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Short Communication

Challenges of Incorporating Digital Health Technology Outcomes in a Clinical Trial: Experiences from PD STAT

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Abstract. Digital health technologies (DHTs) have great potential for use as clinical trial outcomes; however, practical issues need to be addressed in order to maximise their benefit. We describe our experience of incorporating two DHTs as secondary/exploratory outcome measures in PD STAT, a randomised clinical trial of simvastatin in people with Parkinson's disease. We found much higher rates of missing data in the DHTs than the traditional outcome measures, in particular due to technical and software difficulties. We discuss methods to address these obstacles in terms of protocol design, workforce training and data management.

Keywords: Parkinson's disease, clinical trials, digital outcomes, sensors, data management

INTRODUCTION

Digital health technologies (DHTs) encompass a broad set of tools, such as wearable sensors, smartphone applications, and computer tasks, which generate digital data relevant to health. Compared to clinical rating scales, participant questionnaires and other traditional health data outcome measures, they have a number of potential advantages. These include objectivity, precision, scalability, continuous

data collection, and ability to test remotely—a particular advantage in the current pandemic. DHTs are increasingly being used in clinical trials of neurodegenerative disease, especially Parkinson's disease (PD), and the majority of pharmaceutical companies plan to incorporate them in future trials [1]. However, their use in clinical trial settings comes with a number of considerations and practical issues that are distinct from traditional clinical trial outcome measures, including unfamiliarity with platforms, connectivity difficulties and lack of data visibility. Here we describe our experience of using two digital measures (Bradykinesia-Akinesia Incoordination (BRAIN) Tap Test (BTT) [2]; PD Monitor (ClearSky

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Medical Diagnostics Ltd., York, UK) [3]) within a clinical trial in terms of data completeness achieved and the challenges experienced.

DIGITAL MEASURES

BRAIN (Bradykinesia-Akinesia Incoordination) Tap Test (BTT)

The BTT is an online keyboard finger-tapping task administered via a QWERTY keyboard. Participants are asked to alternately tap the ‘s’ and ‘;’ keys as fast and as accurately as possible for 30 s with each hand in turn. Software compatibility was an issue for implementation in previous studies, but there were no issues with data capture [2, 4].

PD Monitor (ClearSky Medical Diagnostics Ltd., York, UK)

The PD Monitor records finger and thumb movements in 3D space by using two small electromagnetic tracking sensors (Polhemus, VT, USA), one each attached to a participant’s thumb and forefinger, and an electromagnetic source connected to a nearby computer (Fig. 1). Each hand is recorded separately. The movements recorded are the same as the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) upper limb bradykinesia items (finger tapping, hand opening, hand pronation-supination) and rest tremor items. PD Monitor has previously been evaluated in numerous clinical studies worldwide [3, 5–7]. In earlier studies, problems were encountered with the correct initialization of the equipment, rectified by improving the



Fig. 1. PD Monitor equipment showing electromagnetic sensors attached to participant’s thumb and forefinger that measure movements in 3D space, in relation to an electromagnetic source (box).

Instructions For Use and clearly labeling equipment to avoid misconfiguration; there were no issues with data capture.

TRIAL SETTING

The PD STAT study was a UK-based multicentre randomised clinical trial that recruited 235 participants from 23 sites between March 2016 and May 2020 [8]. It assessed the neuroprotective potential of simvastatin versus placebo in people with mild-moderate PD. Participants were evaluated over 26 months. The primary outcome was change in the MDS-UPDRS part III motor subscale score [9] in the practically-defined off-medication (OFF) state, which at the time of conducting the trial was generally considered the gold standard measure of disease severity. Planned secondary motor outcomes included other elements of the MDS-UPDRS, a 10 m timed walk and BTT, the number of key taps being the reported outcome. PD Monitor was incorporated as an additional exploratory digital motor outcome of upper limb bradykinesia and tremor, added to the protocol after study initiation in the seven highest recruiting PD STAT study centres.

IMPLEMENTATION OF DIGITAL MEASURES

Both digital measures were supervised tasks administered by the research team during scheduled study visits.

A unique single-use passcode (‘token’) was generated for each participant and used by the research staff to log in to the BTT website portal. Training was provided to site staff by the Clinical Trials Unit (CTU) team at remote site initiation visits, at regular site retraining video conferences and by way of written instructions. BTT was administered to participants in the OFF state at the baseline, 12-, 24-, and 26-month visits alongside the 10-m walk test and the MDS-UPDRS part III. Data were downloaded at the coordinating Peninsula CTU, with data completeness monitored contemporaneously by CTU staff and reasons for missing data documented.

PD Monitor data were collected in both ON and OFF states. Staff training was provided in person by the PD Monitor team when the equipment was delivered to the sites and telephone/video support was offered at regular intervals. Data were collected at the 12-month and either the 24- or 26-month visits. Data

123 were uploaded to a secure cloud-storage database and
 124 analysed by the data research team separate to the
 125 CTU team.

126 **DATA COMPLETENESS**

127 Data completeness for the motor outcomes (pri-
 128 mary, timed walk and digital) are presented in Table 1,
 129 with reasons for missing digital data detailed in
 130 Table 2. BTT data were available for 69–85% of par-
 131 ticipants across the different visits, compared with
 132 79–100% and 79–98% for the MDS-UPDRS part III
 133 and 10m timed walk test respectively. The most com-
 134 mon reason for missing BTT data was blocking of the
 135 BTT website by firewalls within study centres. Data
 136 were also lost due to an unavoidable change in the
 137 software provider.

138 PD Monitor measurements were scheduled to be
 139 taken from 80 participants with 56/80 (70%) complet-
 140 ing the task at the 12-month visit. OFF measurements
 141 at the 12-month visit were lost in 39/56 (70%)

142 participants due to a failed software update which
 143 meant that the OFF state measures were inadvertently
 144 overwritten rather than retained. Measurements at the
 145 24/26-month visits were missed mainly due to home
 146 visits, visits undertaken remotely due to the COVID-
 147 19 pandemic and failure of staff to use the equipment
 148 in the clinic.

149 **DISCUSSION**

150 DHTs hold much promise in terms of enriched
 151 trial data and more inclusive research. However, our
 152 experience of incorporating DHTs into our clinical
 153 trial, PD STAT, has identified simple, practical chal-
 154 lenges to digital data collection that impacted data
 155 completeness.

156 In PD STAT we incorporated two digital measures
 157 which were deployed in the in-clinic supervised envi-
 158 ronment, with less risk in terms of external sources
 159 of variability (e.g., undertaking tasks unsupervised
 160 in the home environment) and concerns related to

Table 1

Data completeness of motor assessments conducted at various time points in PD STAT. Figures provided are absolute numbers of participant data collected/participants available (%)

Outcome measure		Clinic visits			
		Baseline	12-month	24-month	26-month
Traditional	UPDRS III – OFF	228/228 (100)	198/205 (97)	178/193 (92)	146/185 (79)
	10m walk	223/228 (98)	196/205 (96)	168/193 (87)	146/185 (79)
Digital	BTT	193/228 (85)	172/205 (84)	154/193 (80)	128/185 (69)
	PD Monitor	OFF	ND	17/80 (21)	21/56* (38)
		ON	ND	56/80 (70)	34/56* (61)

UPDRS III, Movement Disorder Society Unified Parkinson’s Disease Rating Scale part III motor subscale score; OFF, off-medication state; ON, on-medication state; BTT, BRAIN (Bradykinesia-Akinesia Incoordination) Tap Test; ND, not done; *PD Monitor data were scheduled to be collected at either the 24- or 26-month visit.

Table 2

Reasons for digital motor measures data unavailability in PD STAT

Category	Reason	Number assessments impacted	
BTT	Accessing DHT portal	Technical issues/security access	36
		Change of licence	28
	Data collection	No access token	11
		Virtual visit due to COVID-19	29
		Home visit – no keyboard/internet	15
	Data management	Data not downloaded	27
	Participant-related	Participant in ON state	1
		Participant declined	1
		Other	16
	Total missing/total available (%)		164/811 (20.2%)
PD Monitor	Data collection	Home visit – equipment not available	36
		Virtual visit due to COVID-19	26
		Staff failed to use device in clinic	20
	Data management	OFF state assessment data overwritten by ON state assessment data	50
		Other	10
		Total missing/total available (%)	142/272 (52.2%)

BTT, BRAIN tap test; OFF, off-medication state; ON, on-medication.

161 data attribution. Nevertheless, despite the apparently
 162 lower risk locality and method of deployment, we still
 163 experienced significant impact on data capture.

164 One of our digital measures, the BTT, has been
 165 widely used in other studies, primarily to facilitate
 166 data capture from participants unsupervised in their
 167 own homes, for example in a longitudinal study identifying
 168 people at risk of PD [4]. The other DHT, PD Monitor,
 169 previously validated in PD as a supervised test of upper limb
 170 bradykinesia and tremor [3], was incorporated within the
 171 protocol as an additional substudy to facilitate its further
 172 evaluation as a motor measure, as well as to assess its
 173 feasibility as an outcome measure in a randomised clinical
 174 trial. Our experience with these measures has highlighted
 175 learnings for DHT deployment in relation to protocol
 176 design, workforce training and data management.

178 *Protocol design*

179 When selecting DHTs for use in trials, it is important
 180 to ensure the DHT is valid for assessment of the outcome
 181 of interest and can be feasibly deployed in the intended
 182 trial environment [10], including any costs for technology
 183 support or further development. Given the successful prior
 184 largescale use of BTT, we did not anticipate the problems
 185 we encountered with organisational firewalls and connectivity
 186 in study centres (which were mostly in NHS hospitals)—
 187 issues that were not found to be relevant to use of the
 188 measure in the home. Had we undertaken feasibility
 189 assessments across a few pilot sites, we may have
 190 identified these issues and built mitigation into the
 191 protocol. Implementing the PD Monitor within a study
 192 protocol that had already started meant that opportunities
 193 for robust feasibility testing were limited and some of
 194 the risk mitigation strategies (such as incorporating
 195 DHT reminders in the data-capture documentation) were
 196 not in place.

198 Our protocol was amended during the PD STAT
 199 study to allow for home visits as a means of reducing
 200 study burden for participants; however, the impact of
 201 this amendment on the DHT outcomes was a further
 202 reduction in data capture due to additional hardware
 203 requirements (e.g., a QWERTY keyboard for BTT,
 204 transporting the PD Monitor to participants' homes)
 205 and connectivity issues. These difficulties were
 206 compounded when visits were conducted remotely as
 207 a result of the COVID-19 pandemic. Home and remote
 208 visits are increasingly utilised to support retention,
 209 particularly for frail participants and those more
 210 remotely located from the study site. However, those

211 in rural or economically deprived localities are more
 212 likely to experience connectivity challenges. Failure
 213 to anticipate these challenges could therefore bias
 214 data collected utilising DHTs.

215 *Workforce training*

216 The FDA requires all those responsible for data
 217 capture using mobile technologies to have adequate
 218 training, education and experience [11]. Training was
 219 provided at site initiation and/or deployment of each
 220 of the technologies. Additional training was available
 221 on request for new staff and as a means of providing
 222 updates. However, despite this, some data losses
 223 were due to misunderstandings relating to the method
 224 of DHT deployment (in the case of BTT, the use of
 225 tokens for participant identification and the means
 226 by which these were requested), or due to lack of
 227 engagement with the DHT (for example, forgetting
 228 to take the PD Monitor device to clinic rooms for the
 229 study visits). It is important to ensure that site staff
 230 are well trained in technologies to be deployed, with
 231 easy access to relevant training and technical support.
 232 This is particularly important for longer duration
 233 studies such as ours where staff turnover at sites is
 234 likely to be encountered. Utilisation of training
 235 devices and practice runs prior to study initiation
 236 would be useful. Co-design of DHTs with study
 237 staff and patients to ensure maximum usability
 238 would help mitigate this risk.

239 *Data management*

240 The use of DHTs opens the possibility of centralised
 241 data capture and monitoring, with provision of
 242 technical support in real time, as well as potential
 243 for data quality and completeness monitoring to be
 244 automated with programmed alerts. Clinical Trials
 245 Transformation Initiative recommendations include
 246 presentation of DHT-captured data to investigators
 247 at sites, in order to support discharge of their
 248 oversight responsibilities with regard to data integrity
 249 [12]. In our study, data from neither measure was
 250 visible to study site investigators. However, the
 251 BTT data were visible to the central trial co-ordinating
 252 team, which allowed for reasons for missing data to
 253 be explored and mitigated, such as by provision of
 254 additional staff training. The PD Monitor data were
 255 not visible to the investigators or the central trial
 256 team, as data were uploaded directly to the DHT
 257 development team. The DHT data analysts had
 258 insufficient understanding of the study protocol to
 259 appreciate that data capture

errors had occurred due to a software malfunction. Ensuring clear communication with a shared understanding of the data management plan would have prevented this data loss with the PD Monitor in our study.

CONCLUSION

DHTs hold significant promise as outcome measures in clinical trials. We have identified challenges with their deployment that limit data completeness. Ensuring appropriate workforce training, pilot evaluation in study sites and data visibility at sites and the central co-ordinating team are mitigations that could be considered in order for the benefits of DHTs to be fully realised.

CONFLICT OF INTEREST

SS is a director and shareholder of ClearSky Medical Diagnostics Ltd. JA is a shareholder of ClearSky Medical Diagnostics Ltd. AJN developed the current version of the BRAIN test.

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