore, if the intervention is effective only in less severe patients, the possible presence of this bias will be reported[29].

Lastly, the duration of the clinical review has not been considered as a variable, thus, there will not be possible to draw conclusions on the time consumed in patient attention in the different study arms.

In conclusion, this clinical trial has been designed to determine whether automated symptom monitoring systems (Parkinson's Holter) improve the clinical control of patients with motor fluctuations. We expect the first results in 2021.

DECLARATIONS

Authors' contributions

ARM conceived and designed the study, and drafted this paper.

JHV, AB, JMC and DAP contributed to the study design.

CPL contributed to study logistics preparation, including software for managing Parkinson's Holter data during the trial.

AM contributed to the statistical analysis plan.

All authors have read and approved the manuscript.

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Role of the funders: none

Competing interests

ARM is a shareholder of Sense4Care, the company that will market the tested device in the short term. A.R.M. participated with other authors in obtaining funding for the study and in the protocol design. Given his conflict of interest, he will manage the project as the sponsoring centre's coordinator but will not participate in the data collection, study monitoring, statistical analysis or interpretation of results.

The remaining declare that they have no competing interests.

Collaborators

(Note for editors: the name is in clearer font, the first surname is underlined (in Spain we have a second surname, which should NOT be used to index the author)

This research is being conducted by the "Monitoring Parkinson's patients Mobility for therapeutic purposes" (MoMoPa) research group, which includes, in addition to the authors of this papers: Hospital de Sant Joan Despí Moisès Broggi (Nuria Caballol Pons, Anna Planas-Ballvé), Hospital Universitari Mútua Terrassa (Mariateresa Buongiorno, Pau Pastor, Ignacio Alvarez), Hospital Universitario de Toledo (Núria López Ariztegui, Mª Isabel Morales Casado), Hospital Universitario Ramón y Cajal (Gema Sánchez), Hospital General de l'Hospitalet (María Asunción Ávila Rivera), Terapia Integral Uparkinson (Anna Prats), Hospital general de Elche (María Álvarez Saúco), Hospital de la Santa Creu i Sant Pau (Alexandre Gironell Carreró), Hospital Universitario 12 de Octubre (Álvaro Sánchez Ferro, Antonio Méndez Guerrero), Hospital Sant Camil (Elisabet Franquet Gomez), Hospital de Tortosa Verge de la Cinta (Sonia Escalante Arroyo), Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla (Laura Muñoz-Delgado, Daniel Macías-García, Silvia Jesús, Astrid Adarmes-Gómez, Pablo Mir), Hospital Clínico de Valencia (José Mª Salom Juan, Antonio Salvador Aliaga), Hospital General de Alicante (Silvia Martí Martínez, Carlos Leiva Santana), Hospital del Mar (Victor M. Puente Pérez, Irene Navalpotro Gómez), Hospital Vall d'Hebron (Sara Lucas del Pozo), Hospital Universitario Fundación Alcorcón (Lydia Vela Desojo), Hospital Álvaro Cunqueiro (Antonio Koukoulis Fernández, Mª Gema Alonso Losada), Hospital Universitario de Burgos (Mª Esther Cubo Delgado), Hospital Universitario Marqués de Valdecilla (Jon Infante Ceberío, María Sierra Peña, Isabel González Aramburu, Mª Victoria Sánchez Peláez), Hospital Universitario Infanta Sofía (Marina Mata Álvarez-Santullano, Carmen Borrúe Fernández, Mª Concepción Jimeno Montero), Clínico Virgen de la Victoria (Mª José Gómez Heredia, Francisco Pérez Errazquin, Lina Carazo Barrios), Hospital Royo Vilanova (Alfredo López López), Hospital de Llíria (Mª Pilar Solís Pérez), Hospital Univ Lucus Augusti (Rubén Alonso Redondo, Jessica González Ardura), Hospital Donostia (Javier Ruiz Martínez, Ana

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Table 1. Schedule of the study evaluations.

	Inclusion	Baseline evaluation	Visit week 12 ± 2	Unscheduled visit	Visit week 26 ± 2
Inclusion criteria	X				
Informed consent	X				
Sociodemographic data	X				
Year of diagnosis	X				
Hoehn & Yahr Scale	X				
Baseline treatment	X				
Freezing of Gait Questionnaire		X	X	X	X
Unified Parkinson's Disease Rating Scale		X	X	X	X
39-item Parkinson's Disease Questionnaire		X	X	X	X
Diary of motor fluctuations			X	X	X
Parkinson's Holter			X	X	X
Record of health visits and contacts			X	X	X
Record of therapeutic changes / Exercise programs			X	X	X
Adherence			X	X	X
Record of adverse effects			X	X	X
Usability and satisfaction					X

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FIGURE LEGENDS

Figure 1. Parkinson's Holter.

Figure 2. Parkinson's Holter summary data table.

Figure 3. Parkinson's Holter weekly record.

Figure 4. Page 1 of the diary of motor fluctuations.

Figure 1
Parkinson's Holter.

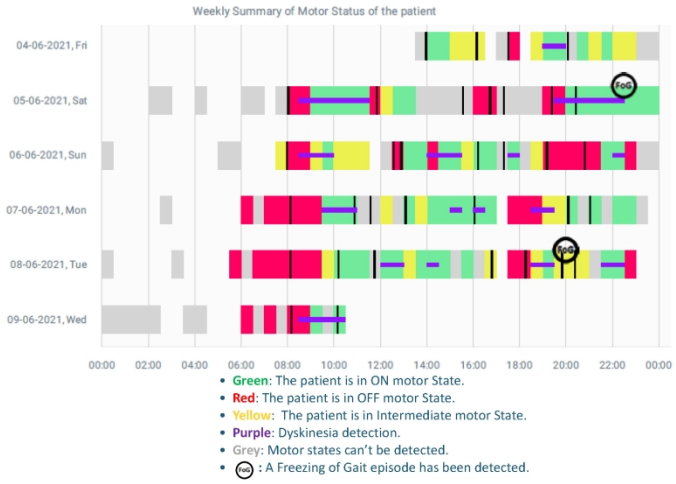
135x50mm (300 x 300 DPI)

User ID:	481226
Age:	69
Hoehn & Yahr:	2.5
Study start:	04/06/2021
Study end:	09/06/2021
Days monitored:	6
Time Monitored:	89.5 hours

N° FoG Episodes:	2
Average FoG Episodes/day:	1±0
Average minutes walking/day:	72.1±33
Average number of steps/day:	7088±3067.4
Total Time without diagnosis (% time monitored):	26.5 hours (29.6 %)
Total Time in OFF (% time monitored):	20.5 hours (22.9 %)
Total Time in Intermediate (% time monitored):	13 hours (14.5 %)
Total Time in ON (% time monitored):	29.5 hours (33 %)
Total Time with dyskinesias (% time monitored):	20 hours (22.3 %)

Parkinson's Holter summary data table

165x134mm (96 x 96 DPI)



Parkinson's Holter weekly record

297x210mm (300 x 300 DPI)

Date (day / month / year): ____ /____ /_____ Subject ID_____

TIME	ASLEEP	OFF	**ON** without dyskinesia	**ON** with no troublesome dyskinesia	**ON** with troublesome dyskinesia
00:00-00:30					
00:30-01:00					
01:00-01:30					
01:30-02:00					
02:00-02:30					
02:30-03:00					
03:00-03:30					
03:30-04:00					
04:00-04:30					
04:30-05:00					
05:00-05:30					
05:30-06:00					
06:00-06:30					
06:30-07:00					
07:00-07:30					
07:30-08:00					
08:00-08:30					
08:30-09:00					
09:00-09:30					
09:30-10:00					
10:00-10:30					
10:30-11:00					
11:00-11:30					
11:30-12:00					

Page 1 of the diary of motor fluctuations.

62x80mm (300 x 300 DPI)

STAT-ON

USER MANUAL (Rev 1.6)

SENSE4CARE

June-2020

Company information:

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User Guide, Rev 1.6. This device has been made under the Council Directive 93/42/EEC, being certified as a Medical Device Class IIa.

Sense4Care guarantees that the device has been built under the ISO 9001:2015 for the design, manufacturing and commercialization of industrial electronic controls. Furthermore, Sense4Care also guarantees that the device has been built under the ISO 13485:2016 for the design and manufacturing of electronic controls as well as medical devices.

STAT·ON SENSE4CARE

Table of content

0. Warnings, care and use instructions

Please, read carefully the user manual before using the device. Check that everything is correct before using the system.
Use only accessories supplied and/or authorized by the manufacturer
The product must be repaired by Authorized staff by the manufacturer
Equipment modifications must be done by Authorized staff by manufacturer
This device must be used by health professional staff.

Indications

STAT-ON is a waist-worn inertial device, configured by a doctor and used by the patient, that collects the movements from patients with Parkinson disease.

Device Sensor

- Do not expose the system to liquids. Liquid exposure may permanently damage the system.
- Do not use the system under 0ºC conditions or over 40ºC. Wait at least two hours for the system to return to room temperature before it is turned on.
- Operate system with room humidity between 45% and 85%.
- Keep the electrical cord away from walking paths.
- Improper routing of cabling may result in a choking hazard.
- Do not put metallic elements on the charging pad.
- Do not use in oxygen rich-environments.
- Do not use with inflammable agents.
- Do not use with flammable anaesthetics.
- Preferably use in waking hours and daily living activities. Do not use the sensor in sports. If so, inform the health professional about it. Manufacturers recommend not to sleep with the sensor since it can be oppressive and might cause physiological discomfort. The sensor must be managed only in clinical environments.
- Vehicles (car, motorcycle, bus or train) could affect the output of some algorithms.
- Do not use the sensor in medical interventions (surgical procedures, X-ray sessions, magnetic resonances…).
- The sensor and the smartphone must be at a distance of 1.5 meters from any other medical device when they communicate in order to not to produce interferences.
- Limited warranty covers any defect in the device under normal use during warranty period (2 years). Warranty does not cover any problem that is caused by conditions, malfunctioning or damage not resulting from normal use. It is not allowed to open the enclosure, otherwise, Limited warranty will not be applied.
- Battery is non-replaceable. The box is closed and it only can be opened by qualified personnel. Contact the manufacturer support in case of some malfunctioning of the battery.
- Use the battery supplied and/or authorized by the manufacturer
- There is no risk of reciprocal interference from the presence of the equipment during investigations or treatment

Belt

- Ironing allowed but use low heat
- Do not dry clean
- Maximum washing temperature up to 100ºC
- Do not bleach
- Do not tumble dry

Charge system

- Do not use another charger. The charger base may be damaged.
- The user must plug the charger system in a position that enables to unplug it easily.
- The battery has a life expectancy of 6 years.

Disinfection Procedure

- The device is not in contact with the patient. It is not necessary to clean the device but we recommend to clean it after some use with wet wipes.
- Do not submerge the device into water for cleaning up the device.
- Do not use abrasives as they may damage the sensor.
- The multiple cleaning of the device does not affect the integrity of the case material.

Isolation

- Type BF. Applicable parts are the sensor device and the belt.

Disposal instructions

Affixed to this device in accordance with European Council Directives 2002/96/EC.

These directives call for separate collection and disposal of electrical and electronic equipment. Sorting such waste and removing it from other forms of waste lessens the contribution of potentially toxic substances into municipal disposal systems and into the larger ecosystem. Please, return to SENSE4CARE S.L. at the end of its operating life.

Contraindications

- The STAT-ON device is not indicated for:
  - Healthy people or people without movement disorders.
  - Children
  - Parkinson's Disease patients with Hoehn & Yahr Scale 5.

- The STAT-ON device does not detect Parkinson's Disease. The device monitors Parkinson's Disease once it is already diagnosed by a Neurologist or an expert.
- The device and its App must be only used by Neurologists or Health experts (e.g. nurses, rehabilitation experts, therapists).

Secondary or side-effects / Adverse reactions

- The STAT-ON device cannot be worn by a person in wheelchair or using crutches. The results will not be valid in these conditions.
- The STAT-ON device must be worn correctly as the Instructions for User indicates. Otherwise, results will not be valid.

1. Quick start

1.1. Download the app

Please use the QR code or go to:

https://www.sense4care.com/support/

Figure 1. QR Code to download User Manual and Apps

Download the STAT-ON app. It requires Android 5 or higher or iOS 10.2 or higher.

1.2. Press the sensor's button

Press the button and wait until the LED blinks in white. **IMPORTANT NOTE:** The button is only used to wake up the system the first time of use and to annotate EVENTS. It is not a "standby" button.

1.3. Pair the device with your smartphone

Open the app, push the Bluetooth button on the app.

Figure 2. Upper screen capture: Bluetooth area and Battery indicator

Search your STAT-ON device → "*STATONxx*" where xx are the last 2 numbers of the Serial Number (see STAT-ON label at the sensor, S/N). The pin is formed with the last 6 numbers of the Serial Number.

1.4. Configure your data

Please, fill the missing information in order to adjust the algorithms press the 'save' button. Then the sensor should stop blinking in white colour, meaning it has been configured. Once the sensor detects movement, its LED blinks in Green colour. Now the sensor is already working.

Figure 3. Configuration menu

1.5. Place the sensor

Place the sensor correctly within the belt aperture and put on the belt. The sensor should be placed at the left side of the waist above the iliac crest as shown in the Figure 4.

Figure 4. Placement of the sensor

2. Intended Use

STAT-ON is a waist-worn inertial recorder, configured by a doctor and used by the patient for clinical, ambulatory, or home environments, that collects the results of the motor disorders and events of the Parkinson's Disease patient's in a period of time.

3. About STAT-ON

The STAT-ON system consists of a monitoring device, its base charger, a belt, and a mobile application. The system provides numerical and graphical information of the motor symptoms associated with Parkinson's disease. Furthermore, data related to the general motor activity of the patient are calculated.

The device collects the inertial signals of the patient's movement continuously, processes it in real time by means of artificial intelligence algorithms and stores the results in its internal memory. The sensor must be only managed in clinical environments and only health staff can operate the App and the device. The patient should wear the sensor in their daily life activities with the aim of providing relevant information to health professionals.

The smartphone application connects to the STAT-ON device via Bluetooth (BLE). The App is used both for configuring the system and for downloading the data previously generated by the sensor. The mobile application can send the data enclosed into a report by email or digital support to any user, caregiver, therapist or neurologist.

STAT-ON has been developed under the PARK-IT project, funded by the European Commission (Grant Agreement: *756861 — PARK-IT 2.0 — H2020-SMEInst-2016-2017/H2020-SMEINST-2-2016-2017*).

4. STAT-ON kit components

The STAT-ON is composed by the following components:

4.1. The sensor device

The sensor device (Figure 5), also called STAT-ON, has been developed under the PARK-IT project. The sensor is a 90x12.75x62.5mm^3 device with 83g of weight. It is composed by an ultra-low power high-performance nano-accelerometer, a microcontroller, and a Bluetooth Low Energy system, among others. The sensor has a battery life of seven days continuously in normal conditions. Manufacturer recommends to charge the device every day in case of forgetting doing it every 6-7 days. The system is waterproof with a IP65 protection.

Figure 5. The sensor device

4.2. The belt

The belt is made of Polyester (94%) and elastane (6%). Its fabric allows a complete adjustment to the body while being comfortable. Hook and loop fastener is used to fasten the belt securely. The belt has passed the Oeko-Tex® Standard 100 tests, guaranteeing no toxicity of the belt. The belt must be worn directly over a t-shirt or a thin clothing.

Figure 6. Specific belt

4.3. The charger system

The STAT-ON device can be charged wirelessly. It is necessary to use a charger compatible with the sensor:

- 5W of power
- Qi communication V1.1

It is mandatory that the charger base system contains a declaration of conformity with FCC regulations for Electromagnetic Compatibility with STAT-ON.

The AC Charger connected to the base charger must have the following parameters:

Standard: IEC-60601 Medical electrical equipment

Output Voltage: 5V

Output current: 2A

Connection: Micro USB – B

A charger kit (Base+AC Charger) might be purchased at ***www.sense4care.com.***

Figure 7. Top and Bottom view of a wireless charger base

5. Operator Use

STAT-ON is a waist-worn inertial device that collects the outcomes of several algorithms that are based on the computation of inertial signal. In other words, it collects data from a triaxial accelerometer, which is embedded within the device. In this section explained, it is the way of using the device.

It is highly recommended to follow the mobile app instructions at the beginning, which will conduct you through the first steps required for the system to work.

5.1. Location and orientation of the device

The belt, which is provided with the sensor, must be used to attach the sensor to the user. The sensor must be worn on the left hip and its largest flat side should be facing the user. The status LED, the button and the label should be facing upwards. The following image shows how the sensor should be placed.

Figure 8. Location and orientation of the sensor

The sensor must be placed on the left part of the waist. If the sensor is located in a different way that the showed in Figure 8, measurements collected might not be valid.

The sensor (within the belt) should be worn over a thin clothing as shown in Figure 8. The belt should be fastened tightly to prevent the sensor from moving, but allowing the user to be comfortable with it. The belt has a hole for viewing the status LED and enables pressing the event-button. It was designed to prevent the sensor from sliding out of it.

5.2. Sensor interface and modes

As shown in the following figure, the sensor device has a button and two led indicators next to the STAT-ON logo. The device also contains a small vibrator motor and a buzzer.

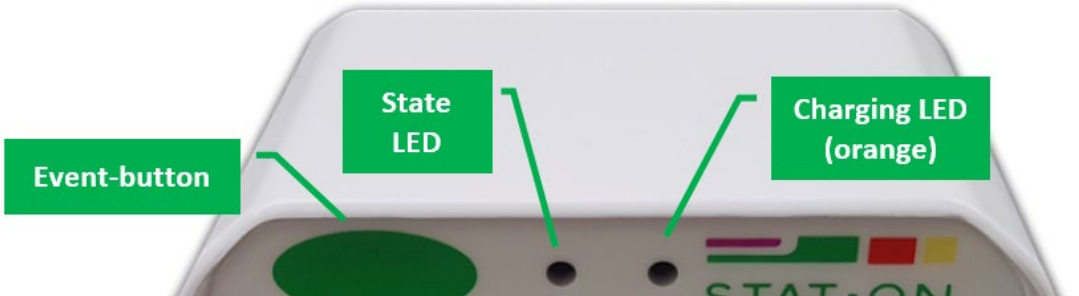


Figure 9. Sensor's interface

5.2.1. Button

The device button must be pressed by the operator (health professional or caregiver) and not by the patient. It has two uses:

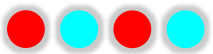
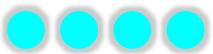
1- Turn on the sensor when it is in shutdown mode (See Section 5.3.2 for Shutdown mode).
2- Mark user events (user events are optionally specified by the medical professional, e.g. mark medication intake events, meals, sleep, etc.).
3- Stop an alarm after it triggers.

The device will vibrate shortly after the button is pressed.

5.2.2. State LED indicator

The colour pattern of the state LED specifies the current status of the sensor device. The following table describes the possible states of the sensor and its colour sequences.

Main state	Secondary state	Sequence	Description
SHUTDOWN	-		Always off
CONFIGURATION_PENDING	-		White blink
CONFIGURATION_PENDING	CONNECTED		White-blue
CONFIGURATION_PENDING	LOW_BATTERY		White-magenta
MONITORING	-		Green blink
MONITORING	CONNECTED		Green-blue

MONITORING	LOW_BATTERY		Green-magenta
SLEEP	-		Always off
SLEEP	CONNECTED		Blue blink
SLEEP	LOW_BATTERY		Magenta blink
MEMORY_FULL	-		Red blink
MEMORY_FULL	CONNECTED		Red-blue
MEMORY_FULL	LOW_BATTERY		Red-magenta
SYNCHRONIZATION	-		Fast blue blink
FORMAT	-		Always blue
ERROR	-		Always red

5.3. Possible sensor states

5.3.1. Connected and low battery indication

The sensor will indicate that has an active Bluetooth connection or a low battery level by blinking the led in blue or magenta colour respectively. These indications will be combined with the sensor's current main state. For example, if the sensor is monitoring while having low battery, it will not only blink in green colour but alternate green and magenta colours.

5.3.2. Shutdown

The sensor will come in this state initially. While in this state, the sensor will do nothing until its button is pressed. To power it up, place the sensor on its charging pad and make sure the charging process starts (the orange led must switch on), then wait until the battery is fully charged (the orange led switches off). Then, press the sensor's button and it should enter *CONFIGURATION_PENDING* state.

In addition, the sensor will automatically enter this state if the battery level is too low, to power it up, **the button should be pressed after charging the sensor**.

5.3.3. Configuration pending

When the device is in this state, its status LED will blink in white colour. The device will not record data nor execute algorithms while in this state. In order to leave this state and start monitoring,

the user should configure the following parameters: Patient ID, Age, Leg Length and Hoehn & Yahr value. These should be configured through the STAT-ON App via Bluetooth. Read section *6.6* of this document for detailed information on how to configure the sensor.

Once the sensor is configured, it will alternate *SLEEP* and *MONITORING* states, which are the normal operation states.

5.3.4. Monitoring, sleep and standby

When the sensor is correctly configured and has detected some movement, it enters *MONITORING* state. In this state, the patient's movement is monitored and the algorithms are executed. In addition, its status LED will blink in green colour. This is the normal operation state and implies that the sensor is running correctly. However, if no movement is detected for some minutes or if the sensor is charging, the device may enter *SLEEP* state in order to save power. The device will resume monitoring after detecting any movement.

Given that the power save mode is enabled and disabled automatically; the user does not need to power the device on or off.

The *STANDBY* state is an optional state that can be enabled once the sensor is correctly configured. It can be enabled using the <Standby> button at the configuration area. This option forces the sensor to pause monitoring without losing its configuration (see section *6.6.7*). Once the sensor's button is pressed, the sensor will resume monitoring.

5.3.5. Full memory

If the internal memory of the device fills up, its status led will blink in red colour. Since there is no space in memory, the sensor will not record any new data. It is therefore recommended to synchronize the device data using the STAT-ON App. After the data is sent, the device memory will be automatically cleared and the sensor will be able to monitor again. Formatting (clearing the memory of the sensor) can be also done, but in this case, the stored data not yet synchronized will be completely lost.

5.3.6. Synchronization

The synchronization process consists of transferring the stored data from the sensor to the smartphone. This can only be done by using the STAT-ON App (see section *6.5- Synchronization Area*). While this process is ongoing, the status led will quickly blink in blue colour and the App will show a progress bar. After receiving all the data from the sensor, the app will generate the corresponding files and reports automatically.

5.3.7. Format

The format process completely clears the device memory. Formatting the sensor is only recommended if the device will not be used for a long time. Synchronizing the data contained in the sensor is recommended before starting the format process; otherwise, all the stored data not yet transferred to the smartphone will be lost. After formatting the device, its previous configuration will also be lost, thus the sensor needs to be configured again to re-enable it. The format sequence can be started by using the App, by pressing the <DELETE> button (see section *6.6.8- Delete button*).

5.3.8. Error

If the sensor detects an internal system malfunction, it will enter *ERROR* state. The status led will stay in red colour. Most processes and operations, like monitoring or executing algorithms,

are interrupted if an error happens. When the sensor connects with the STAT-ON App while in error state, it will transfer the error code to the App and the App will offer to perform a sensor reset. If the error persists after the reset or occurs periodically, please write down the error code displayed on the App and contact support@sense4care.com.

5.4. Charging the device

The following steps describe how to charge the STAT-ON sensor:

1- Place the charging Pad on the table making sure the white part is facing down. Plug the provided USB cable to the charging pad and plug the other end into a power outlet.
2- Place the STAT-ON sensor on the centre of the charging pad. The sensor's largest flat side marked with a ((•)) symbol should be touching the charging pad.
3- While the battery is charging, the sensor's orange LED indicator will illuminate. In addition, the led indicator on the charging pad will blink in yellow colour. The charging process can last up to 8 hours.
4- Once the battery is fully charged, the orange LED indicator from the sensor will switch off. The LED indicator from the charging pad will stay enabled and yellow, without blinking.

Figure 10. Do's and Don'ts

Charging State	Sensor LED	Charging pad LED
CORRECTLY CHARGING	(always orange)	(orange blink)
END OF CHARGE	(always off)	(always orange)
POWER SUPPLY ERROR	(always off)	(red blink)
GENERAL ERROR	(always off)	(always red)

The previous table describes the possible states indicated by the sensor and the charging pad. The sensor does only charge when its LED is ON.

Additional charging considerations:

- Do not place any object on the charging pad, whether the device is being charged or not.
- It is possible to charge the sensor inside the specific belt. However, the sensor may need to be located more precisely at the centre of the charging pad. In addition, its internal temperature may get higher, thus interrupting the charging process.
- In case the *POWER SUPPLY ERROR* occurs, make sure that the AC to USB adapter used is the one provided by Sense4Care.
- In case the *GENERAL ERROR* occurs, check the battery level and, if it is still low, take the sensor from the charging pad and place it again. Make sure the sensor is placed on the centre of the charging pad.
- If any problem persists, contact Sense4Care for technical support.

5.5. Switching On/Off the system

After unpacking the system, the sensor device will stand in shutdown mode. Before using the sensor at first time, please fully charge the device battery and press the sensor's button to switch it on.

Once the button is pressed, the system will enter in the configuration mode, from which the user will be able to configure the sensor with the App. Then, the system will work autonomously. That means that the user will not have to switch it on or off.

The system will enter sleep mode if no movement has been detected for some minutes. It will automatically exit this mode and start monitoring after movement is detected. This work mode allows saving energy, thus extending the autonomy of the sensor.

If the user expects not to use the sensor in a long time, keeping it in shutdown mode is recommended. Shutdown mode is activated after formatting the device using the STAT-ON App (see section *5.3.7- Format*). It is recommended to synchronize all the data before formatting in order not to permanently lose all the data stored in the sensor. It is also important to charge the device battery before switching it off.

5.6. Regular use

The STAT-ON system is a wearable inertial device that monitors the symptoms of PD patients. **This is a medical device and only health professionals must manage it.** Outcomes of the sensor might be used to adjust or evaluate a therapy, to adjust the diets of the patient, or evaluate the result of the therapy.

The system works autonomously, that is, the patient does not need to interact with the device. The health professional will provide the sensor to the user correctly configured (see sections 5.3.3 and 5.3.4) and previously charged (charge the sensor at least 5 hours during the previous 24hours of using the sensor). The user will wear the sensor for registering the symptoms of PD during the days of the study proposed by the health professional.

The healthcare staff can ask the caregiver to press the button at a certain time, such as lunch, dinner, medicine intake, etc.

The patient should wear use the system a minimum of 5 days and a minimum of 24 hours within these 5 days to generate enough inertial data to personalize the algorithms. It is recommended to use the sensor for 7 days. From this moment, a report can be generated at any time. The doctor will download to his/her mobile phone the information generated by the sensor at the doctor's office with the STAT-ON application, which will automatically generate a report of the motor state and symptoms during the days of study.

After this step, the sensor will enter in the initial state, being necessary to configure the app parameters in order to put on the sensor in other patient.

6. Application management

6.1. Device compatibility and downloading the app

The STAT-ON App can run on any Smartphone or tablet running Android 5 or higher, the device must support Bluetooth Low Energy (BLE) and 1GB RAM minimum.

The STAT-ON device also works in iOS for Apple devices. It is required to use iOS 10.2 or higher.

The app can be downloaded at *Google Play* (Android) or the *App Store* (iOS), search for "STAT-ON", and make sure its developer is Sense4Care. Press <install> and the app will be automatically downloaded and installed.

6.2. Managing multiple patients

As stated in the Section 2 (Intended Use), the STAT-ON device is suitable for evaluating the motor state of a patient with Parkinson's disease. The value of the "*Patient ID*" item, which can be set through the App's *Configuration Area*, is used to associate all the data related to each user. There is no limit of number of patients registered by the smartphone at the same time, it depends on the memory of the smartphone, however, we recommend to use no more than 6 patients.

The **Patient ID number must be changed each time a sensor is given to a different patient**, moreover, it is highly recommended to keep a record containing each patient's personal data together with its Patient ID value in order to **ensure that the same value is not shared by different patients**.

In order to simplify the situation where a single user (usually a healthcare worker) handles various sensors and multiple patients, **the results and reports are obtained solely from the data transferred during the current synchronization event**. Therefore, no historical record is kept inside the App's database (i.e. the data monitored is used for generating the reports and then discarded and not used anymore). **However, the App does store all the generated reports** (.pdf and .csv) inside the STAT-ON specific directory at the smartphone memory. Given the generated reports are tagged using the Patient ID number, it is still important to keep a value for each user and configure the sensor accordingly.

6.3. Main screen

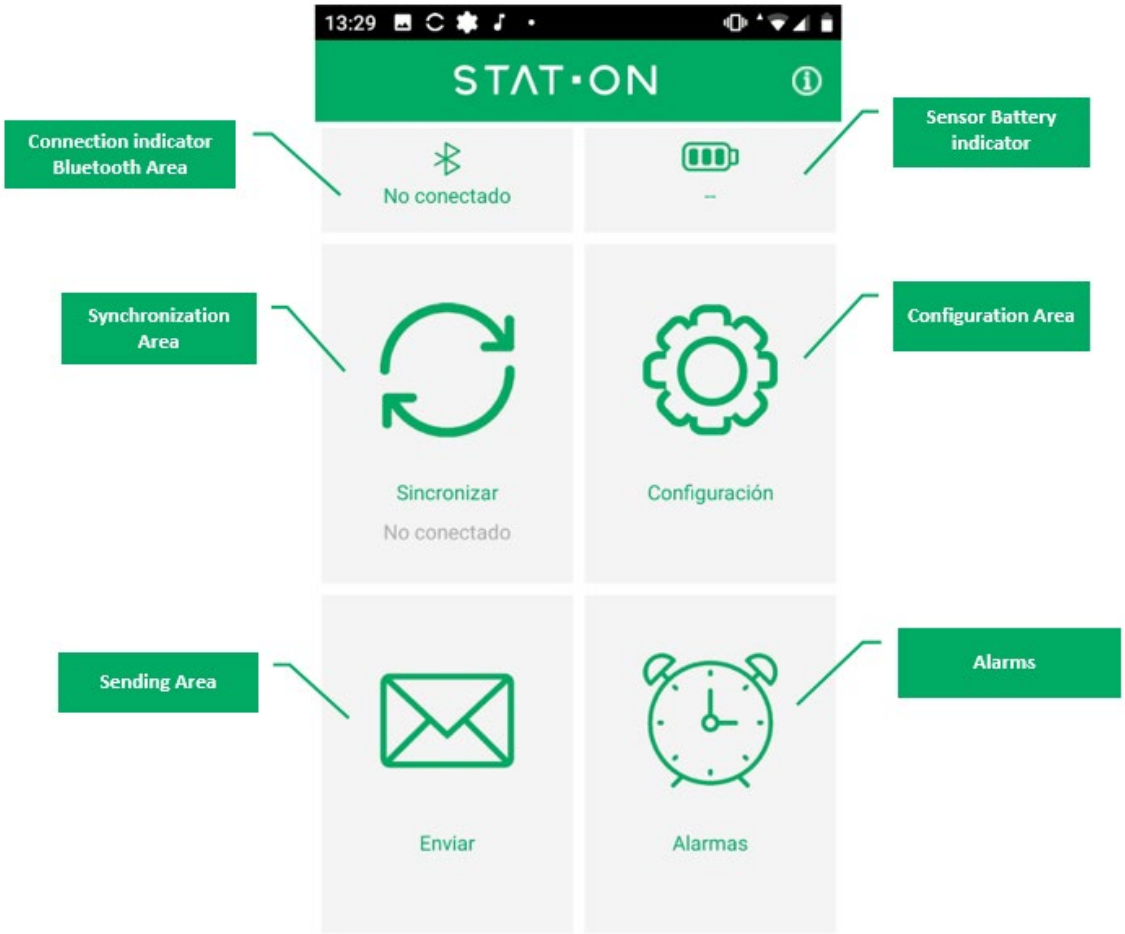


Figure 11. Main screen caption

After opening the App, it shows the main screen, which enables the access to all the areas and features of the STAT-ON App. It also indicates whether there is an active connection with a sensor and shows its battery level. While on the main screen, the App connects automatically to the paired STAT-ON sensor. When a sensor device is connected, the Bluetooth area and battery indicators change their colour. "*Connected*" appears under the Bluetooth logo and the battery level is shown as well.

Figure 12. Top of the main screen when connected

6.4. Bluetooth area

The Bluetooth area is used for managing the paired devices and choosing the sensor to connect to. The Bluetooth area is accessed by pressing on the Bluetooth logo on top of the main screen.

The switch on top of the screen is used for enabling and disabling the Bluetooth of the smartphone/tablet. Bluetooth has to be enabled for the app to connect with the sensor.

Below the Bluetooth switch, the currently connected sensor is displayed, if any. Only one STAT-ON sensor should be connected at the same time.

In order to search for the connectable sensors, the scan button should be pressed. Then all the available sensors will appear inside the area below. The device's Bluetooth name starts with *StatOn* and then contains the two last digits of its serial number (e.g. "*StatOn00*").

Press on the STAT-ON device you wish to pair to. A PIN/Passkey request may pop up. If the PIN request does not show up, check the smartphone notifications. Each device has a six-digit numerical PIN/Passkey, which is provided with the sensor packaging.

Before leaving the Bluetooth area, make sure that the correct device appears under the 'connected sensor'.

6.5. Synchronization area

The Synchronize Area can only be used when connected to a sensor. It contains only one button, which starts the synchronization process if the sensor contains any data.

When synchronizing, all the results from the sensor are transferred to the smartphone using Bluetooth. This screen also shows the last time a synchronization had been performed.

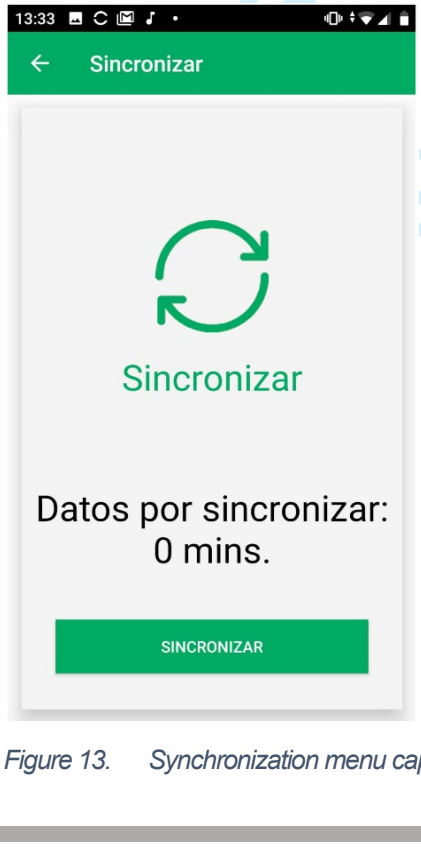


Figure 13. Synchronization menu caption

The App will notify the user if the synchronization process fails. If the synchronization problems persist, contact Sense4Care for support.

6.6. Configuration area

The values inside the configuration area are stored inside the sensor, thus an active Bluetooth connection is required for its use. Apart from the pin (which is optional), all the parameters from this area must be configured for the sensor to work correctly and exit the "configuration pending" state. Once the user configures all the parameters, the user has to push the <SAVE> button.

If the sensor has any results from previous stored monitorizations (i.e. is not synchronized), it will not be possible to change some parameters from this area. Synchronizing or deleting the pending results is required before the parameters can be changed.

The following sections explain each parameter in detail.

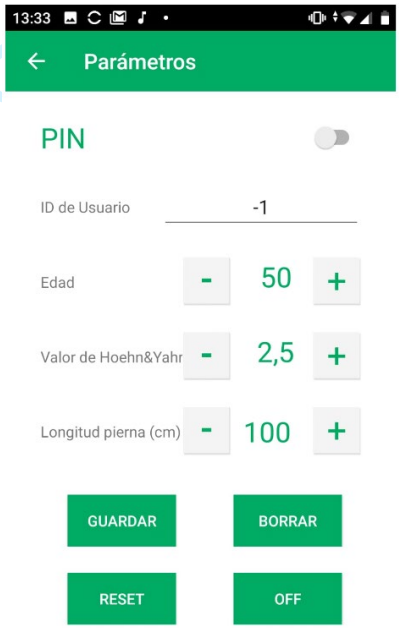


Figure 14. Configuration menu caption

6.6.1. PIN configuration

This switch enables a 4-digit pin protection for the Configuration area. It is an optional feature, which shall only be used if the access to this area needs to be restricted.

6.6.2. Patient ID

This value identifies the user that wears the sensor. Any value different than -1 should be used. As explained in the section 6.2 (*Managing multiple patients*), the Patient ID is key for keeping the record of each patient correctly related. It can only be modified if it is not yet configured or if the sensor has no pending data to send (i.e. smartphone and sensor have synchronised).

This value must be modified each time the sensor changes from patient to patient, and should be assigned to a sole patient (should not be the same for different patients).

6.6.3. Age

The Age parameter should be configured before the monitoring starts for the algorithms to work properly.

6.6.4. Hoehn & Yahr value

The algorithms require the patient's stage in the Hoehn & Yahr scale in OFF state. The range of values accepted goes from one to five.

6.6.5. Leg Length

The leg length value (in cm) corresponds to the distance between the ground and the user's hip. By default it is 100cm.

Figure 15. Leg length, from the ground to the end of the hip (end of the iliac crest)

6.6.6. Save button

After configuring the Patient ID, Age, Hoehn&Yahr and Leg Length parameters, the SAVE button should be pressed. Then the configuration is sent to the sensor. A pop-up will inform of the operation result, if it was successful, the sensor will exit the 'configuration pending' state.

6.6.7. Standby button

This button will only be available once the sensor is correctly configured. Pressing it makes the sensor pause the monitoring process without losing its configuration. The sensor will resume the monitoring process once the button is pressed.

6.6.8. Delete button

Pressing this button will clear all the data currently stored in the sensor whether it has been sent to the App by synchronizing or not. It is important to synchronize the sensor's data before the delete button is pressed in order to ensure that no data is lost. After formatting, the sensor will enter in shutdown mode. And the sensor's button should be pressed to re-enable it.

The previously generated reports and raw data files WILL NOT be deleted, thus, they can still be accessed using the smartphone's file explorer.

6.7. Alarms Area

In the alarms area, the user can configure up to ten alarms each day. The alarms will be stored and will trigger on the STAT-ON sensor, not on the smartphone. The usage of the system alarms is optional.

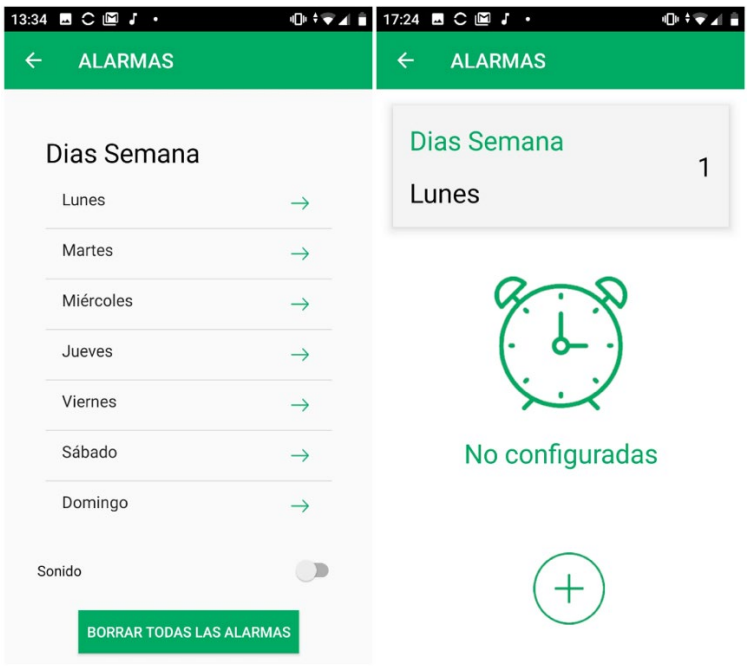


Figure 16. Alarm screen captions

Programmed alarms can be seen on each day's screen by pressing the left and right arrows, the + symbol is used for creating a new alarm and the trash icon is for deleting the currently viewed alarm. When an alarm triggers, the sensor will vibrate until the sensor's button is pressed. If the "Sound" switch is enabled using the App, the sensor will Beep, too.

6.8. Send area

The send area can be accessed by pressing envelope button of the main screen.

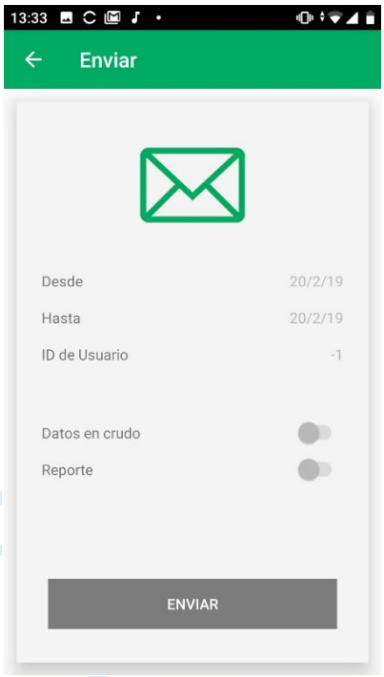


Figure 17. Send screen caption

On the time period section, the current monitoring process start and end timestamps are displayed.

In addition, two switches can be selected in order to choose which files will be shared.

If “Raw data” is selected, a .csv file containing the algorithm results that were generated each minute of monitoring. If “Report” is selected, a .pdf summary containing several data and graphs will be generated. Both options can be selected at the same time as well. See section 7 for a detailed description of the results generated.

Once the period and the report type have been selected, the <SEND> button should be pressed. It acts like the common “Share buttons”, so the user can choose any other communication App (like e-mail) for transferring the documents. A copy of the generated documents is also stored inside the storage of mobile device, under the <STAT-ON> folder.

At the bottom of the screen, the <SEND> button will open a standard ‘share’ dialog, any mailing or file share method can be used.

7. Reports description

This section describes the reports generated by the STAT-ON device in order to obtain a correct understanding of the variables provided by the sensor.

Through the mobile application two types of reports can be generated that aim to facilitate the task of understanding the data generated by STAT-ON by clinical professionals. The application offers the possibility of generating a summary report of the patient's condition and some graphics that condense the behaviour of the symptoms as well as some gait parameters. The purpose of this first report is of ordinary use for conventional clinical practice. The second report is more extensive, and it includes a large part of the parameters extracted from the algorithms as well as the information contained in the first report. The main purpose of this second mode of reports is its use in the field of research.

The data is presented as a graph with fixed temporal resolution, 30 minutes for data per day, 24 hours for weekly data. In the case of the variables that are presented per day, the average of those higher values of each half hour is computed, obtaining a value every 30 minutes, only those periods greater than 0 being marked on the graph. The values that are presented in format 24h temporary are:

- Cadence
- Number of steps
- Step length
- SMA (quantity of movement)
- Stride fluidity
- Dyskinesia
- ON state
- OFF state
- INT state
- Number of Freezing of Gait(FoG) episodes
- Duration of FoG Episodes
- Falls
- Events

The weekly-based graphs are processed by means of the average of those values higher than zero per day. Finally, some variables are useful as totalizers during the monitored period. These totalizers can be represented by three methods. The first one is presented by the absolute average (and its standard deviation), for example, hours in OFF state or in ON state or the average length of the stride. Those variables that represent events (e.g. Falls or FoG) are summed with direct summation. Finally, these totalizers can be represented in relative format, this is provided as the percentage of the monitored valid time that presents some symptom.

7.1. STAT-ON measurements

In PD, various symptoms associated with patient's motor states can be differentiated. One of the most usual clinical practices is visually analysing how patients walk in order to evaluate bradykinesia. In the activity of walking, several symptoms converge with different origins within the neurophysiology of PD. In gait, two movements of different nature are coordinated, on the one hand, automatic movements classically associated with a symptomatology related to

hypokinesia and, on the other hand, voluntary movements that are associated with bradykinesia. It should not be forgotten that the pathophysiology of bradykinesia is the cardinal symptom per excellence of PD and, furthermore, this symptom has a greater degree of correlation with the level of dopamine deficiency and, therefore, with the fluctuations between motor states in PD. Peak-dose dyskinesia is a side effect of the medication that provides a clear indication of the patient's motor status, being associated with ON state.

FoG is another symptom that is of special interest because it is one of the most disabling symptoms of PD. FoG has different characteristics from other parkinsonian symptoms, for example, it has not been possible to clearly correlate the frequency of FoG episodes with other motor symptoms of PD, such as stiffness and bradykinesia. Although in many cases it is not a particularly useful symptom to assess the patient's motor status, it is useful to evaluate the evolution of this symptom and the mobility difficulties of the patient.

The detection method of ON / OFF states in patients with PD depends on the characterization of the motor symptoms that the patient presents in each of the states. In this sense, two specific detectors are used, which analyze the presence of dyskinesia and the bradykinetic gait. The outputs of the detectors are merged into a global classifier that provides the estimation of the motor state.

The bradykinesia detector is based on the analysis of patients' gait and has been validated in several studies that can be found in [1]–[4]. Given that this detector is self-adaptive, it must have a minimum data period of three days.
The detector of choreic dyskinesia is based on the detection of the frequencies of dyskinesia maintained during prolonged periods of time. The outputs of these algorithms are combined through a decision tree, which performs the detection of the motor states. The detail of these algorithms can be found in [5].

The presented architecture has implications for the interpretation of the data presented in the graph. The most relevant is that the sensor emits an OFF verdict when the patient walks. In other words, in those patients who have very deep OFF states in which they cannot move, STAT-ON will not be able to issue a verdict. On the other hand, ON states are associated with the prolonged physical dyskinesias in time, in addition to the bradykinesia level. As aforementioned, since the bradykinesia algorithm is self-adaptive, another implication is that **the system will only show this information if a minimum of 3 days of data has been captured.**

The FoG detector is based on the analysis of windows of 1.6 seconds and, therefore, this is the minimum temporal resolution. This means that, although episodes of freezing lasting less than 1.6 seconds are detected, all of them will be reported as 1.6 seconds long. Another example can be that two episodes of 1.8 seconds and 3.1 seconds will be reported as episodes of 3.2 seconds. This means that when STAT-ON reports a FoG episode of 1.6 seconds it will last from 0 to 1.6 seconds, whereas when a 3.2 seconds episode is reported it will result in a duration between 1.6 seconds to 3.2 seconds. For more details on this detector go to [6].
It must be noted that the total number of reported falls might be confused since the system also analyses the movements when the patient removes the sensor belt or puts it on. These moments involve movements that could be similar to a fall and the system could generate a false positive. The detection of activities, and more specifically the length and speed of the step, are algorithms specifically developed and adjusted with data from patients of PD. You can find the details of

this group in [7]. Below, a detailed description of each of the graphs and data generated by the STAT-ON system is presented.

7.2. Extended report

This report presents two separate parts, on the one hand, the "*summary page*", where a table is presented as a summary and, on the other hand, a series of graphs that are described in the following sections.

7.2.1. Summary page

The summary page of the report presents a series of numerical data as a summary of the physical activity of the patient and the prevalence of symptoms that the patient has presented during the monitored period.

User ID:	171113-S01
Age:	68
Hoehn & Yahr:	OFF: 3, ON: 2
Study start date:	3/28/2018
Study ending date:	4/1/2018
Total days monitored	5

Total FoG Episodes	87
Average FoG Episodes per day	18±4
Average minutes walking per day	58±19
Average number of steps per day	3094±560
Number of falls	4
Time in OFF (% regarding total time monitored)	7.2 hours (34.5 %)
Time in Intermediate (% regarding total time monitored)	9.6 hours (43.6 %)
Time in ON (% regarding total time monitored)	8.4 hours (38.2%)
Time with dyskinesias (% regarding total time monitored)	1.6 hours (7.3 %)
Total time monitored	22 hours

Figure 18. Summary page example

In the first table you can find the minimum necessary data of the patient and the monitored period:

- User ID: Numeric identifier of the patient, this is a number configurable from the app that serves to anonymize the patient's data and that only clinical professionals have access to the relationship between the captured data and the identity of the patient.
- Age: Age of the patient.
- Hoehn & Yarh: PD stage evaluation, provided are the values in OFF and ON state.
- e-mail: e-mail to where the report will be sent.
- Study start date: Day and Hour of the start of the monitored phase.
- Study ending date: Day and Hour of the end of the monitored phase.
- Total days monitored: Total number of days in which the patient has been monitored.

In the second table a summary of the symptoms and physical activity during the monitored period is shown:

- Total FoG Episodes: Total number of FoG episodes that have been measured during the monitored period. It is a totalizer which has a strong dependence on the length of time monitored.
- Average FoG Episodes per day: It is a comparable relative measure between patients or separate monitoring periods. Standard deviation is also provided, which gives evidences as to whether the patient has FoG episodes consistently every day or whether there are days that show more than others.
- Average minutes walking per day: It is a good indicator of physical activity presented by the patient.
- Average number of steps per day: In patients without gait disorders, it provides very similar information to walking minutes, but in the case of presenting gait disorders this parameter is significant to assess the disease.
- Number of falls: Number of falls that the patient has presented during the monitoring period. Given the aforementioned factors, it must be noted that this monitoring system does not present a feedback system with the user, so the system can confuse actions such as removing or putting the sensor on the waist as a fall generating false positives.
- Time in OFF (% regarding total time monitored): Percentage of time monitored in which the patient presents OFF state.*
- Time in Intermediate (% regarding total time monitored): Percentage of time monitored in which the patient presents INTERMEDIATE state.*
- Time in ON (% regarding total time monitored): Percentage of time monitored in which the patient presents ON state.*
- Time with dyskinesia (% regarding total time monitored): Percentage of time monitored in which the patient has evidenced dyskinesia episodes.*
- Total time monitored: Total monitored time in hours.

*For an extended explanation of the measurement, see the explanation of the corresponding graph.

7.2.2. Graphs

7.2.2.1. Weekly Motor State

One of the most relevant graphs in which it shows the motor state of the patient in periods of maximum 7 days. This means that a graph is generated for every 7 days (or less) of monitoring. Below, it is shown an example of the motor state.

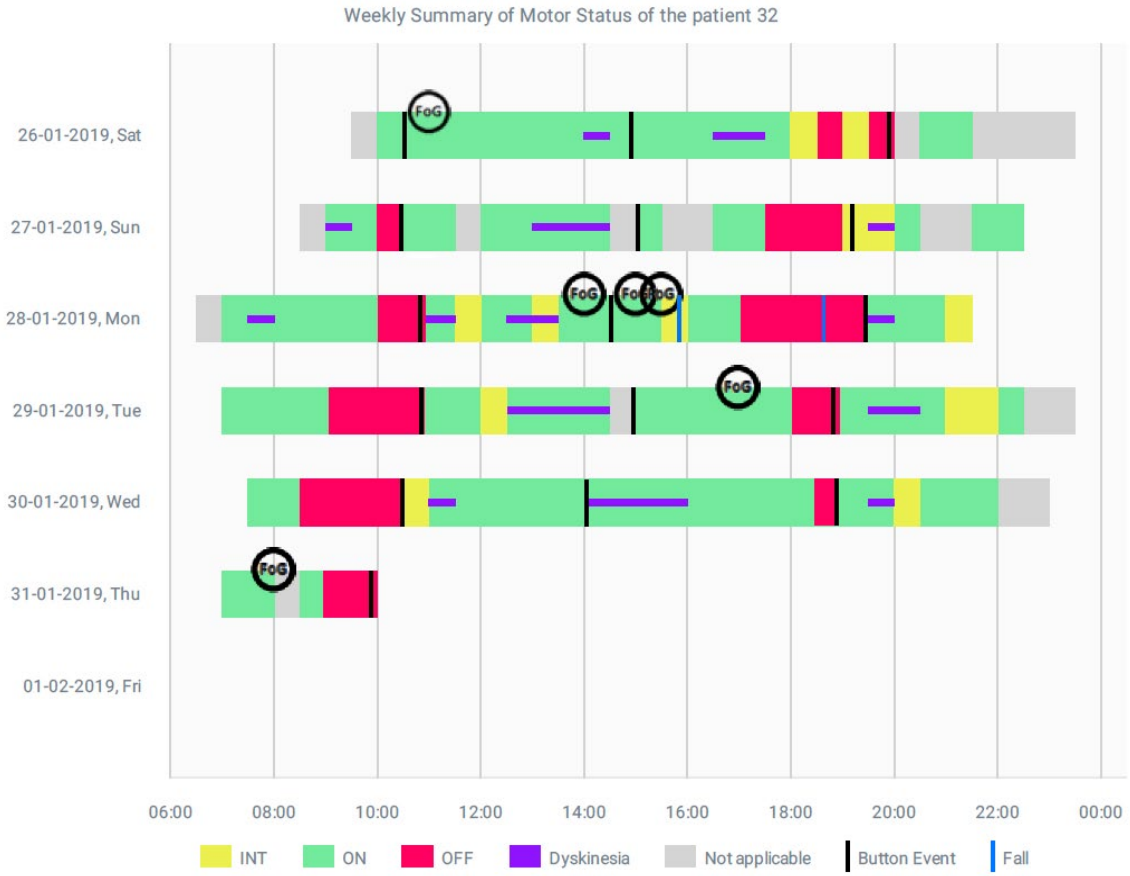


Figure 19. Weekly motor state. Button event was pressed at medication intake

The daily time is included on the horizontal axis, while the monitored days are indicated on the vertical axis. The colours in the graph represent the different states of the patient regarding the colour in which they are represented:

- Green: The patient is in ON state.
- Red: The patient is in OFF state.
- Yellow: The patient is in an intermediate state.
- Magenta: It has been detected choreic dyskinesias.
- Grey: No state has been detected (no dyskinesias, no walking detection).

7.2.2.2. *Weekly Time* in *OFF state*

This graph shows the daily-accumulated time in OFF state that has been detected. On the horizontal axis, it is shown the days monitored (maximum one week) and on the vertical axis the percentage of monitored time that the patient has been in OFF state. Although the bars are based on the percentage of monitored time that has been detected as OFF state, information is added about the number of hours the patient has been in this state. This graph must be carefully analysed, although it can be very useful, it can present aberrant data due to very short periods of monitoring or very long periods of inactivity. Whenever this graph is analysed, three factors must be taken into account: the total monitoring time, the sum of hours in OFF state and the total time with any motor state verdict. It is highly recommended to analyse this graph jointly with the weekly motor state.

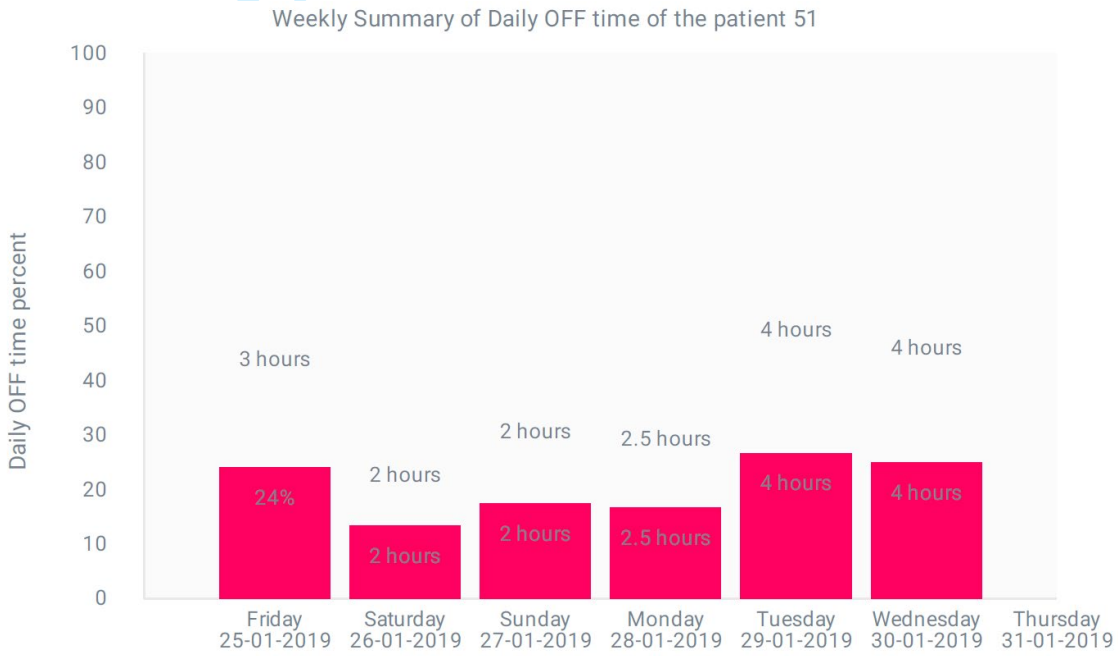


Figure 20. Time in OFF state

7.2.2.3. *Weekly FoG episodes*

On the vertical axis, it can be observed the days monitored (maximum one week) and on the horizontal axis the number of episodes detected per day. In this graph, it is shown the number of episodes detected per day, the average length of these episodes (as explained above in a resolution of 1.6 seconds) and the maximum duration of an episode of FoG per day.

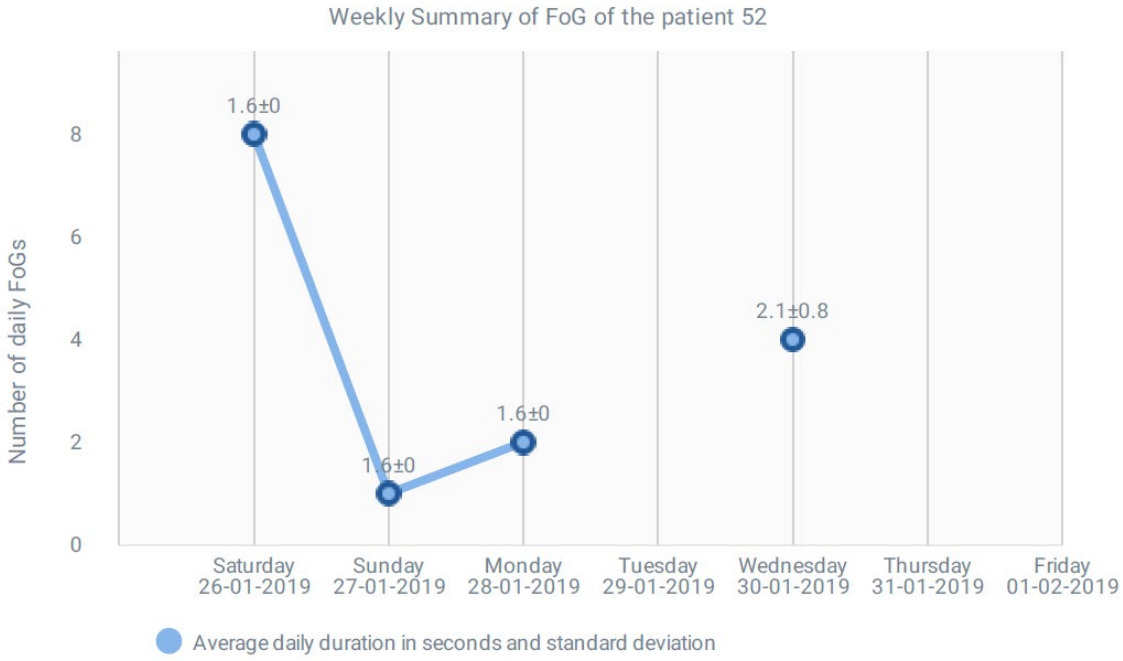


Figure 21. Number of FoG episodes

7.2.2.4. Weekly stride fluidity

The following graph presents the weekly evolution of the average stride fluidity that the patient presents during the monitoring period. The stride fluidity is a measure of acceleration that is obtained as an intermediate result of the bradykinesia detector, which has a value (ranging from 2 to 25) and which is related to the fluidity of the movement that the patient presents when walking. This way, we can evaluate the evolution of the difficulty that the patient has when walking as an average per day, the greater the value the greater the fluidity. This value is correlated with the so-called Factor 1 of UPDRS III (see Analysis of Correlation between an Accelerometer-Based Algorithm for Detecting Parkinsonian Gait and UPDRS Subscales) On the horizontal axis you can see the days monitored (maximum one week) and on the vertical axis the measure of fluidity. Below an example is shown:

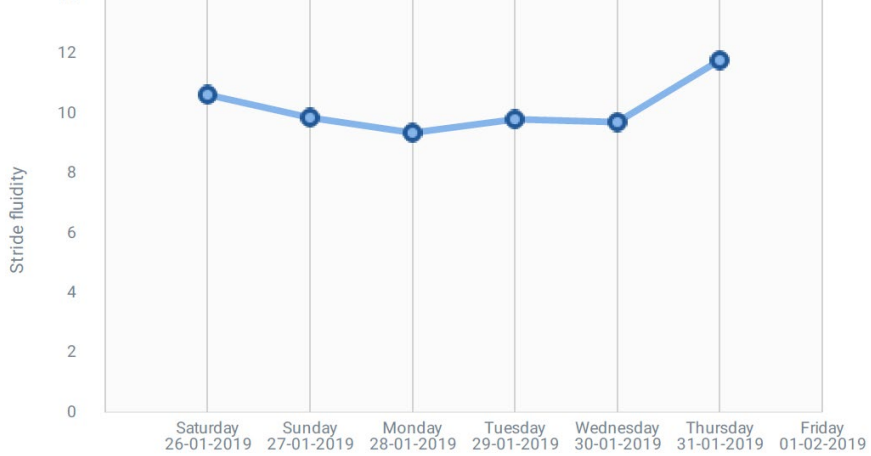


Figure 22. Weekly stride fluidity

7.2.2.5. *Weekly physical activity*

Among the sensor output parameters, there are also data about the physical activity that the patient has performed during the entire monitoring period. The variables shown are:

- Step length
- Stride speed
- Cadence
- Energy expenditure
- Number of steps

In each of the graphs, on the horizontal axis, all the monitored days are shown, and on the vertical axis, the average per day of the units corresponding to each one of the measurements. Here are some examples:

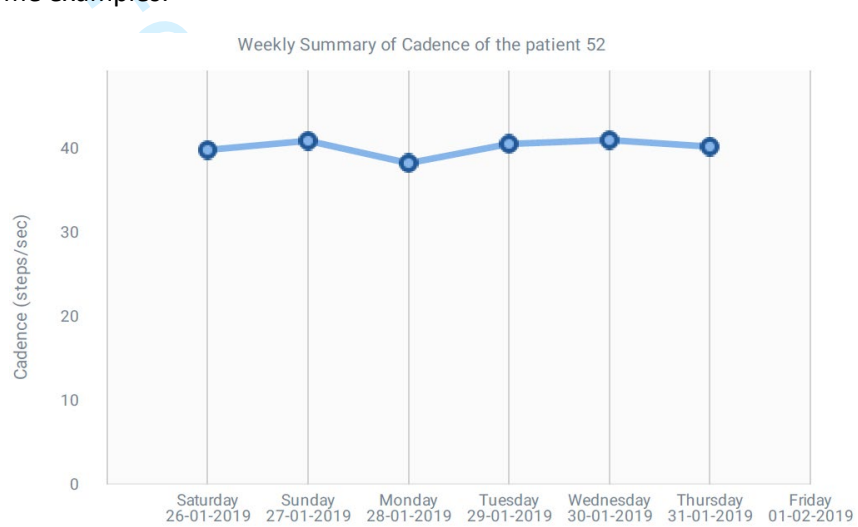


Figure 23. Weekly average cadence

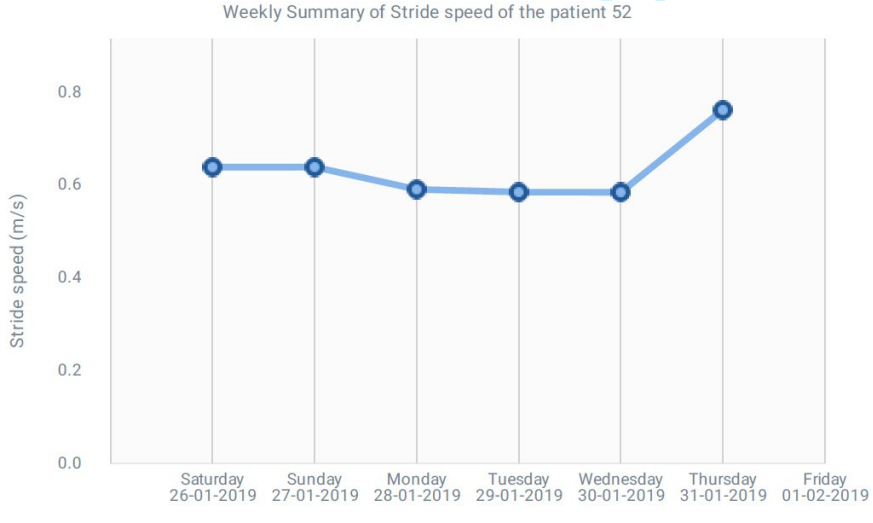


Figure 24. Weekly average Stride speed

7.2.2.6. *Daily motor symptoms*

STAT-ON, in the extended report, generates a graph of motor symptoms per monitored day where it can be seen, in addition to the motor status, the dyskinesia and the number of FoG episodes that the patient has suffered as well as the hours of appearance. The resolution in all the daily charts corresponds to half an hour. In the following figure, an example of this graph is shown.

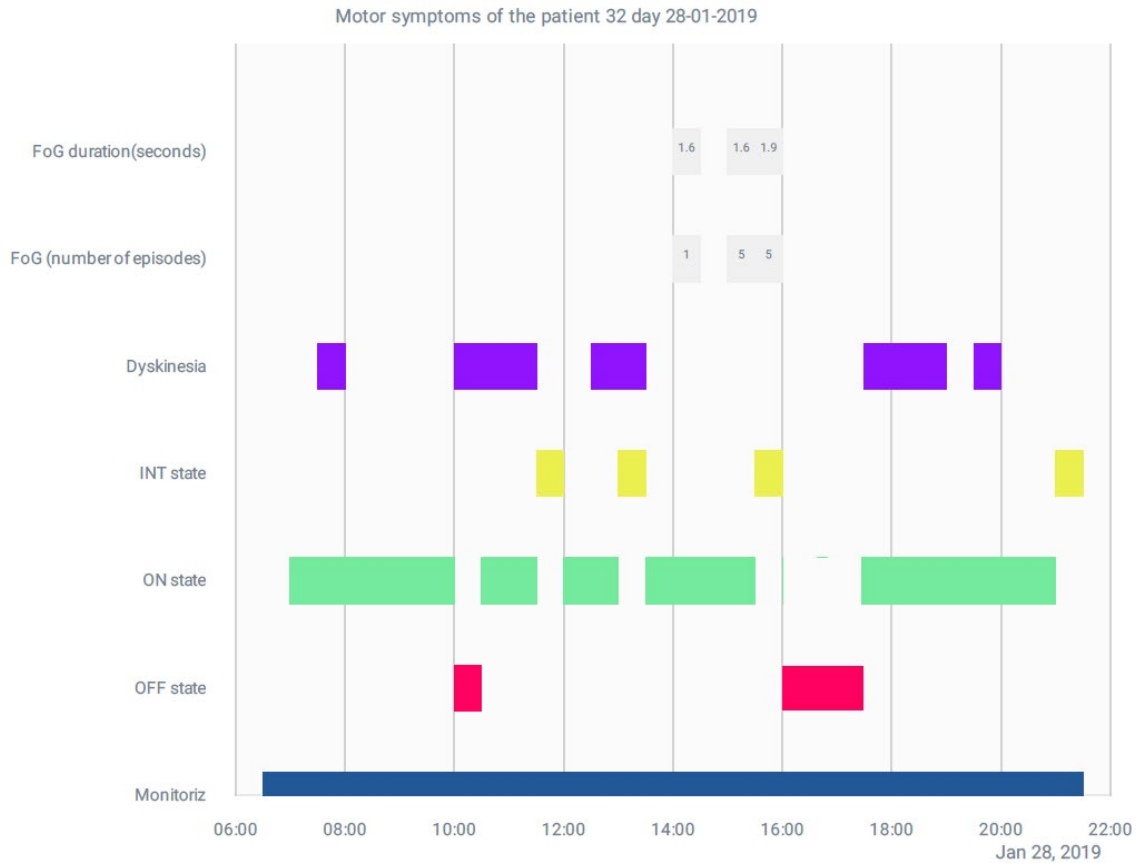


Figure 25. Daily motor states and FoG episodes

On the horizontal axis it is shown the hours of the day and on the vertical axis a series of labels that describe the corresponding row:

- Time Monitored: Time in which the sensor is running.
- ON/OFF/INT state: representation of the motor state detected in the patient. Red corresponds to OFF state, Green to ON state and yellow to Intermediate state.
- Dyskinesia: periods in which choreic dyskinesias have been detected in the patient.
- FoG Episodes: In this row, the number of FoG episodes are represented. In case that a FoG episode is detected, a box with the number of episodes is drawn.

7.2.2.7. *Daily stride* fluidity

The system generates a graph of stride fluidity when the patient is walking where the daily evolution of the stride fluidity of the patient's gait can be assessed. In addition, in the

background of the graph, the detected motor state is also drawn (red OFF, green ON, yellow INT). Finally, note that the thresholds calculated (as self-adaptive algorithm), upper (green) or lower (red), are also drawn. These thresholds indicate when bradykinesia is considered and, given that patients do not walk in the same way, they are patient-dependent. On the horizontal axis it can be observed the hours of the day and on the vertical axis the units corresponding to the stride fluidity (m/s^2).

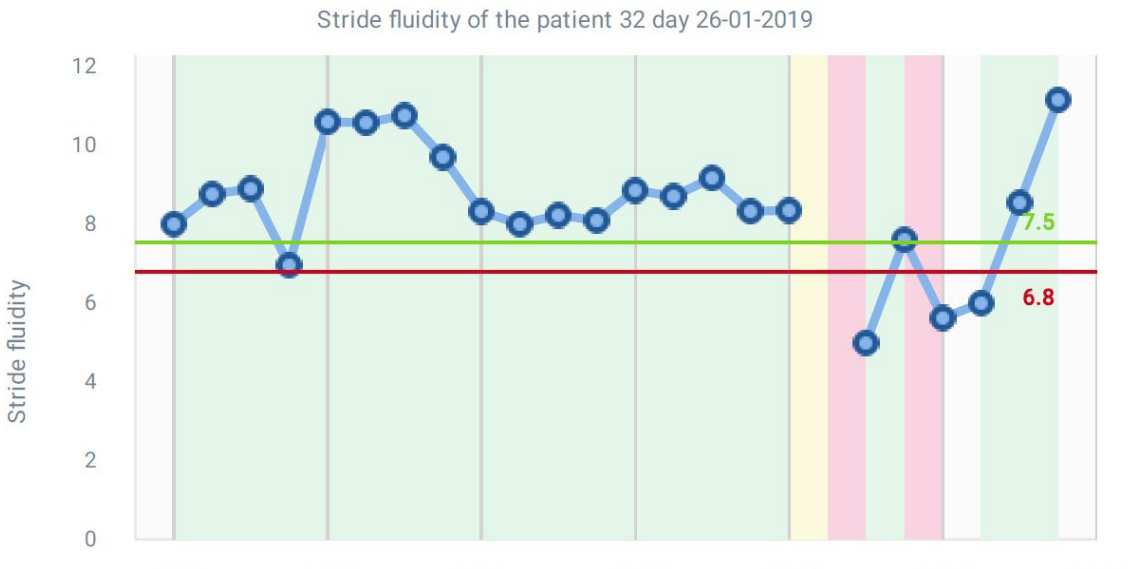


Figure 26. Daily stride fluidity and motor states

7.2.2.8. Daily physical activity

This group of indicators provide information about physical activity that the patient has performed along the day and the days that he/she has been monitored. These variables are:

- Step length
- Cadence
- Energy expenditure
- Number of steps

In each of the graphs, the hours of the day are shown on the horizontal axis, and the units corresponding to each of the measurements are shown on the vertical axis. In addition, the detected motor state is added in the background of the graph (red is for OFF state, green is for ON state, and yellow for INT state). Here are some examples:

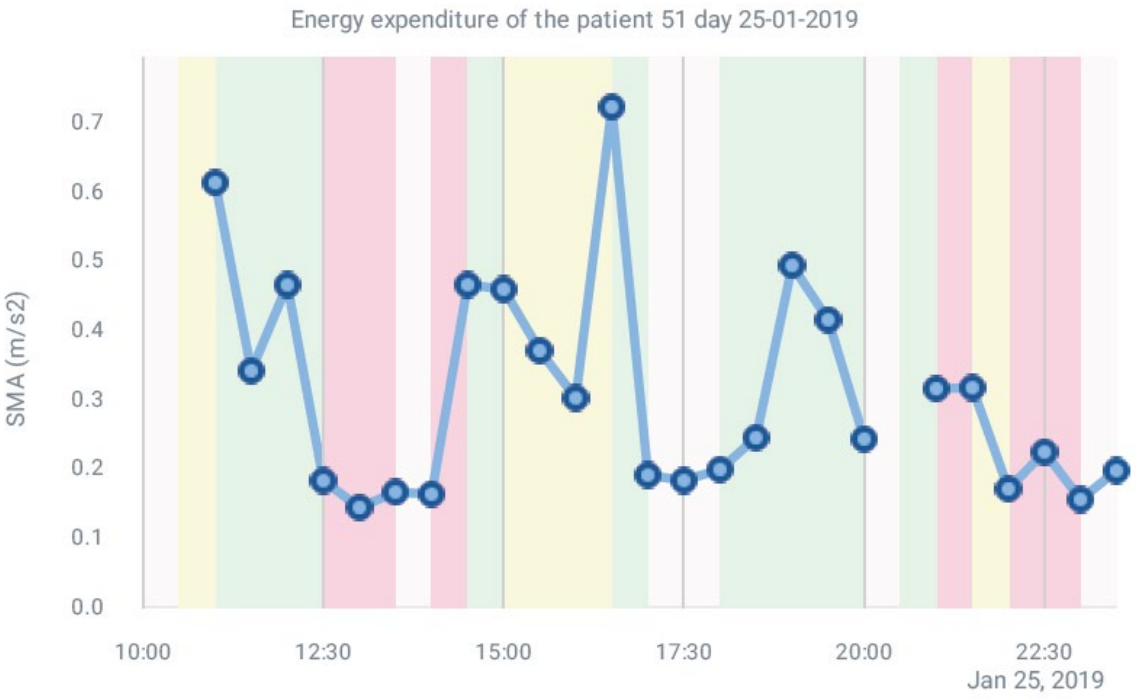


Figure 27. Daily energy expenditure and motor states

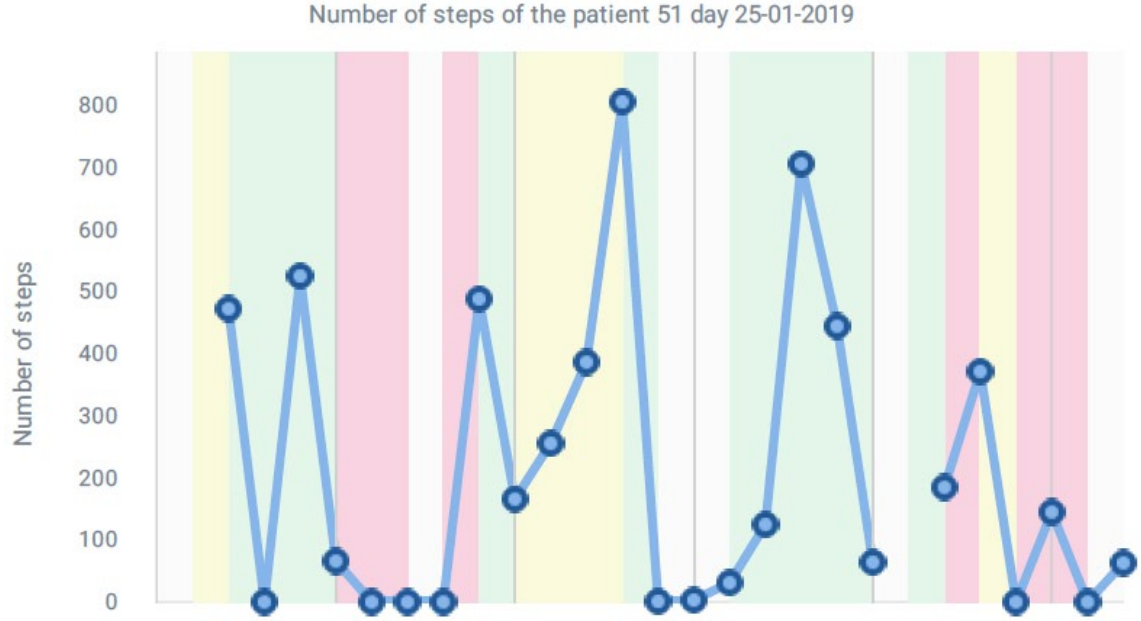


Figure 28. Daily number of steps

7.3. Reduced report

This report is a selection of the extended report that includes all those graphs that are of special interest in order to help the clinical professionals to have a more complete and objective view of the state of their patient:

- Summary page (7.2.1)
- Weekly motor state (7.2.2.1)
- Weekly time in OFF state (7.2.2.2)
- Weekly FoG episodes (7.2.2.3)

REFERENCES

[1] C. Pérez-López *et al.*, "Assessing Motor Fluctuations in Parkinson's Disease Patients Based on a Single Inertial Sensor," *Sensors*, vol. 16, no. 12, p. 2132, Dec. 2016.

[2] A. Rodríguez-Molinero *et al.*, "Analysis of correlation between an accelerometer-Based algorithm for Detecting Parkinsonian gait and UPDRS subscales," *Front. Neurol.*, vol. 8, no. SEP, pp. 3–8, 2017.

[3] A. Rodríguez-Molinero *et al.*, "A Kinematic Sensor and Algorithm to Detect Motor Fluctuations in Parkinson Disease: Validation Study Under Real Conditions of Use," *JMIR Rehabil. Assist. Technol.*, vol. 5, no. 1, p. e8, Apr. 2018.

[4] À. Bayés *et al.*, "A 'HOLTER' for Parkinson's disease: Validation of the ability to detect on-off states using the REMPARK system," *Gait Posture*, vol. 59, no. September 2017, pp. 1–6, 2018.

[5] C. Pérez-López *et al.*, "Dopaminergic-induced dyskinesia assessment based on a single belt-worn accelerometer," *Artif. Intell. Med.*, vol. 67, pp. 47–56, Feb. 2016.

[6] D. Rodríguez-Martín *et al.*, "Home detection of freezing of gait using support vector machines through a single waist-worn triaxial accelerometer," *PLoS One*, vol. 12, no. 2, 2017.

[7] T. Sayeed, A. Samà, A. Català, A. Rodríguez-Molinero, and J. Cabestany, "Adapted step length estimators for patients with Parkinson's disease using a lateral belt worn accelerometer.," *Technol. Health Care*, vol. 23, no. 2, pp. 179–94, 2015.

8. Frequently asked questions (FAQs)

Q: I have pressed the button but the sensor does not turn on (its LED does not blink):
Place the sensor on a charging pad, the orange led may light up. After a few minutes, press the sensor's button.

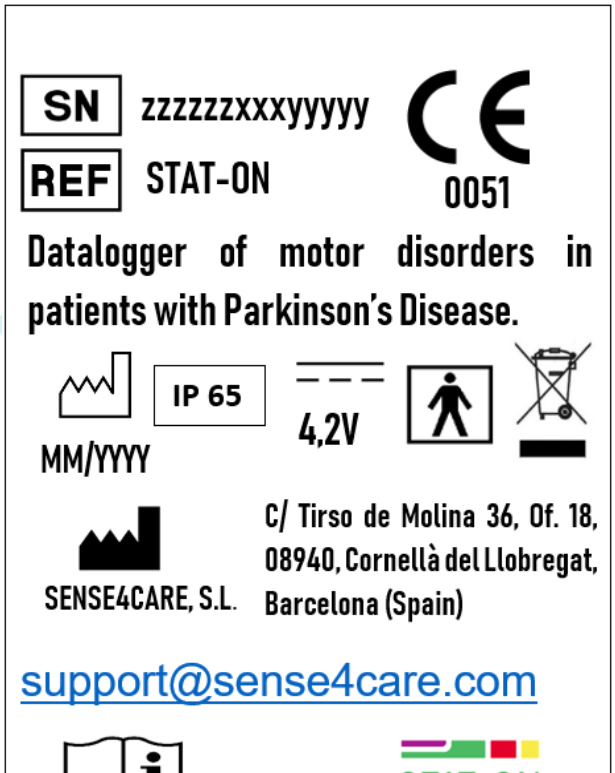
Q: When do I have to press the button?
The button is only pressed when the sensor is in shutdown Mode or standby mode. This is not a ON/OFF button. To switch the sensor OFF, do it with the App.

Q: How do I stop the sensor?
In order to save power, the sensor enters *sleep mode* automatically when no movement is detected for some minutes and wakes up automatically as well, thus, there is no need to turn the sensor ON/OFF. However, if the sensor will not be used for a long period of time it can be shut down by clearing its memory (see the *Format* section 5.3.7).

Q: Which is the minimum time that the user should wear the sensor?
The sensor needs a minimum of 24 hours of data, which should be captured within three different days (i.e. 8h/day * 5 days approx.). However, it is recommended to wear the sensor, at least, for a week. The user must use it during the activities of daily living.

Contact support@sense4care.com for any other issues.

9. Device Labelling



x: stands for the lot number

y: stands for the number of device within the lot

z: stands for month and year of fabrication (MMYYYY)

STAT-ON SENSE4CARE

10. Symbols and labels

Manufacturer

Date of manufacture

Serial Number

Reference number

Input power

Shock protected, type BF.

Consult instructions for use

Do not dispose (excluding belt)

93/42/EEC Directive compliance – IMQ Notified Body

0051

11. Privacy

In compliance with the General Data Protection Regulations (GDPR), SENSE4CARE, S.L guarantees that collected data is uniquely stored within the device and that only the user is responsible of the use of these data. In its present form, STAT-ON is not capable to share the collected data to a third party without the user consent.

Sense4Care S.L. will only access to data under the expressly consent of the user and the owner of the STAT-ON device. Shared data to Sense4Care S.L. will be always pseudonymised, in any case. Pseudonymised data that the user provides us will be incorporated into a file of our responsibility and will be kept under the strictest measures of security and confidentiality.

You can exercise the rights of access, rectification, deletion, opposition and portability by contacting C / Tirso de Molina 36, Of.18; 08940 - Cornellà de Llobregat, Barcelona; or to the following email: info@sense4care.com.

STAT-ON SENSE4CARE

12. Technical specifications

Communications	
Bluetooth specification	Bluetooth 4.0 (Bluetooth Low Energy)
Bluetooth bandwidth	2,4 GHz
Wireless charging standard	WPC v1.1 Qi Industry Standard
Wireless charging bandwidth	100-205 kHz
Electrical features	
Power Supply (charger)	100-240 Vac, 0.3-0.6 A, 50-60 Hz
Battery: Type	Lithium-Polymer
Battery: Capacity	1100 mAh
Battery: Charging time	<6 h
Battery: Maximum charging current	500 mA
Battery: Maximum discharge current (peak)	135 mA
Average consumption (normal use)	2.5 mA
Physical features	
Height	62,5 mm
Width	90 mm
Depth	21,20 mm
Weight	86 g
Enclosure material	ABS-FR(17) UL94, UV Protection White - Matte
Environment specifications	
Temperature operation range	From 0°C to 40°C
Temperature in charging conditions	From 0°C to 40°C
Storing conditions	The system must be stored at a temperature close to 20ºC and with batteries charged about 30% to 50% of capacity. We recommend relative humidity storage from 45 to 85%. We recommend that batteries be charged about every half year to prevent over discharge. Directly heat cell body is strictly prohibited. Battery may be damaged by heat above 100ºC.
Atmospheric pressure conditions	700hPa to 1060hPa
Certification	
Protection against and dust and water	IP65
Battery in medical use	IEC62133
Design, fabrication and commercialization of industrial electronic controls.	ISO 9001:2015
Medical Quality Management System and Medical Devices sales, development, manufacturing, delivery and maintenance including related services	ISO 13485:2016
Medical Device certification	CE Marked number: 0051

STAT-ON SENSE4CARE

13. Certification

#	Standard	Harmonized	Application
1	EN 1041:2008 Information supplied by the manufacturer of medical devices	YES	Used to establish the information needed for product use and general aspects of the presentation of information
2	EN 15223-1:2016 Symbols for use in the labelling of medical devices	YES	Used to set the appearance of graphical symbols included in the labelling of our product.
3	EN ISO 60601-1:2006/A1:2013 Medical electrical equipment. Part 1: General requirements for basic safety and essential performance.	YES	Used for establishing the basic safety and essential performance. Date of cessation of conformity for previous ed. 31.12.2017
4	EN ISO 60601-1-2:2015 Medical electrical equipment. Part 1-2: General requirements for basic safety and essential performance. Collateral standard: Electromagnetic compatibility. Requirements and tests.	YES	Used for establishing the safety and functionality EMC requirements
5	EN 60601-1-6:2010 Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability	YES	Used for establishing usability requirements for medical electrical equipment
6	EN 60601-1-11:2010 Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment	NO	Se utiliza para establecer los requisitos y las pruebas para el dispositivo como equipo eléctrico médico y sistemas médicos eléctricos utilizados en el entorno de atención médica domiciliaria.
7	EN 62304:2006+/AC:2008 Medical device software. Software life cycle processes.	YES	Used for establishing the life-cycle of software
8	EN ISO 14971:2012 Medical devices - Application of risk management to medical devices	YES	Used for establishing the risk management process for the product
9	EN 80002-1:2009 Medical devices software. Guidance on application of ISO 14971 to medical device software	NO	Used for establishing the risk management process for the software
10	EN ISO 62366:2008 Medical devices. Application of usability engineering to medical devices	YES	Used to minimize use-errors
11	MEDDEV 2.7.1 (2016) Clinical Evaluation Clinical Evaluation – A guide for manufacturers and notified bodies	NO	Guidance for device Clinical Evaluation
12	EN ISO 14155:2011 Clinical investigation of medical devices for human subjects. General requirements	YES	Applies only chapter 4 and recommendations for the review of data and medical and scientific information published / available as Annex A.
13	EN 62353:2014 Medical electrical equipment – Recurrent test and test after repair of medical electrical equipment.	NO	Used for establishing the test after repair and preventive maintenance plans
14	RED 2014/53/EU The Radio Equipment Directive	YES	Used for establishing the radio Equipment requirements

15	ETSI EN 300 328 V2.1.1 Harmonised Standard covering the essential requirements of article 3.2 of Directive 2014/53/EU	YES	Wide Band Data Transmission equipment standard.
16	ETSI EN 301 489-1 V2.2.0 Article 3.1b Directive 2014/53/EU - RED	NO	ElectroMagnetic Compatibility (EMC) standard for radio equipment and services; Part 1: Common technical requirements;
17	ETSI EN 301 489-3 V2.1.1 Article 3.1b Directive 2014/53/EU - RED	NO	ElectroMagnetic Compatibility (EMC) standard for radio equipment and services; Part 3: Specific conditions for Short-Range Devices (SRD)
18	ETSI EN 301 489-17 V3.2.0 Article 3.1b Directive 2014/53/EU - RED	NO	ElectroMagnetic Compatibility (EMC) standard for radio equipment and services; Part 17: Specific conditions for Broadband Data Transmission Systems;
19	ETSI EN 303 417 V1.1.1 Wireless power transmission systems Harmonised Standard covering the essential requirements of article 3.2 of Directive 2014/53/EU	NO	Wireless power transmission systems, using technologies other than radio frequency beam, in the 19 - 21 kHz, 59 - 61 kHz, 79 - 90 kHz, 100 - 300 kHz, 6 765 - 6 795 kHz ranges;
20	EN 60601-1-11:2015 Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment	NO	It is used to establish the requirements and tests for the device such as medical electrical equipment and electrical medical systems used in home environments.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym See title page (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry See after abstract (page 3)
	2b	All items from the World Health Organization Trial Registration Data Set See after abstract (page 3)
Protocol version	3	Date and version identifier N/A
Funding	4	Sources and types of financial, material, and other support See “funding” section (page 19)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors See title page and “Authors contributions” section (page 19)
	5b	Name and contact information for the trial sponsor See title page (page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities See “funding” section, paragraph 1 (page 19)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) See “Ethics" section, paragraph 1 (page 15)
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention See “introduction” section, paragraphs 1-4 (page 5)
	6b	Explanation for choice of comparators N/A
Objectives	7	Specific objectives or hypotheses See the last two paragraphs of the introduction. (page 6)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) See “Study Design” section, paragraph 1
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained See “study setting and duration” section paragraph 1 (page 7)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) See “Participants” section paragraphs 1-3 (page 7)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered See “Interventions” section, paragraph 1 (page 8)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Please, see last paragraph of “Procedures” (page 9)

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended See "Outcome variables and measurement instruments", all section (page 11-12).
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) See fifth paragraph of "Procedures" (page 10) and Table 1 (page 20)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations See "Sample Size" section, paragraphs 1-3 (page 13)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size N/A

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions See last paragraph of "Interventions and randomization" (page 9)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned See last paragraph of "Interventions and randomization" (page 9)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions See last paragraph of "Interventions and randomization" (page 9)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how See "Blinding" (page 12)

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial See "Blinding" paragraph 1-2 (page 12)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol See "Outcome variables and measurement instruments", all section (page 11)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols See second to last paragraph of the "data analysis plan" section. (page 13)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol See "Ethics and dissemination" (page 15)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol See "data analysis plan", paragraphs 1-5 (page 13)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) See "data analysis plan" paragraphs 6-9 (page 14)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) See the first paragraph and the second to last paragraph of the "data analysis plan" section. (page 13)
Methods: Monitoring		

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed See "Monitoring" section, paragraph 1 (page 12)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Please see "Outcome variables and measurement instruments", "Data analysis plan" and Table 1
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor See "Monitoring" section, paragraph 1 (page 12)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval See Ethics and dissemination, paragraph 1 (page 15)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) This item is included the original protocol, but we have not considered it of interest for the article. If necessary we will introduce it upon request of the editor.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) See the first paragraph of "Ethics and dissemination", paragraph 1 (page 15)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial See "Ethics and dissemination", paragraph 2 (page 15)

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site See “Declarations” section (page 19)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators To be included upon editor’s request
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation See “Ethics and dissemination” section (page 16)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions See last paragraph of “Ethics and dissemination” section (page 16)
	31b	Authorship eligibility guidelines and any intended use of professional writers This is in accordance to BMJ authorship criteria.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code No plans yet. Not decided.
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates To be included upon editor’s request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.