The patient-reported impact of Charcot-Marie-Tooth disease in the real world: the design and conduct of a digital lifestyle study (CMT&Me)

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Abstract

Background

Charcot-Marie-Tooth disease (CMT) is a rare, chronic, progressive motor and sensory neuropathy that affects the peripheral nervous system, leading to progressive, predominantly distal muscle weakness, atrophy, sensory loss and progressive limb dysfunction. As with many rare diseases, there is a lack of patient-reported data with which to understand and address patient needs. This study aims to explore the real-world impact of CMT from the patient perspective.

Methods

This is a prospective, digital lifestyle study of at least 2,000 people with CMT, ≥ 18 years, resident in the following countries: France, Germany, Italy, Spain, the UK and the USA. Participants will be recruited using community-based methods, via patient advocacy groups, social media, and word of mouth. Participants will use a smartphone application (CMT&Me) to check eligibility, provide consent, and contribute data. The dataset will include: 1) personal profile on enrolment – demographics, lifestyle characteristics, diagnosis, and current and previous treatments; 2) a selection of validated generic and disease-specific patient-reported outcome instruments: EuroQol 5 Dimensions 5 Levels (EQ-5D-5L), Brief Fatigue Inventory (BFI), Patient-Reported Outcomes Measurement Information System (PROMIS™) Pain Intensity 3a, Pain Interference 6b and Sleep Disturbance 8a, Work Limitations Questionnaire (WLQ), Falls Efficacy Scale – International (FES-I), Lower Extremity Function Scale (LEFS), and Quick Disabilities of Arm, Shoulder & Hand (QuickDASH). Descriptive data analysis will be conducted upon registration of the 1,000th participant and at 12-monthly intervals from study launch.

Conclusions

This digital, patient-reported study is designed to help researchers and clinicians understand the real-world impact of CMT and the unmet needs of patients.

Background

Charcot-Marie-Tooth disease (CMT) is a rare, chronic, progressive motor and sensory neuropathy that affects the peripheral nervous system, leading to progressive, predominantly distal muscle weakness, atrophy, sensory loss and progressive limb dysfunction (1). With an estimated prevalence of 1 in 2,500 people, it is the most frequently inherited neuropathy and one of the most common neurogenetic disorders (2).

CMT compromises patient lifestyles, everyday activities, career and family choices (3). There is currently no cure for CMT (4). Treatment focuses on physical therapy to maintain movement, muscle strength, and

flexibility, combined with occupational therapy, orthotics, pain management and psychological and social support (5). Surgical intervention may be required for more severe forms of the disease.

As with many other rare conditions, there is a lack of data about the burden of CMT with which to make informed decisions to improve disease management and outcomes. In particular, little evidence has been collected directly from people who have the condition, nor has much data been gathered in the real-world setting.

Patient reports often provide unique perspectives and in-depth depictions of disease burden and the impact of treatment. Thus, the role of patient-reported outcome (PRO) data is becoming increasingly recognized in strengthening disease understanding, and in the development, regulatory approval, use and reimbursement of treatments. To date, much PRO evidence has been generated in the clinical trial setting, with little data collected from patients being managed in real-world clinical practice. Real-world evidence (RWE) can provide more granular, longer-term data, from a broader patient population, than is typical in clinical trials, so there is clear value in its collection and analysis. In rare diseases like CMT, where there are likely to be challenges in conducting adequately sized and controlled clinical trials, RWE is of particular worth.

A growing recognition that RWE has a complementary value to randomized controlled trial evidence has been matched in recent years by regulators and health technology assessment (HTA) agencies publishing guidance for use of RWE. RWE is valued by regulators as a basis for regulatory decision-making, including approval of new indications for licensed drugs, as seen in the 21st Century Cures Act (6) and European Medicines Agency adaptive pathways (7). RWE is also accepted by many HTA agencies (e.g., the National Institute for Health and Care Excellence, and the Canadian Agency for Drugs and Technologies in Health) and payers in HTA submissions; including for orphan drugs (8).

There is a current need for a real-world study to explore the burden of CMT – a study that collects data directly from patients, about their experiences of living with, and managing, their condition.

The objective of this study, which is currently in the data collection phase, is to provide a detailed view of the impact of CMT and its treatment on patients in the real-world setting, including factors such as epidemiology, natural history, and clinical, humanistic and economic burden.

Results

Not applicable.

Discussion

CMT is a rare chronic disease and little is known about the burden it imposes on patients, their caregivers, and society. There is a lack of data collected in the real-world setting, directly from people who have the condition. Digital tools that enable real-time data reporting open up possibilities of publishing and acting

upon the data faster, which is important to those affected by the disease. They are also useful for capturing data during periods of reduced patient access to clinics (e.g., the COVID-19 pandemic).

This international, longitudinal, real-world digital PRO study explores the burden of CMT experienced by patients. The study provides a detailed view of the impact of CMT and its treatment on patients in the real-world setting, including factors such as epidemiology, natural history, and humanistic and economic burden. Close and collaborative partnerships with CMT PAGs, who are 'experts by experience', will not only aid participant recruitment but also ensure true patient centricity of the research.

As requesting clinical confirmation of diagnosis is either onerous or possible to circumvent, participants are eligible for this study based on self-reported CMT diagnosis alone. While this means responses to questions within the study are therefore subject to error due to misinformation bias, data will be monitored on an ongoing basis for outliers – and filtered accordingly – to mitigate. Linkage studies (i.e., with existing registries of known CMT patients) also offer a powerful way of addressing the potential for error – the informed consent includes an opt-in to facilitate such studies. The risk of recruiting false patients in the first place is very limited, however, given that the main method of recruitment is through CMT patient advocacy group networks.

Conclusion

In conclusion, this international, longitudinal, real-world digital PRO study – the first of its kind – will undoubtedly help researchers and clinicians to understand the real-world impact of CMT and the unmet needs of patients.

Methods

Trial design

This is a prospective, real-world, patient-reported lifestyle study. Adults with CMT use a smartphone app, CMT&Me (Vitaccess Ltd; Oxford, UK), to enter regular data about CMT, its management, and its impact on their lives, over a period of at least two years.

Study setting

Participation is entirely via the CMT&Me app. There are no physical study sites. Data is collected from participants in the following countries: France, Germany, Italy, Spain, the UK, and the USA.

Eligibility criteria

Inclusion criteria are as follows:

- adult (age ≥18 years) diagnosed with CMT (self-reported diagnosis only)
- resident in one of the study countries
- willing to use their own smartphone/tablet
- willing to provide informed consent

There are no specific exclusion criteria.

Informed consent

Participants enrol and provide informed consent via the CMT&Me app. Participant briefing materials are presented in a series of pages on the app, each followed by an informed consent statement relating to that section. Participants who agree to all the statements are considered to have given informed consent. Consent includes agreement to the possibility of data being cross-referenced with other medical databases.

Risks

As this is a non-interventional study, participants are not expected to be at risk of physical harm. Participation may trigger negative feelings in some participants. Participants are able to contact the research team if they have concerns or questions and are advised to contact their medical team where necessary.

Outcomes

As the aim of the study is to provide a detailed view of the impact of CMT on patients in the real-world setting, we are aiming to collect as much data as possible. Outcomes are therefore broad, with few predefined analysis metrics.

Outcomes are as follows:

Demographics

- Date of birth
- Height and weight (to determine body mass index)
- Sex
- Home postal code
- Healthcare system identifier (e.g., National Health Service number) [outcome only collected in countries where permitted]
- Smoking status

- Exercise status
- Diet status
- Alcohol consumption status

CMT characteristics

- CMT subtype
- Comorbidities

CMT diagnosis and treatment

- Age at symptom onset
- Age when medical care was first sought
- Age at diagnosis
- Diagnostic tests performed to achieve CMT diagnosis
- Clinical examinations performed to understand CMT diagnosis
- Physical therapies received for CMT
- Medicines received for CMT
- Walking aids/orthotics received for CMT
- Type of medical professionals seen for CMT
- Frequency of visits to the emergency department

CMT symptoms

- Symptoms experienced
- Brief Fatigue Inventory (BFI)
- Patient-Reported Outcomes Measurement Information System (PROMIS™) Pain Intensity 3a
- PROMIS™ Pain Interference 6b
- Cramp frequency
- Cramp intensity

Work/study

- Work Limitations Questionnaire (WLQ)
- Work/study status
- Days of work missed due to CMT

Health-related quality of life (HRQoL)

- EuroQol 5 Dimensions 5 Levels (EQ-5D-5L)

Physical function

- PROMIS™ Sleep Disturbance 8a
- Falls Efficacy Scale – International (FES-I)
- Lower Extremity Function Scale (LEFS)
- Quick Disabilities of Arm, Shoulder & Hand (QuickDASH)

Sample size

We aim to enrol approximately 2,000 participants. A formal sample size calculation has not been performed as hypothesis testing is not planned and analysis is descriptive in nature.

Recruitment

Recruitment is community based, with potential participants made aware of the study via direct communication from CMT patient advocacy groups (PAGs), PAG and Vitaccess Ltd (CMT&Me app developer and study contract research organization) social media accounts, and word of mouth, including via PAG community networks and patient ambassadors.

Would-be participants are able to download the CMT&Me app from Apple's App Store or Google Play, but study registration is contingent on meeting eligibility criteria.

The app was launched sequentially across the study countries in the following stages:

- Stage 1
  - US English (15 October 2018)
  - UK English (9 November 2018)
- Stage 2
  - Germany (31 January 2019)
  - Italy (31 January 2019)
- Stage 3
  - Spain (8 April 2019)
  - US Spanish (8 May 2019)
- Stage 4
  - France (1 July 2019)

Data collection and management

Participants are asked to complete a profile shortly after enrolment, which includes data on demographics, lifestyle characteristics, diagnosis and treatments, many of which are expected to remain fairly stable over the duration of the study. For those data that may change over the duration of the study (e.g., treatments, healthcare visits), participants are able – and encouraged – to add, edit or remove them.

Participants are also asked to complete a number of PRO instruments – after enrolment and then either monthly (EQ-5D-5L, BFI, PROMIS™ Pain Intensity 3a and Interference 6b, bespoke questionnaires for the study, PROMIS™ Sleep Disturbance 8a) or quarterly (WLQ, FES-I, LEFS, QuickDASH) – that assess HRQoL, specific symptoms, and function. Summary descriptions of all PRO instruments are provided below.

EQ-5D-5L

The EQ-5D-5L comprises two parts: the EQ-5D-5L descriptive system and the EQ Visual Analogue Scale (EQ-VAS) (9).

The descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels (no problems, slight problems, moderate problems, severe problems, and extreme problems – i.e., higher scores represent worse health). The scores for the five dimensions are combined in a five-digit number describing the participant's health state.

The EQ-VAS records the participant's self-rated health on a vertical, visual analogue scale with endpoints labelled “the best health you can imagine” and “the worst health you can imagine”. Higher scores represent better self-perceived health.

BFI

The BFI assesses participants’ fatigue severity (10). The measure uses a 10-point numeric rating scale, and a recall period of 24 hours. A global fatigue score is calculated by averaging all nine items.

PROMIS™ Pain Intensity 3a and Interference 6b

The PROMIS™ Pain Intensity 3a includes two items that assess pain intensity over the last seven days (average and worst pain), and one for pain intensity “right now”; each scores using a five-point scale (11). Possible scores range from 2 to 10 where higher scores represent worst pain. This measure is generic rather than disease-specific.

The PROMIS™ Pain Interference 6b assesses the extent to which pain hinders engagement with social, cognitive, emotional, physical and recreational activities, sleep, and enjoyment in life over the last seven days using a five-point scale (12). Possible scores range from 6 to 30 where higher scores represent greater interference. This measure is generic rather than disease-specific.

Bespoke questionnaires for this study

Two cramp-specific items were developed for inclusion in the study, measuring cramp frequency and intensity. The cramp frequency item asks, “In the past 7 days, how many days did you experience cramp?” and has five possible response options: had no cramp, 1–2 days, 3–4 days, 5–6 days, every day. The cramp intensity item asks, “In the past 7 days, how intense was your cramp at its worst?” and has five possible response options: had no cramp, mild, moderate, severe, very severe. Higher scores on both items represent greater cramp frequency and intensity respectively.

WLQ

The WLQ measures the impact of CMT on participants' work ability and productivity across four domains: time management, physical demands, mental-interpersonal demands, and output demands (13). Possible domain scores range from 0 to 100 and the recall period is the previous two weeks. WLQ domain scores will be converted into an estimate of productivity loss using an algorithm.

PROMIS™ Sleep Disturbance 8a

The PROMIS™ Sleep Disturbance 8a assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep over the last seven days using a five-point scale (14). Possible scores range from 8 to 40 where higher scores represent worse sleep disturbance. This measure is generic rather than disease-specific.

FES-I

The FES-I measures the level of concern about falling during social and physical activities inside and outside the home, whether or not the person actually carries out the activity (15). The “usual” level of concern is measured on a four-point Likert scale (1 = not at all concerned to 4 = very concerned), with participants asked to consider how they usually carry out the activity. Possible scores range from 16 to 64 where higher scores represent greater concern about falling.

LEFS

The LEFS evaluates difficulties because of lower limb problems in 20 activities, including work/school activities, hobbies, moving around the home, dressing, lifting, standing, sitting, walking, and running (16). The level of difficulty is assessed for “today” using a five-point Likert scale (0 = extreme difficulty or unable to perform activity; 5 = no difficulty). Lower scores represent greater difficulties experienced because of lower limb problems.

QuickDASH

The QuickDASH measure uses 11 items to gauge physical function and symptoms in people with any or multiple musculoskeletal disorders of the upper limb (17). All questions are rated 1 to 5 (no difficulty/none/not at all through to unable/extreme difficulty). Possible scores range from 11 to 55 where higher scores represent greater difficulties with physical function and symptoms.

Plans to promote participant retention and complete follow-up

If, at any study time point, participants do not complete data entry for a certain section of their profile or a PRO instrument within a one-week window, their data will be considered missing for that time point. They will still be able to enter data again at later required time points.

To promote engagement with the study app and continued data entry, participants will receive in-app messages, encouraging them to complete required data entry, thanking them for doing so, and stressing the importance of their contributions to research. Participants will also receive information about the study, updates on its progression, and emerging results via the study app, social media, and regular email newsletters.

CMT&Me also contains non-study features that are designed to help participants learn about or track their condition.

Data management

To promote data quality, rules were set for question responses (e.g., range limits for continuous variables, minimization of free-text data fields, limits to number of response options that can be selected). Data will also be checked and cleaned before analysis.

Each participant will log in to CMT&Me using unique self-generated login credentials, which are unknown and inaccessible to the study team. Data saved by participants in CMT&Me will be transferred to a central database, then aggregated and de-identified, as soon as is practicable. No personal data will be held on participants' devices. Personally identifiable information (PII) will be encrypted with unique encryption keys at rest and all data will be encrypted in transit. All study data will be stored on a secure server.

Confidentiality

All PII will be protected by industry-standard methods, ensuring full confidentiality is maintained. PII is not held on participants' devices and cannot be viewed by the study sponsor or any external researchers who apply for access to the study data. Data will be stored in a central database in aggregated, de-identified form.

Statistical methods

Statistical methods for primary and secondary outcomes

Data management and analysis will follow a pre-defined statistical analysis plan. As this is an exploratory observational study, differences and patterns in the data will be analyzed, but without exploring causation. All analyses will be descriptive, and no hypotheses tested.

Aggregated de-identified data will be summarized as follows:

- For continuous variables, distributions: number, mean, standard deviation, median, minimum, maximum, 95% confidence interval
- For categorical variables, summaries: n, frequency and proportion

For both variable types, the number and proportion of missing data will also be reported.

Descriptive distribution statistics for each PRO instrument score, or domain score, will be presented for baseline (first data entry timepoint) and at each time point thereafter, including at study end. Distribution statistics will also be generated to describe the outcomes at each time point for the absolute value and the calculated change from baseline.

Interim analyses

Interim analyses will be conducted upon registration of the 1,000th participant and at 12-monthly intervals from study launch.

A final analysis will be presented at study end (currently two years from study launch), based on data from all participants who have completed at least one PRO instrument, the necessary elements of their profile, and have been enrolled in the study or have withdrawn.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Missing data will be handled as set out in the scoring guidelines for the PRO instruments, and according to best practice for the profile. All missing data will be assumed to be missing at random, and no adjustments will be made to account for missing data.

Plans to give access to the full protocol, participant-level data and statistical code

Members of the public and external researchers can apply via the study website to be granted access to aggregated and anonymized study data. Access decisions will be granted under the purview of the study scientific advisory board (SAB).

Oversight and monitoring

A key tenet of governance and monitoring is that the framework is transparent and public, and so accessible to would-be participants considering enrolling, as well as to enrolled participants. As such, all oversight and monitoring arrangements will be published on publicly available study webpages: https://vitaccess.com/cmt-and-me.

Composition of the data monitoring committee, its role and reporting structure

An SAB was convened during the study design phase to protect participants' interest. The SAB is responsible for the following:

- Effective operational management of the study
- Ensuring that the study operates in the best interests of participants
- Ensuring that the study operates to the highest levels of academic rigor

The SAB acts as an advisory/review body for the following:

- Publication strategy and publications
- Data analyses
- Study evolution: possible amendments to the study protocol
- Communication: input into materials and communication with the participant cohort and wider CMT community.

The SAB also acts as a decision-making body for third party data access requests.

In line with good practice recommendations (18), the SAB comprises independent clinical and PAG representatives from each study country, plus sponsor and Vitaccess representatives. The SAB will meet in person at least annually (where feasible), and by teleconference at least every six months.

Adverse event reporting and harms

There is no obligation to report adverse events recorded by participants. Participants who report receiving the sponsor's product PXT3003 (or other experimental drugs) would have already been enrolled in clinical trials, and it is assumed they would therefore be followed up under the relevant adverse event-reporting pathways.

Frequency and plans for auditing study conduct

The SAB will audit the study conduct on an ongoing basis.

Plans for communicating important protocol amendments to relevant parties

The study team will be responsible for communicating protocol amendments to relevant parties as necessary and must be approved by the SAB.

Dissemination plans

The sponsor and study team have developed a publications plan for the study, which was approved by the SAB, to include conference presentations and journal publications. Study progress and results will be communicated to participants on an ongoing basis through regular email, social media, and in-app communication (newsletters and data nuggets).

Abbreviations

BFI: Brief Fatigue Inventory

CMT: Charcot-Marie-Tooth disease

EQ-5D-5L: EuroQol 5 Dimensions 5 Levels

FESI-I: Falls Efficacy Scale – International

HTA: Health technology assessment

IRB: Institutional review board

LEFS: Lower Extremity Function Scale

PAG: Patient advocacy group

PII: Personally identifiable information

PRO: Patient-reported outcome

PROMIS™: Patient-Reported Outcomes Measures System

QuickDASH: Quick Disabilities of Arm, Shoulder & Hand

RWE: Real-world evidence

SAB: Scientific advisory board

SAP: Statistical analysis plan

VAS: Visual analogue scale

WLQ: Work Limitations Questionnaire

Declarations

Ethics approval and consent to participate

Institutional review board (IRB) approval (Salus IRB, Texas, USA; protocol number 5101-03-2018) was obtained for conducting the study in France, Germany, Italy, the UK and the USA. Local ethics approval from El Comité de Ética de la Investigación con medicamentos del Hospital Universitario y Politécnico La Fe (Valencia, Spain; protocol code PHA-CMT-2018-01) was obtained for conducting the study in Spain.

Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SL contributed to conception and design of the study and wrote the first draft of the manuscript. KM, XP, ML & YB conceived and designed the study and drafted the manuscript. FPT, MS, SA, TS, RSM, GMF, FG, AG, SB, DT, MR, AM and CH contributed to conception and design of the study and reviewed the manuscript. All authors contributed to the review of the manuscript and approved the final version.

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