




# BMJ Open TELEmedicine for EPilepsy Care (TELE-EPIC): protocol of a randomised, open controlled non-inferiority clinical trial

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## ABSTRACT

**Introduction** Epilepsy is a chronic condition requiring consistent follow-up aimed at seizure control, and monitoring of anti-seizure medication (ASM) levels and side effects. Telemedicine (TM) offers invaluable support to patient follow-up, guaranteeing the prompt availability of a team of experts for persons with epilepsy (PWE) widely distributed across the country. Although many health institutions have endorsed the use of TM, robust data on effectiveness, safety and costs of TM applied to epilepsy are lacking. TELEmedicine for EPilepsy Care (TELE-EPIC) will evaluate the effectiveness of video consultation (VC) via TM compared with usual care (UC) for the monitoring of PWE (TELE-EPIC\_RCT). Moreover, TELE-EPIC will apply an innovative Volumetric Absorptive Microsampling (VAMS) device for quantitation of ASM through finger prick blood sampling as an alternative to venipuncture sampling (TELE-EPIC\_VAMS).

**Methods and analysis** TELE-EPIC\_RCT is a multicentre, open, pragmatic two-arm randomised controlled trial prospectively including adult and paediatric outpatients with established diagnosis of epilepsy consecutively attending the Epilepsy Centres of Bologna and Rome, respectively. The primary outcome is the non-inferiority of VC on seizure control compared with UC after an 18-month follow-up. Secondary outcomes are adherence to treatment, ASM-related adverse events, quality of life, mood disorders, patient and caregiver satisfaction, safety and costs. TELE-EPIC\_VAMS is a cross-validation study for blood ASM quantitation through a novel, VAMS-based device, comparing (1) VAMS versus plasma samples (reference standard method); and (2) nurse-collected versus self-collected blood by VAMS device.

**Ethics and dissemination** The study has been approved by the local ethics committee (349-2019-SPER-AUSLBO). Complete information about the state of project, relevant events and results will be regularly updated on the project's webpage on ClinicalTrials.gov. The project's results and data on the potential impact of TM in epilepsy will be disseminated on social media. A closeout meeting will be convened for the communication and dissemination of the project, highlighting its main achievements and impacts.

**Trial registration number** NCT04496310

## INTRODUCTION

Epilepsy is a chronic disorder with a point prevalence of 6.38 per 1000 persons and an annual incidence of 67.77 per 100 000 persons.<sup>1</sup>

## Strengths and limitations of this study

- TELEmedicine for EPilepsy Care (TELE-EPIC) is the first randomised controlled trial that will provide robust data on the effectiveness of video consultations (VCs) via telemedicine (TM) in both adult and paediatric persons with epilepsy (PWE).
- TELE-EPIC includes key indicators for assessing the provision and possible health inequities of VC through TM (ie, coverage, hours available for VC, technical issues, patient satisfaction) as study outcomes.
- TELE-EPIC includes a cross-validation study which applies an innovative method of anti-seizure medication (ASM) measurement based on self-sampling (Volumetric Absorptive Microsampling) that will lower travel and medical costs for PWE.
- The generalisability of the cross-validation study's results will be limited to countries systematically applying ASM measurement in the healthcare of PWE.

Common consequences of living with epilepsy include detrimental effects on education, driving, social and employment restrictions, and stigma,<sup>2</sup> with consequent loss of independence, mood disorders,<sup>3</sup> and impairment of quality of life (QoL).<sup>4</sup> The same factors indirectly affect caregivers, especially for children with severe disease/concomitant developmental disorders.<sup>5</sup>

Epilepsy has significant economic costs<sup>6</sup> and has been ranked as the second most burdensome neurological disorder by the WHO's 2010 Global Burden of Disease study.<sup>7</sup>

Pharmacological treatment is only symptomatic and bears serious side effects. Both old-generation and new-generation anti-seizure medications (ASMs) are associated with heterogeneous adverse drug reactions (ADRs), including neurotoxicity, hypersensitivity reactions, haematological, hepatic and pancreatic toxicities. Pharmacokinetic/pharmacodynamic interactions may also occur with other widely used medications and ASM,

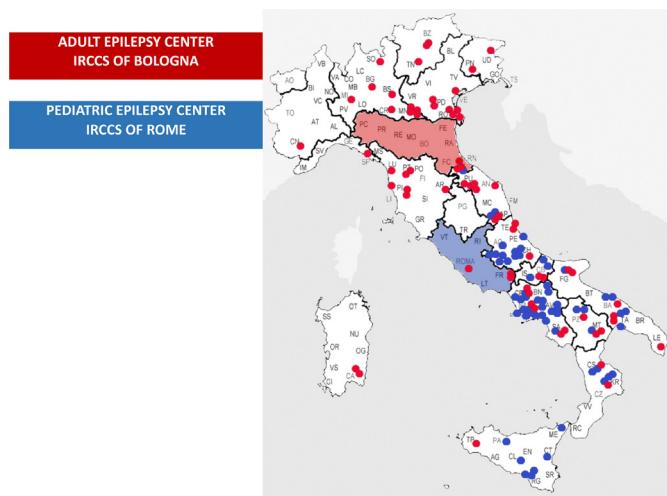


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**Figure 1** Provenience of extraregional patients referring to the Clinical Units over a 2-month period. Italian map showing the provenience of the extraregional outpatient visits referred to the Clinical Units involved in the study over the period 1 February 2018–30 March 2018. Adult Epilepsy Centre of IRCCS in Bologna (BO), Emilia-Romagna region (in red): visits are shown as red dots across several Italian regions. Paediatric Epilepsy Centre of Bambino Gesù Hospital, IRCCS in Rome (RM), Lazio region (in blue): visits are shown as blue dots across several regions.

including antimicrobials and oral anticoagulants.<sup>8,9</sup> Moreover, up to 30% of patients are drug resistant<sup>10</sup> and require a higher amount of ASM in many cases for a lifetime, with long-term cognitive effects.<sup>11</sup> Therefore, persons with epilepsy (PWE) require regular and timely counselling, ideally carried out by a single neurologist for surveillance of ADR and therapeutic adjustment based on ASM plasma levels. Dried blood spot (DBS) sampling is an alternative method of blood collection for the determination of ASM concentrations by liquid chromatography-tandem mass spectrometry (LC-MS/MS).<sup>12</sup> The technique has several advantages over conventional venipuncture blood sampling, for example, reduced blood volumes and simplified sample collection workflows. Volumetric Absorptive Microsampling (VAMS) is a relatively recent microsampling technique used to obtain dried specimens of blood and other biological matrices for quantitative bioanalyses, claimed to bring some significant advantages over DBS, in particular better sampling volume accuracy.<sup>13</sup>

As in Italy, most specialised centres are centralised in a few regional capitals, a large number of patients living beyond the major city boundaries often need to travel long distances to reach qualified health providers. The difficulties in accessing major health centres are aggravated by driving restrictions for PWE, with negative health consequences, unequal access to healthcare and high travel costs.

The Epilepsy Centres of IRCCS, Istituto delle Scienze Neurologiche in Bologna and IRCCS, Bambino Gesù Hospital in Rome, both full Members of the European Reference Network EpiCARE, are tertiary referral centres assessing adults and children with epilepsy, respectively,

from all Italian regions. They offer a multidisciplinary approach for different epilepsy syndromes with areas of integrated expertise and provision of highly specialised services (targeted outpatient clinics for surgery, pregnancy, vagus nerve stimulation clinic, transition to adult care for epileptic encephalopathies), avoiding multiple referrals. During 2017, 1058 outpatients attended the Adult Epilepsy Centre of IRCCS in Bologna, 30% of whom come from outside the Emilia-Romagna region. Similarly, the Paediatric Epilepsy Centre in Rome saw about 1235 outpatients/year, 35% of whom come from outside Lazio (figure 1, table 1). The high number of consultations sought by PWE lengthens in-office waiting lists, increases direct and indirect health costs (lost working days, travel/accommodation expenses), and possibly impacts QoL.

Telemedicine (TM), namely the use of telecommunication systems to deliver healthcare services, where distance is a critical factor, has the potential to provide equal access to healthcare, improve patient outcomes and reduce costs.<sup>14</sup> TM can be principally classified according to (1) *mode* (text: short messaging service, chat platform, emails, fax; video: by means of mobile devices, personal computers (PCs); audio: phone, audio applications); (2) *time* (real time/synchronous: by video, audio, text; asynchronous: emails); (3) *purpose of communication* (diagnosis; follow-up); and (4) *individuals involved* (ie, patients, caregivers, physicians, other health professionals).<sup>15</sup>

Among the various types of TM intervention, ‘teleconsultation’ refers to ‘interactions that happen between a clinician and a patient for the purpose of providing diagnostic or therapeutic advice through electronic means’ (<https://www.paho.org/ish/images/docs/covid-19-teleconsultations-en.pdf?ua=1>; <https://iris.paho.org/handle/10665.2/28414>).<sup>16</sup> Real-time video consultation (VC) is a modality of teleconsulting involving, synchronously, an in-office physician and patients/caregivers at home. VC might be effective in assisting patients with a chronic condition such as epilepsy, providing appropriate treatment and advice for self-management and support (also to parents and guardians).<sup>17</sup>

Until 2019, the application of TM for epilepsy was rare. Only a few studies worldwide compared telephonic visits or VC with conventional care, suggesting no difference in some clinical outcome measures, and improvement of some surrogate outcomes (satisfaction, costs).<sup>18–20</sup> The end of 2019 was marked by the SARS-CoV-2 outbreak in China that rapidly spread to the rest of the world. The COVID-19 pandemic encouraged several pilot studies on TM that applied digital technologies for management of PWE and surveillance of different aspects of epilepsy.<sup>21–22</sup> However, no randomised controlled trials (RCTs) on the effectiveness and safety of VC via TM procedures in epilepsy have been performed yet. Moreover, there are several research gaps of knowledge still to be addressed concerning TM applied to epilepsy. In particular, the long-term efficacy and safety of TM in terms of seizure control and ADR minimisation are still unknown. Moreover, the type of patient with epilepsy, in

**Table 1** Visits provided by the two Clinical Centres over a 2-month period: provenience, type of visits and type of patients assessed

|  | Adult Epilepsy Centre<br>IRCCS in Bologna (ER) |            | Paediatric Epilepsy Centre<br>IRCCS in Rome (LZ) |           |
|--|--|------------|--|-----------|
| Visits/year (1 Jan–31 Dec 2017)        | 1058   |            | 1235   |           |
| Visits in 2 months (1 Feb–30 Mar 2018) | 314  |            | 244  |           |
| Provenience                            |  |            |  |           |
| Outside the province                   | 146 (46.5%)                                    |            | 102 (41.8%)                                      |           |
| Outside the region                     | 70 (23.3%)                                     |            | 68 (27.9%)                                       |           |
| Type of visit                          |  |            |  |           |
| To targeted clinics                    | Pregnancy                                      | 32 (10.2%) | Epilepsy surgery                                 | 18 (7.4%) |
|  | VNS  | 17 (5.4%)  | VNS  | 2 (0.82%) |
|  | Transition to adult care                       | 6 (1.9%)   |  |           |
| Emergency consultations                | 6 (1.9%)                                       |            | 13 (15.3%)                                       |           |
| Routine first/control visits           | 253 (80.6%)                                    |            | 211 (86.5%)                                      |           |
| Epilepsy patients                      |  |            |  |           |
|  | Total 297                                      |            | Total 237  |           |
| SF/stable                              | 132 (44.5%)                                    |            | 120 (50.6%)                                      |           |
| Drug resistant                         | 110 (37%)                                      |            | 30 (12.7%)                                       |           |
| Clinically 'unstable'                  | 55 (18.5%)                                     |            | 87 (36.7%)                                       |           |

ER, Emilia Romagna; LZ, Lazio; SF, seizure-free; VNS, vagus nerve stimulation.

terms of age, epilepsy type and severity, that can better benefit from TM interventions should be better defined. The TELEmedicine for Epilepsy Care (TELE-EPIC) Project will try to fill these gaps in a pragmatic clinical high-quality care context, both for adult and paediatric PWE.

We hypothesise that VC by TM devices for epilepsy follow-up will enhance patient care, easing the access to tertiary centres and improving patient-centred outcomes without worsening seizure control. From a safety perspective, TM may also facilitate therapeutic reconciliation with proactive tailored treatment. The possibility of actually viewing administered medications can minimise the occurrence of ADR, prevent drug interactions and reduce the likelihood of look-alike sound-alike medication errors (eg, drugs with similar names/pharmaceutical strengths but containing different active substances). This proactive 'real-world' clinical monitoring is advocated by the latest European pharmacovigilance legislation to promote safe prescribing.<sup>23</sup> In this frame, the innovative application of next-generation technologies of microsampling (VAMS), coupled with LC-MS/MS for quantitative analysis of ASM, may add a number of advantages. The VAMS technique can facilitate specimen collection for ASM therapeutic drug monitoring (TDM) out of the clinic, allowing individuals to self-collect accurate blood aliquots, anywhere, with minimal instructions.

One of the aims of the project is to apply a recently validated VAMS-based method for blood quantitation of several ASMs<sup>24</sup> for cross-validation of VAMS reliability in a TDM setting by comparing: (a) the VAMS-based method versus plasma samples method (reference standard

method); and (b) nurse-collected VAMS versus self-collected ones.

The present study is part of a strategic plan by the IRCCS, Istituto delle Scienze Neurologiche of Bologna to implement TM for the management of neurological chronic diseases, and it was inspired by a previously designed RCT in narcolepsy aimed at demonstrating the non-inferiority of follow-up VC via TM versus the standard in-person outpatient visits.<sup>25</sup>

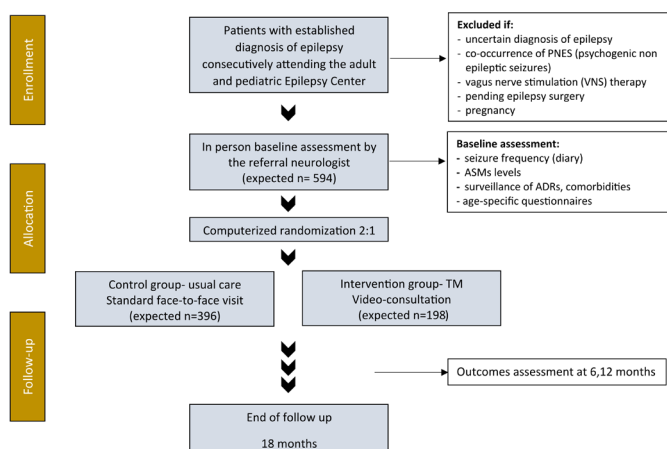
## METHODS AND ANALYSIS

### Aims

The general aim of TELE-EPIC is to evaluate the effectiveness, safety and costs of TM applied to epilepsy follow-up tools (VC; microsampling) as an alternative to usual care (UC) (in-office visit; venipuncture blood sampling). The specific aims are (1) to assess the non-inferiority in seizure control (primary outcome) of follow-up procedures through VC with mobile devices versus UC in both adult and paediatric PWE, possibly improving patient-centred outcomes, that is, adherence to treatment, adverse events (AEs) and/or ADR, QoL, mood disorders, patient and caregiver satisfaction, safety and costs (TELE-EPIC\_RCT); (2) to compare ASM blood concentrations obtained by VAMS to matched plasma concentrations adopting the same LC-MS/MS reference method (MassTox TDM BASIC kit, Chrom-systems, Germany) and to also compare ASM concentrations in nurse-collected versus self-collected blood by VAMS (TELE-EPIC\_VAMS).



**Figure 2:** Flow-chart of the randomized controlled trial (TELE-EPIC\_RCT)



**Figure 2** Flow chart of the randomised controlled trial (TELE-EPIC\_RCT). ADRs, adverse drug reactions; ASMs, anti-seizure medications; TM, telemedicine.

## Study design

### TELE-EPIC\_RCT

This is a multicentre, open, pragmatic two-arm RCT prospectively including consecutive outpatients with epilepsy of all ages, to assess the non-inferiority in seizure control of patient management (provided by expert epileptologists) through VC with a TM device versus UC. The non-inferiority design is justified by the possibility that management by TM instead of UC could worsen seizure control.

TELE-EPIC\_RCT will also assess patient-centred outcomes such as adherence to treatment, AE, QoL, mood disorders, patient and caregiver satisfaction, safety and costs, in the two groups. We expect the TM approach to significantly improve other patient-centred outcomes compared with UC.

## Participants and setting

Adult (age  $\geq 18$  years) and paediatric (age  $< 18$  years) outpatients with established diagnosis of epilepsy consecutively attending the Epilepsy Centres of Bologna and Rome, respectively, will be enrolled over a 1-year period. All the patients included underwent an accurate clinical, neurophysiological and neuroradiological assessment at the sites of the study. Epilepsy diagnosis was established according to the current International League Against Epilepsy (ILAE) classification.<sup>26</sup> We excluded (1) patients with comorbid psychogenic non-epileptic seizures, as documented by video-electroencephalogram (EEG) recording or home-video of the events; (2) patients requiring a direct and close assessment, that is, patients with vagus nerve stimulation therapy that need titration or adjustments of stimulation parameters, or pregnant woman; (3) cases with pending epilepsy surgery or intracranial evaluation that cannot be delayed beyond the scheduled follow-up visits (at 6, 12 and 18 months).

The two referral centres have similar patient flows and organisation in terms of patient management. Following an accurate diagnostic work-up, PWE are followed up in an

outpatient control regimen. Control visits are scheduled depending on clinical severity. Over a 2-month period (1 February–30 March 2018), the two centres provided 314 visits (for 297 outpatients) and 244 visits (for 237 outpatients), respectively. The percentages of consultations for extraregional PWE were 23.3% for the adult centre of IRCCS, Bologna, and 27.9% for the paediatric centre of IRCCS in Rome (table 1). Both centres assessed PWE with variable severity, including cases with intellectual disability (ID) or other major disability (30% and 38.4%, respectively). The percentage of (1) seizure-free (SF) PWE, (2) PWE with refractory epilepsy<sup>27</sup> and (3) PWE in an ‘unstable’ condition, requiring closer medical monitoring (SF that were tapering ASM, recent relapse of seizures for poor compliance) overlapped in the two centres (table 1).

## Procedures and intervention

The flow chart of the TELE-EPIC\_RCT is illustrated in figure 2. All consenting PWE will undergo a baseline in-person visit by the referral neurologist, focused on seizure frequency (as reported in the seizure diary), assessment of ASM levels, surveillance of ADR, AE and possible comorbidities, according to the standard procedures.

PWE who provide informed consent will be enrolled and randomly allocated to TM care or to UC in a 1:2 ratio. Randomisation will be stratified by age, namely in the recruiting Epilepsy Centre (children in Rome, adults in Bologna). The randomisation list and allocation will be generated by an automatic web-based system after inclusion.

After recruitment, a 6-month, 12-month and 18-month follow-up period will be scheduled. PWE allocated in the UC group will be seen by standard in-office consultations with outcome assessment, counselling and follow-up. On-call consultations are possible if required by the patient, by contacting a clinician through an in-office phone call, 3 hours/week. For the VC group, an expert epileptologist, by means of an equipped in-office PC, will examine the patient connected through a personal device (PC or tablet), providing remote outcome assessment, counselling and follow-up.

If required, on-call VC will be available by contacting a provider through TM, 3 hours/week. VC will be performed through an institutional-approved platform (Microsoft Teams application).

To professionalise and ensure the quality of the VC experience, VC visits will be conducted in dedicated outpatient spaces. Standard video conferencing set-up requirements will be applied: sitting in front of a plain background (ie, a blank wall) with even lighting, keeping the computer’s camera at eye level.

Patient-centred outcomes will be assessed in all individuals at baseline and during the follow-up, using standardised methods and age-specific electronic self-administered questionnaires, as detailed in table 2. Questionnaires will also be administered to relatives/caregivers of paediatric patients and adult PWE with ID.

**Table 2** Primary and secondary (patient-centred) outcomes and related measurement tools for paediatric and adult PWE

|  | Age group                |                    | Timing              |
|--|--------------------------|--------------------|---------------------|
|  | Paediatrics (0–18 years) | Adults (≥18 years) |                     |
| <b>Seizure control</b>                                   |                          |                    |                     |
| Seizure diary  | √                        | √                  | 0, 6, 12, 18 months |
| <b>Patient satisfaction and patient-centred outcomes</b> |                          |                    |                     |
| Beck depression inventory                                |                          | √                  | 0, 6, 12, 18 months |
| Quality of life in epilepsy                              |                          | √                  | 0, 6, 12, 18 months |
| State-trait anxiety inventory 1 (STAI 1)                 |                          | √                  | 0, 6, 12, 18 months |
| STAI 2   |                          | √                  | 0, 6, 12, 18 months |
| Child behaviour checklist                                | √                        |                    | 0, 6, 12, 18 months |
| Paediatric quality of life inventory (PedsQL)            | √                        |                    | 0, 6, 12, 18 months |
| PedsQL_ parents  | √                        |                    | 0, 6, 12, 18 months |
| Clinical global impressions                              | √                        | √                  | 6, 12, 18 months    |
| <b>Safety and costs</b>                                  |                          |                    |                     |
| Adverse events profile                                   | √                        | √                  | 0, 6, 12, 18 months |
| Costs questionnaire                                      | √                        | √                  | 6, 12, 18 months    |
| <b>Technical issues</b>                                  |                          |                    |                     |
| Failure system reports*                                  | √                        | √                  | 6, 12, 18 months    |

\*Only VC via TM arm.

PWE, persons with epilepsy; TM, telemedicine; VC, video consultation.

## Outcomes

The primary outcome is the non-inferiority of VC on seizure control (assessed through a seizure diary) after an 18-month follow-up. Seizure control is defined as avoiding clinical worsening according to at least one of the following: (1) fall of at least two positions of the following frequency categories: daily/multiple per day; multiple/week, weekly; multiple/month, monthly; multiple/year, annual; (2) relapse after SF; (3) new onset/relapse of convulsive seizures, tonic/atonic seizures with fall, status epilepticus.

Secondary outcomes are adherence to treatment, AE and/or ADR, QoL, mood disorders, patient and caregiver satisfaction, safety and costs. Secondary outcome measures are collected at baseline and after randomisation at the end of the 6-month, 12-month and 18-month follow-up period. Table 2 details, for each outcome, the measurement tool applied based on age groups and the timing of the assessment.

## Sample size and statistical considerations

A total of 594 patients (198 arm TM, 396 UC) is required to prove that the 95% lower limit of one-sided CI will be above the non-inferiority limit of 7.5% (the difference of clinical worsening between the two arms), to prove the non-inferiority of TM versus UC, with 80% power.

The achievement of the sample size is highly feasible, in consideration of the catchment area of both the Epilepsy Centres and the long enrolment period.

Primary analysis will be undertaken on an intention-to-treat basis. A per-protocol analysis of the primary

outcome will also be carried out, excluding participants with protocol deviations (people assigned to the VC arm requiring in-person care due to clinical worsening).

A logistic regression model with clinical worsening as the dependent variable and arms (TM vs UC) as the independent variable will be used to evaluate the primary outcome. Corrections based on clinical severity (refractory epilepsy, ID, comorbidities) will be considered. Subgroup analysis stratified by age will be performed. Non-parametric analysis will be used to evaluate the secondary outcomes.

## Safety assessments

It is possible that a lower-than-expected number of PWE accepts the offer to participate in TELE-EPIC. They may show resistance to participating in the TM group for fear of less accurate assistance or due to the digital divide. This possibility should be minimised by a 2:1 randomisation ratio. Moreover, patients will be assured that, in the event that they are assigned to the VC arm, they would have regular access to the Emergency Hospital of reference in case of medical emergencies and, in the event of concerning clinical symptoms that cannot be managed via TM, they will be visited directly by the referral epileptologist.

In addition, we could have a high drop-out rate in the TM group due to technical difficulties. We will deal with both these aspects by educating the PWE on the TM procedures and technical assistance. In particular, at the moment of enrolment (baseline, in-person visit), patients assigned to the VC arm will receive accurate information

and written instructions from the study coordinator on the use of the PC-based VC. To simplify the visit and avoid technical problems, a link will automatically be sent to the patients for direct access to the video-call through Microsoft Teams.

### Patient and public involvement

Patients and the public were not involved in the study design.

### Roles

The Epidemiology and Statistics Unit of the IRCCS, Istituto delle Scienze Neurologiche di Bologna (two epidemiologists and one statistician) will act as the coordinating centre with the role, in both recruiting centres, of supervision and auditing of trial conduct (monthly check in the recruiting phase, bimonthly in the follow-up phase), data monitoring and final statistical analysis. One epileptologist for each centre, as principal investigator, will be in charge of decision on eligibility, recruitment and clinical follow-up of participants. One study coordinator for each centre will manage any organisational activity of the trial (eg, participant reception, scheduling of follow-up visits, data entry supervision, etc).

### Data entry, coding and security

A contract research organisation will be designated to provide several clinical trial management services, principally including (1) development and validation of electronic case report forms (eCRFs), ad hoc designed by clinicians for the project; (2) design, implementation and validation of electronic systems to collect patient-reported outcomes (e-PRO); (3) development and validation of a complex flow aimed at the creation of questionnaire packages based on age groups.

All clinical data will be entered electronically in the e-CRF directly by the clinician during the visit (clinical data). PWE or caregivers will be asked to directly fill in the e-PRO questionnaire through a personal electronic device or, if not available, via a tablet provided by the study staff.

The e-CRF is designed and validated for data security and storage according to international standards [US Food and Drug Administration (FDA): 21 Code of Federal Regulations (CFR) Part 11; European Union (EU) Good Manufacturing Practice (GMP): Annex 11; International Conference on Harmonization/Good Clinical Practice (ICH/GCP); Veterinary International Conference on Harmonization/Good Clinical Practice; Good Automated Manufacturing Practice/General Data Protection Regulation (VICH/GCP; GAMP 5; GDPR). Personal information about participants will be processed in accordance with the GDPR and national regulation on data protection. The coordinating centre and the two principal investigators will have access to the final trial dataset.

### TELE-EPIC\_VAMS

This is a cross-validation study for ASM analysis through a VAMS-based device (Mitra, Neoteryx, Torrance,

California, USA) comparing (1) VAMS-based method versus plasma samples method (reference standard method) in a routine laboratory setting; and (2) nurse-collected versus self-collected blood by VAMS, according to international guidelines.<sup>28</sup>

TELE-EPIC\_VAMS will cover the adult cohort of the study. At baseline, venous blood samples (5 mL) will be drawn at 08:00 from each outpatient recruited at the Epilepsy Centre of IRCCS in Bologna (about 300 adults). Blood samples will be collected using VAMS devices at the same time by a nurse and by the patient himself or herself. Venous blood samples will be centrifuged at 1700 g for 10 min at 4°C and stored at -20°C. VAMS specimens will be dried for 1.5 hours at room temperature (21°C–25°C) and then stored at room temperature in sealable polyethylene bags containing silica gel without light exposure. For cross-validation assessments, the same set of study samples, (1) VAMS blood versus plasma and (2) nurse-collected versus self-collected VAMS blood, will be analysed for ASM quantitation by LC-MS/MS within 1 month from the collection. The difference between the two obtained values should be within 20% of the mean for at least 67% of the determinations.<sup>28</sup>

To estimate the impact of ASM measurement on patient management, we will carry out a subgroup analysis exploring the association between the finding of out-of-range ASM plasma levels and the variable 'clinical management', arbitrarily defined as any therapeutic intervention aimed at improving seizure control or at managing ASM-related AE.

### ETHICS AND DISSEMINATION

The study has been approved by the Independent Ethics Committee of Area Vasta Emilia Centro (349-2019-SPER-AUSLBO) on 1 June 2019.

Signed informed consent form (online supplemental file 1) will be obtained by the referral epileptologist prior to recruitment. Consent for patients aged <18 years old and for individuals with ID will be provided by their parents and/or guardians. Both participants and parents/guardians will be free to withdraw their consent for participation at any time.

Complete information about the state of the project, relevant events and results will be regularly updated on the project's webpage on ClinicalTrials.gov. The project's results and data on the potential impact of telemedicine in epilepsy will be disseminated on social media. A closeout meeting will be convened for the communication and dissemination of the project, highlighting its main achievements and impacts. The final trial publication will follow the International Committee of Medical Journal Editors (ICMJE) authorship criteria (<http://www.icmje.org/>), without use of professional medical writing support.



## DISCUSSION

One of the major challenges in neuroscience is optimising the care of PWE with chronic disease by simplifying patient management and reducing health costs.

Epilepsy is a chronic disease with complex needs encompassing medical and psychosocial aspects. PWE require long-term specialist follow-up, ASM monitoring and familial support, given the restrictions they experience in social, economic life and driving. The Epilepsy Centres of the IRCCS in Bologna and Rome offer specialised care and management for adult and paediatric PWE coming from all Italian regions. During the COVID-19 pandemic, most scheduled control visits were cancelled, with detrimental effects on patients' health. This situation highlighted the importance and usefulness of TM in enabling many key clinical services to continue operating regularly and without interruption in the course of a public health emergency, minimising the risk of infection transmission.<sup>29</sup> Remote systems including different types of communications (phone calls and VC by one-way video links and on live interactive communication) were used to replace face-to-face visits for PWE's follow-up.<sup>30</sup> Many governmental establishments have endorsed the use of TM during the COVID-19 era, encouraging health institutions to implement TM services. In Italy, following the agreement sanctioned on 17 December 2020 by the State-Regions conference ('National guidelines for the provision of telemedicine services'—<http://www.statoregioni.it/media/3221/p-3-csr-rep-n-215-17dic2020.pdf>), several TM services have been formally included among the resources provided by the National Health System (NHS), including VC. An examination of the principal evaluation indicators (ie, coverage, hours available for VC, technical issues, patient satisfaction) is essential for reducing health inequities in TM (<https://iris.paho.org/handle/10665.2/28562>), but these are not routinely assessed in the published studies.

Combining several innovative, patient-centred approaches, the project will assist PWE living sparsely across the country, ensuring complete coverage of the national territory. Specifically, VC via TM, combined with novel methods of ASM measurement based on home self-sampling, represents an innovative, promising approach that will lower travel and medical costs for PWE, their families and the NHS.

We expect that seizure control will not be worse in the TM group compared with UC group. Moreover, management through TM will improve patient-centred outcomes (adherence to treatment, side effects, QoL, patient and caregiver satisfaction, safety and costs), guaranteeing a high quality of care. Secondary outcomes will be further enhanced by applying a validated VAMS sampling, which allows self-collection of an exact quantity of blood sample with minimal training. Since this can be performed anywhere, it also reduces the need for hospital visits.

If the study results are in line with our hypotheses, TELE-EPIC will first provide evidence of the effectiveness of TM for the follow-up of PWE in Italy, also offering

useful information for its implementation in 'real-world' clinical practice. The project offers the opportunity to provide specialised care to PWE, avoiding the disadvantages of a centralised model. In addition to epilepsy, this innovative strategy could also be applied to other neurological chronic diseases (teleneurology) in order to improve disease-related outcomes and optimise NHS resources. Thus, the TELE-EPIC Study will first provide robust, RCT-based data for the application of TM for management of epilepsy.

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