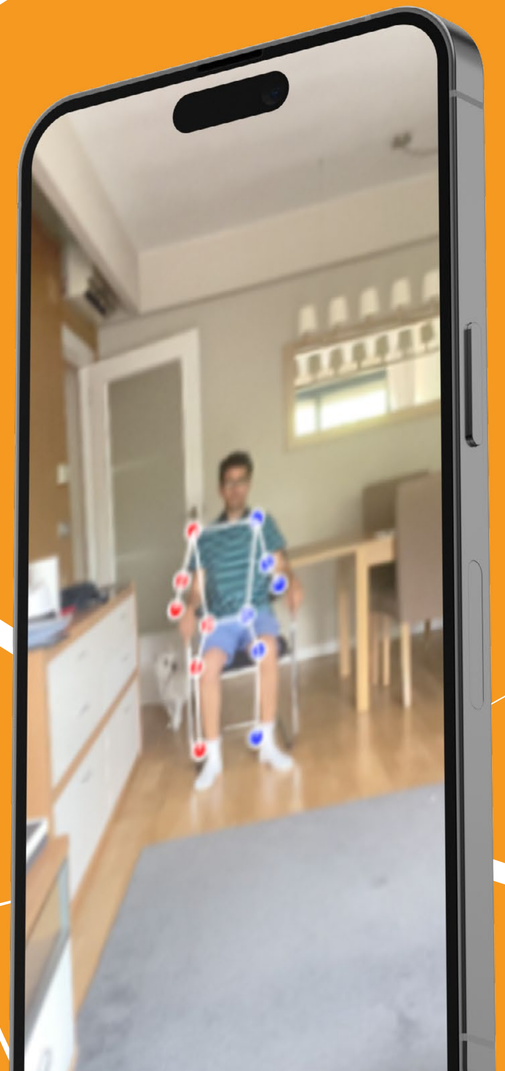
Video-Based Assessments to Digitise COA: validating vTUG for Parkinson’s disease

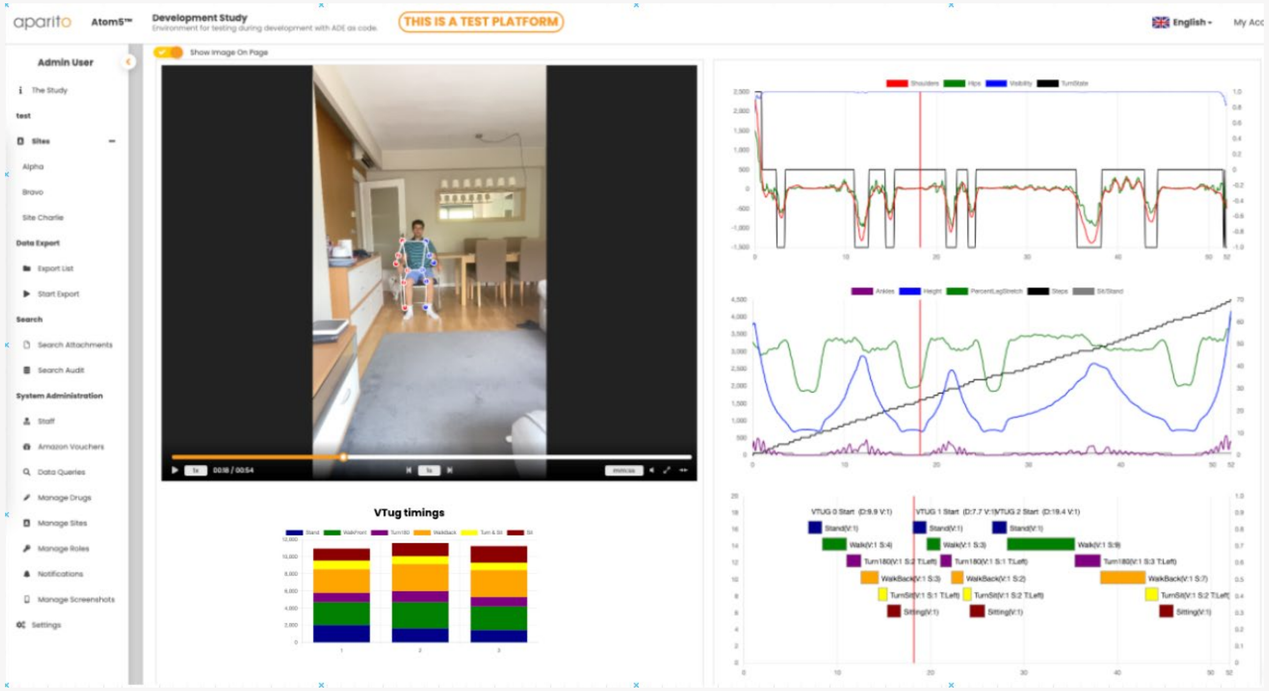
aparito™



Introduction

Digital assessment of patients in their environment is an attractive concept which will improve both patients' routine care and clinical trials. Indeed, the facilitation of regular follow-up - compared to travelling to specialist centres for yearly consultation - is relevant for people living with neurological conditions such as Parkinson's disease (PD). Equally important is the trend toward digitisation of clinical trials (1) and the myriad benefits that partial or full decentralisation can offer, leading to reduced costs, shorter time to market for new therapies and improved return on investment (2).

We are pleased to announce the completion of recruitment for our study to validate the vTUG as a means of monitoring PD patients' gait and balance at home.



Background

The digitisation of clinical trials and clinical workflows is well underway and despite some challenges, has obvious benefits. The digitisation of Clinical Outcome Assessments (eCOAs) – either by adapting traditionally used COAs into electronic means or by creating new and novel eCOAs continues to have some questions regarding the validation and regulatory acceptance of digital endpoints and novel electronic assessments (3).

The vTUG is a module developed by Aparito in collaboration with the DZNE (Deutsches Zentrum für Neurodegenerative Erkrankungen) within our Atom5™ app and platform. This study aimed to test the feasibility and validation of a digitised version of an existing and widely used COA.

Part one of the study was designed to evaluate the in-hospital environment usability of vTUG by the patients. Part two aims to demonstrate the feasibility and usability of the vTUG use in the patient's environment to monitor the progression of PD and the effect of treatment both from the patient's and the operator's point of view.

Deployment of vTUG into the real world enables follow-up of patients living with PD in their everyday lives. Close monitoring of the disease in each patient is an approach that enabled us to develop an eCOA where weekly assessments provide a more meaningful measure of gait and balance than a conventional snapshot visit conducted once a year.

What is Parkinson’s disease (PD)?

PD is a progressive neurodegenerative disorder characterised by the deposition of protein aggregates termed Lewy bodies in the nervous system. PD's motor symptoms result from the loss of dopaminergic cells from the substantia nigra. The etiology of PD is unknown and it is hence called an idiopathic condition (as several family forms exist). Disease progression is variable and the disease may look stable for long periods (4), in particular since many symptoms can be controlled by symptomatic medications.

Although early onset can occur, PD is usually diagnosed between 45 and 60 years of age and affects 1-2% of the population over 65 with a 1.5/1 male prevalence. (5).

Currently, there is no cure, but in more recent years, management - aimed at increasing the activity of the dopaminergic pathways - has improved symptom management. Life expectancy is no longer greatly impacted, but quality of life is likely to be vastly decreased in the later stages of the disease.

Typical clinical findings of the motor symptoms can alter walking stability and balance. They include:

Bradykinesia: 'slowness of movement', hesitation can be tested using finger or toe tapping which are slow and deteriorate in time with progressive fatigue and decrease in amplitude

Tremor: often a ‘pill-rolling’ tremor of the hands at rest

Rigidity: stiffness of muscles at the extremities and trunk

Abnormal gait: shuffling, festinating (progressive acceleration of stride alongside a reduction of stride length), reduced arm swing, freezing (particularly when turning or when faced with doorways, obstacles or changes in terrain)

Postural instability: tested using the pull test, although not usually present at diagnosis.

Current Parkinsonian medication

First-line drug treatment is often based on increasing synaptic dopamine by giving Levodopa, a dopamine precursor which is metabolised into dopamine. Other drugs, Monoamine Oxidase B inhibitors block the breakdown of dopamine. Dopamine Agonists bind to the dopamine receptors and mimic the action of dopamine. Another type of drug, usually given with Levodopa, and called Catechol-O-methyl transferase (COMT) inhibitors uses a different pathway to decrease dopamine breakdown and prolong the action of Levodopa (5).

These treatments are “time-sensitive” and have potential side effects due to overstimulation of dopamine or resurgence of symptoms when the doses wear off. Although the response to anti-Parkinsonian drugs remains good with time their durations of action decrease and their dosages have to be adapted regularly leading to more frequent intakes and therefore increased risk of side effects. Complications can have severe impacts. Poor mobility can lead to increased falls and resultant injuries. Reduced independence is also seen as the disease progresses and mobility deteriorates. This is an important marker to evaluate in the home environment.

What is the TUG and where are we with vTUG?

Gait and balance are important clinical measures of functional movement and are commonly used to gauge disease progression or treatment outcomes in children and adults alike.

The Timed Up and Go test (TUG) is a widely used measure in clinical care and has been used as an endpoint for assessing disease progression and evaluating drug efficacy (6).

Originally developed to assess gait and balance in elderly people (7, 8) it is now used as a predictor of risk of falls and is considered sensitive to change in motor function in patients on dopaminergic therapies.

In the TUG, patients begin seated and are asked to stand up and walk 3 meters, turn, walk back, and sit down. They start the test when they hear the clinician say “Go”. There are five distinct phases of the test:

1. Standing: The individual stands up from a seated position in a chair.

2. Walking: The individual walks 3 meters.

3. Turning: The individual makes a 180-degree turn.

4. Walking back: The individual walks back to the chair.

5. Sitting down: The individual turns and sits back in the chair.

The clinicians record the time to complete the entire sequence and their subjective impression of features of possible neurological conditions. The average score of three repeat tests is obtained.

What is the TUG and where are we with vTUG?

The TUG is associated with strong test-retest reliability and inter- and intra-rater reliability (9, 10). A cut-off time of around ≈11.5s has been suggested to identify those at significant risk of falling (11). It has also been used to differentiate between stages of dementia, with progressive slowing associated with disease severity. The increased time compared to healthy age-matched controls for very mild Alzheimer's Disease (AD) was (AD) ~1.3s, mild AD ~2.4s, and mild-severe AD ~4.5s (12).

A recent review of studies using the TUG to index PD found that reliability was rated as 'good' or 'moderate', and validity 'good' in those assessing balance (13). A report comparing PD patients "on" and "off" medication with age-matched controls found that "on" medication patients took >13s to complete the TUG, whereas the 'off' medication patients took >17s. This was compared to age-matched controls who took <10s to perform the TUG (14).

The TUG test is an effective measure of motor function and PD progression. It is performed in a specialised medical environment. Therefore, the clinical patient's assessment relies on less than one minute's worth of data caught in an artificial environment.

Recent feasibility studies of patients performing the "TUG at home" or "virtual TUG" (vTUG) using digital devices to record performances have been encouraging and could pave the way to more precise, regular and rational patient follow-up (15). Home-based assessments have significant advantages in terms of increased frequency of testing and monitoring, access to isolated populations, and data collection, leading to a more scientific representation of the patient's functional ability and progression.

Collecting data via digital devices opens up to more refined diagnostic tools. For instance, in dementia patients, mild cognitive impairment was diagnosed using a TUG test instrumented with a single body-worn sensor to quantify mobility. The TUG test's distinctive subtasks (standing up, walking, turning or sitting) were analysed and related to particular cognitive domains that cannot be identified when simply measuring overall TUG duration (16). Much more can be expected from other digital analyses such as video recordings coupled with advanced pose-estimation analysis of movement (17).

As all smartphones today are equipped with high-definition cameras, video capture is a simple and inexpensive way of making frequent assessments of patient's health and well-being, within their own homes, but also allows for excellent audit trails of time-stamped videos over time.

The Study

This study aims to validate the vTUG as a means of remotely monitoring patient gait and balance in the home.

The primary objectives of the study are to:

Assess the ability of patients to complete the TUG task independently at home

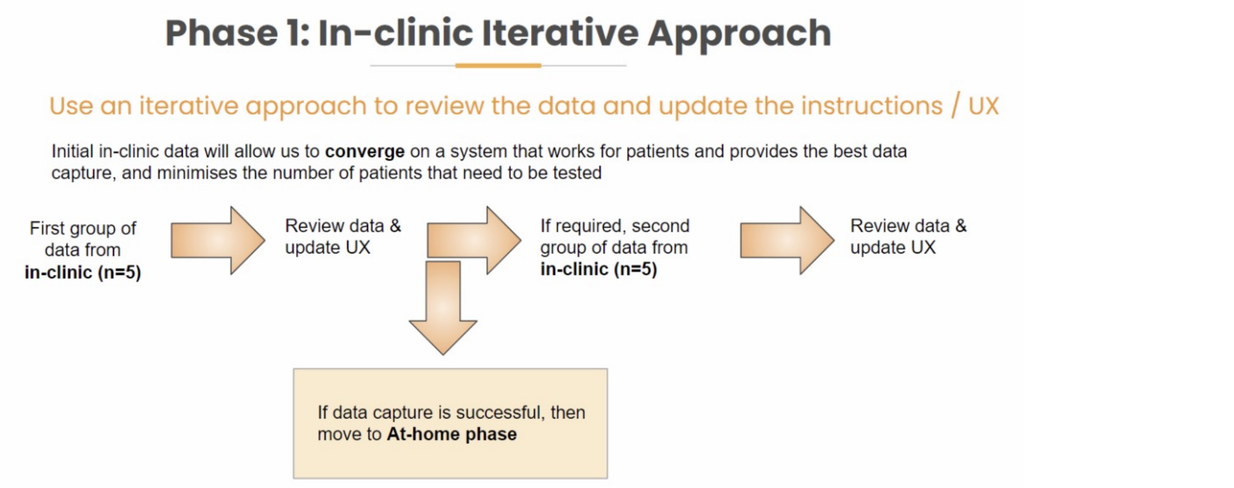
Evaluate the quality of videos collected for clinical assessment

The equipment to perform the vTUG was provided, namely a tripod with a phone mount, a tape measure to be put in place at the 3m mark, and a study-specific app - Atom5™ with a vTUG capture module on it developed by Aparito for recording and uploading the videos.

The patients were mandated to follow the video instructions provided within the app to assemble it. If the patients were physically unable, or could not understand the instructions, the clinician/ caregiver assisted.

Phase One: In-hospital Usability Study

The first stage aimed to assess how usable the Atom5™ App is for patients to video-capture their performance of the vTUG within a clinical setting. An iterative design was employed. The study was conducted at the DZNE study sites in Bonn and Dresden, Germany. After data from the first five patients were collected, feedback was reviewed along with the data for quality and performance. Based on this, some minor modifications were made to the design and flow of the vTUG capture in the Atom5™ before moving on to phase two.



Phase One: In-hospital Usability Study

Following phase one, phase two was instigated with a Longitudinal Feasibility Study. The second phase of the project assessed the usability and feasibility of how well patients can perform the vTUG independently in the home environment.

Recruitment has now been completed with 25 patients consented and on-boarded by local clinicians onto the Atom5™ study app and platform.

The equipment to perform the vTUG was provided in advance in person by post (tripod and tape measure). Based on the opinion of the clinician, the support of a caregiver for safety and equipment setup was discussed if deemed necessary. Patients are advised to use a solid chair (e.g., dining table chair), to wear closed shoes (e.g., trainers) and to avoid walking over any objects on the floor (e.g. rugs)

Patients are required to independently complete a vTUG assessment once a week in triplicates for 12 weeks and upload the videos through the Atom5™ study app. Just before completing the vTUG, the participants are also asked to score their health state on a scale of 0 – 100 and to state whether they are on or off treatment.

Patients will also be asked to comment on their experience using the system usability scale (SUS) and user experience questionnaire (UEQ) at the end of the trial which is also delivered by Atom5™.

Atom5™

Clinical trials can be conducted within patients' homes by leveraging our Atom5™ platform, incorporating disease-specific smartphone apps and integrating video assessments and wearable devices.

Aparito's patient-generated data platform is disease-agnostic and scalable, ready for rapid deployment in global rare disease studies.

Designed and built by regulators and clinicians, Atom5™ is 21 CFR Part 11, GDPR and HIPPA compliant by design and available in 193 countries and 125 languages.

Analysis

The phase one study has confirmed the safety and feasibility for the patients:

- to perform the vTUG, labelled as a “successful performance”

- to deliver video capture of their motion with correct body focus and length of capture of the vTUG, labelled as “correct performance”.

Qualitative analysis, based on clinician and patient reports included:

The ratio of “successful” and “correct” performances over total vTUGs was calculated to conclude the feasibility and safety during this phase and allow phase two to start.

Identification of obstacles to successful and correct completion such as setting up the equipment, instruction clarity or navigating on the app were reviewed. Including patients and/or safety concerns, respectively. These findings and recommendations were implemented into the Atom5™ app and vTUG module flow.

During phase two of investigating at-home usability and feasibility of the vTUG, the same qualitative and quantitative analysis described in phase one of the study will be repeated. Analysis of the mean total vTUG time and of the time of subsections (stand, walk up, turn, walk back and sit down) will also be performed.

Analysis of the different subsections of the vTUG will explore their correlation with clinical scores from the UPDRS. The videos will also be utilised for validating the use of in-house proprietary pose estimation and automated analysis for the vTUG.

Conclusion

In conclusion, this study aims at validating the usability and feasibility of digital outcome assessments and the development of remote endpoints to follow up patients living with PD, including progression of the disease, treatment effects and balance and, possibly testing the effect of new drugs within drug trial boundaries.

The study findings will be published as soon as possible with the aim of implementing a clinically robust eCOA and digital biomarker for future PD trials.

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