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Efficacy and economic evaluation of delivery of care with Tele-continuous EEG in critically ill patients: a multicenter randomized controlled trial (Tele-cRCT Study)

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Abstract

Introduction: Some critically ill patients are disclosed by continuous electroencephalography (cEEG) monitoring due to nonconvulsive seizure (NCS) and/or nonconvulsive status epilepticus (NCSE). Shortage of epilepsy specialists, especially in developing countries, is a major limiting factor to implement the cEEG in general practice. Delivery of care with the Tele-cEEG may be a potential solution as specialists from a central facility can remotely assist local neurologists in distant areas to interpret the EEG findings and suggest proper treatment. Until now, no Tele-cEEG program has been implemented to help improve quality of care, particularly for status epilepticus patients.

Methods and analysis: Tele-cRCT is a 3-year prospective, randomized, controlled, parallel, multicenter, superiority trial comparing delivery of care with "Tele-cEEG" intervention with "Tele-routine EEG (Tele-rEEG)" in patients with clinical suspicion of NCS/NCSE. A group of EEG specialists and Tele-EEG system were set up to remotely interpret the EEG in the 6 regional government study hospitals across Thailand. A de-centralized telehealth system where specialists can flexibly review the EEG from any location and opened communication architecture will be used. Primary outcomes are functional neurological outcome [modified Rankin scale (mRS)]; mortality rates; and incidence of seizures. Secondary outcomes are cost-utility; length of stay; emergency visit/readmission; impact on changing medical decision-making; and health professional perceptions about Tele-cEEG implementation. Functional outcome (mRS) along with costs, and health-related quality of life using Thai-version EQ-5D-5L will be assessed at 3 and 7 days after recruitment and again at time of hospital discharge, 90 days, 6 months, 9 months, and 1 year.

Ethics and dissemination: This study has been approved by the Faculty of Medicine, Chulalongkorn University and Faculty of Medicine, Ramathibodi Hospital, Mahidol University Ethics Committee and registered on Thai Clinical Trials Registry. The results will be disseminated in a peer-reviewed journal.

Trial registration number: TCTR20181022002; Pre-results.

Strengths and limitations of this study

- This study is the first study assessing the efficacy and cost-utility of implementing the Tele-cEEG in critical care
- This study is also among very few studies assessing efficacy of the cEEG on functional outcome and mortality
- This study is limited to implement the Tele-cEEG in only advanced level hospitals in distant areas. As a result, the results cannot be generalized to apply in the smaller scale hospitals where neurologists are not available and drug items and/or investigations are limited.

Introduction

Status epilepticus (SE) is a life-threatening medical and neurologic emergency requiring prompt recognition and treatment. A recent meta-analysis including 43 studies reported a pooled crude annual incidence rate of SE of 12.6/100,000 (95% CI 10.0-15.3) [1]. The pooled case fatality rate and the pooled crude annual mortality rate of SE were 14.9% (95% CI: 11.7-118.7) and 0.98/100,000 (95% CI: 0.74-1.22), respectively [1]. Based on the National Database of Thailand during the 2010 fiscal year, the SE rate in Thailand was 5.10/100 000 population, with a mortality rate of 0.6 death/100 000 population [2].

SE can manifest with either overt convulsive movements or subtle/no overt convulsion. The former and the latter have been known as "convulsive status epilepticus (CSE) and "nonconvulsive status epilepticus (NCSE)", respectively. In practice, EEG recording is required to help in diagnosis of nonconvulsive seizure (NCS)/NCSE, otherwise, it may be under-recognized and left untreated [3]. Our recent meta-analysis revealed that continuous EEG (cEEG) is significantly better than the routine EEG (rEEG) to help detect NCS/NCSE. Overall prevalence of NCS/NCSE is 15.6% in critically ill patients, but higher in post convulsive SE (32.9%), central nervous system (CNS) infection (23.9%), and post cardiac arrest (22.6%) [4]. Evidences of systemic complications and neurological consequences have been clearly demonstrated in CSE [5], but remain unclear for NCS/NCSE. Previous observational studies did not address clear results as to whether the unfavorable outcome of study patients was a direct consequence of NCS/NCSE or the result of other potential confounding factors i.e. patient's

characteristics, etiology, and treatment [6 7]. As a result, the aggressiveness to treat patients with NCS/NCSE is unknown and varies among treating physicians [6].

Although EEG recording is necessary for helping in detection of NCS/NCSE, its routine use, particularly cEEG monitoring, has been still an issue because it is costly and requires specialists to interpret the findings [3]. Due to shortage of epilepsy specialists, especially in developing countries, cEEG implementation in general practice is therefore limited. Delivery of care with a telehealth system [8] may be a promising solution this problem as specialists can remotely assist general physicians in distant areas to interpret EEG findings and suggest proper management. Until now, no one has implicated the Tele-cEEG system in helping improve quality of care particularly for SE patients. By doing this, at the same time we can assess prospectively both the benefit of Tele-cEEG and neurological consequences of the NCS/NCSE.

The Tele-cRCT study is a multicenter randomized controlled trial (RCT). With an RCT design, efficacy evidence of the Tele-cEEG implementation will be addressed with valid results since potential confounding factors will be balanced and adjusted between two groups of comparison. Alongside economic evaluation, cost-utility analysis of the Tele-cEEG will be also addressed and can be introduced to the community in order initiate the adoption of this Tele-cEEG in routine practice.

Methods and analysis

Study design and setting

Tele-cRCT is a 3-year prospective, randomized, controlled, parallel, multicenter, superiority trial comparing delivery of care with "Tele-cEEG" intervention with "Tele-rEEG" in patients

with clinical suspicion of NCS/NCSE. A group of EEG specialists and Tele-EEG system were set up to remotely interpret the EEG in the study hospitals which are 6 regional government hospitals across Thailand. All six study hospitals have met our eligibility criteria which are 1) Regional hospitals defined according to Ministry of Public Health of Thailand as hospitals in service plan A (Advance-level hospital) with capability to treat patients who require advance and sophisticated technology; 2) Having surgical or medical ICUs which are run by qualified medical professionals, and sufficiently require medical equipment in the ICUs, corresponding to any level of three-tiered system ICUs proposed by the American College of Critical Care Medicine (ACCM) [9]; 3) Having capability to operate the EEG recording in the ICUs or wards; 4) Having neurologists who are capable to treat status epilepticus with available necessary medications recommended by 2016 American Epilepsy Society (AES) guideline [10] and having capability to do etiology work up of status epilepticus, suggested by the 2012 Neurocritical Care Society [3], but 5) No qualified epileptologists to interpret the EEG; and 6) cEEG monitoring is not part of the hospital's routine service.

Both intervention (Tele-cEEG) and control (Tele-rEEG) arms will be assisted by a specialist team to interpret the EEG findings and suggest appropriate treatment in order to standardize a "specialist factor" which might affect study outcomes. It should be noted that the EEG recording, even a rEEG, is under-utilized in Thailand due to a severe shortage of epileptologists and neurologists who are comfortable and confident to interpret EEG findings. Routine care for patients suspicious of NCS/NCSE in Thailand does not necessarily include the EEG study. As a result, we decided not to have the third arm with a pure routine care without assistance from specialists, given concerns of selection bias. This is due to the fact that some

of eligible patients assigned to this arm (pure routine care) will not receive any EEG recording. If this happens, the results of this arm will not be compared with the other two arms. Study flow is shown in Figure 1.

Study objectives

Between intervention (Tele-cEEG) and control (Tele-rEEG) arm, our primary objective is to compare the efficacy in terms of functional outcomes (mRS) and mortality rate assessed at 3, 7 days after recruitment, at discharge, 90 days, 6 months, 9 months, and 1 year after hospital discharge, as well as detection rate of seizures during hospitalization. The secondary objective is to compare efficacy of ICU/hospital length of stay (LOS), emergency/readmission, cost-utility, impact on changing of medical decision-making, and healthcare professional perceptions about the Tele-EEG implementation.

Screening and randomization

A dedicated nurse in each study hospital screens for eligible patients in every new admission or new neurology consultation from adult ICUs or medical or surgical wards to see whether or not potential study subjects fulfill one of the five conditions indicated in the inclusion criteria, listed in Box 1. Eligibility is then confirmed with a neurologist at study site. In case of fulfilling eligibility, a nurse will be providing study information to patients or caregivers and then requesting for signed informed consent. A nurse will then log-in in order to fill out the study web-based screening form, if the patient is eligible the system will be automatically operating a central randomization and then assigning study intervention (Tele-cEEG vs Tele-rEEG) along with the patient's subject identification number for the study. A block randomization will be

applied. Since this study is not double-blind where health care teams will not be blinded to the intervention, in order to protect the integrity of the randomization process randomly selecting the block size will be performed prior to randomly select the patient. The block sizes will be 4, 6, 8, and 10. A ratio of intervention and control is 1:1. Statisticians at the central site will generate random sequences of assigned intervention using STATA version 15.0. Study flow and investigator's role are shown in Supplemental Figure 1.

Box 1: Inclusion and exclusion criteria for patient enrolment

Inclusion and exclusion criteria for enrolment
Inclusion criteria
1. Adults, aged ≥ 15 years, who are admitted in surgical or medical ICUs or wards
2. Suffering from at least one of the 5 conditions which are recommended by the 2012 Neurocritical Care Society[1] as well as corresponding with the results of our meta-analysis[2] to be highly associated with NCS/NCSE 2.1 Recent clinical seizure/status epilepticus without return to baseline (pre-status) with - In case of receiving sedative medication: at > 10 minutes after clinical seizure/SE ends, patient's GCS does not return to baseline - In case of not receiving sedative medication: at 2 hours after clinical seizure/SE ends, patient's GCS does not return to baseline 2.2 Severely depressed consciousness from any cause (except for TBI, SAH, ICH) with GCS ≤ 8 2.3 Intracranial hemorrhages with any of - TBI with GCS 6-12 - SAH with Hunt & Hess Classification grade ≤ IV or GCS > 5 - ICH with ICH score ≤ 3 2.4 Suspected NCS/NCSE in patients with altered mental status (cause indeterminate) 2.5 CNS infection with altered mental status
3. Willing to participate with the study, given signed informed consents
4. Patients or caregivers which are defined as the main person, other than a health, social, or voluntary care provider can provide functional outcome data after discharge
Exclusion criteria
1. Patients with post cardiac arrest
2. Patients with advanced stage cancer (stage IV)
3. Patients with AIDs (CD4 count < 200 cells/mm^3 or with certain opportunistic infections)
4. Patients with alcoholic intoxication with/without delirium tremens*
5. Patients with poor functional outcome at pre-admission state (mRS 4-6)
6. Patients with extensive lacerations, skin lesions, or surgical wound where the electrode placement is not able to be applied

Abbreviations: NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; GCS = Glasgow Coma Scale; TBI = traumatic brain injury; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; CNS = central nervous system; mRS = modified Rankin Scale

[1] Brophy GM et.al., 2012; [2] Limotai C et.al., 2019

* These patients are excluded due to the fact that there are a large number of these types of patients in rural areas of Thailand and may significantly outweigh other types of patients included, where there has been no reported magnitude of its association with NCS/NCSE.

Allocation concealment

In order to prevent selection bias, the process of central randomization will conceal the allocation sequence from those assigning participants to intervention groups until the moment of assignment.

Blinding

As the nature of assigned intervention is different and easy to recognize (i.e. continuous (prolonged) versus rEEG (short) EEG recording), participants will not be blinded to the intervention assigned. Health care teams including physicians and nurse also will not be blinded because they will be involved in the patient care using either cEEG or rEEG. However, dedicated outcome assessors will be blinded to patient allocations.

Intervention

This study consists of two arms which apply two different interventions; one with Tele-cEEG (intervention arm) and the other with Tele-rEEG (control arm), see Figure 2. Since important study outcomes are functional outcomes and mortality after SE, a specialist team will assist the control arm (Tele-rEEG) to interpret EEG findings and suggest appropriate treatment in order to standardize a specialist factor which might affect the outcomes.

Tele-EEG system and database: Central facilities for the Tele-EEG system/EEG database and the patient's database were respectively set up at Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC) and the Section for Clinical Epidemiology and Biostatistics, Ramathibodi Hospital (Rama CEB). Two separate EEG review systems will be set up. One for real-time review with TeamViewer® software and the other for off-line review using EEG data uploaded on cloud storage. For off-line review, EEG data uploaded on cloud storage will be downloaded into EEG database server at CCEC on a daily basis. Upon being in charge, each EEG specialist can connect to the EEG machine at study sites and EEG server at CCEC for real-time and off-line review, respectively at anytime and from anywhere via internet ("De-centralized system"), see Figure 3. For both real-time and off-line review, password access control will be used.

Methods of conducting Tele-EEG: The EEG recording must be initiated within 24 hours after recruiting (randomization) patients in both arms (Tele-cEEG vs Tele-rEEG). Within working hours (8 am to 4 pm), an EEG technician will apply the EEG electrodes, where at the same time, an in-charge specialist on that day will be notified to prepare for EEG review. After completing internet connection set-up, Tele-EEG system integrity will be checked at both ends.

For the Tele-cEEG, a specialist will periodically report the EEG findings using standard case record form (CRF) every 2 or 6 or 12 hours, depending on clinical urgency determined by clinical data and initial 30-minute prior EEG findings. EEG will be monitored for at least 24 hours. If seizures are detected, the Tele-cEEG will be continued and

discontinued after 72 hours. However, if seizures are still present at 72 hours, the Tele-cEEG can be continued and then discontinued after seizure cessation for 12 hours. Continuation of Tele-cEEG monitoring after 72 hours will be treated as co-intervention, see Figure 2.

For the Tele-rEEG, a specialist will interpret the EEG findings and feedback the results using the standard CRF to the treating neurologist at bedside within 4 hours after finishing the EEG study. EEG will be monitored and recorded for 30 minutes. Switching the Tele-rEEG to the Tele-cEEG is possible if the initial findings disclose seizures and/or epileptiform activity or periodic discharges. These specific EEG findings were reported by 2012 the Neurocrititical Care Society guideline to be highly associated with NCS/NCSE [3]. In this case, the Tele-cEEG will be treated as co-intervention, see Figure 2.

In both arms, standard consensus protocols for investigations and management of SE will be followed for all patients. An in-charge specialist will discuss the EEG findings with the treating neurologist at bedside and then appropriate management according to the consensus protocols. Flexible connectivity where specialists who review the EEG can access patient medical information on cloud storage via internet ("Open communication architecture"), see Supplemental Figure 2. Communication between specialists and treating neurologists is limited to traditional telephonic modalities and are functionally outside the Tele-EEG system, see Supplemental Figure 2.

EEG reviewing organization: Nine EEG specialists included for this study are all certified epileptologists with training in either Thailand and/or North America (US and Canada). All EEG specialists will be assigned to be on-call for reviewing the EEG. Each on-

call duration lasts for 24 hours (7 am to 7 am on the following day). EEG specialists are responsible to review both the cEEG and rEEG on that day. An EEG specialist will give his/her report to the other EEG specialist on the following day by verbal communication using a unified EEG finding and list of management report forms to ensure continuity of the appropriate management.

Standard consensus protocols for investigations and management of SE were developed using Modified Delphi method [11 12]. All nine EEG specialists were invited to perform on-line Google survey and then face-to-face discussion in order to make consensus protocols on how to report the EEG findings and manage SE. The terminology and definition of the EEG wave forms used in this study will be mainly based on the American Clinical Neurophysiology Society (ACNS) proposed standardized terminology 2012 version [13]. A unified EEG report form will be created as part of web-based CRF. Twenty EEG tracings with a variety of common EEG findings in critically ill patients were prepared and then used to test inter-rater agreement (kappa) among EEG specialists.

Study outcomes: Primary and secondary outcomes are listed in Box 2.

Box 2: Primary and secondary outcomes

Primary and secondary outcomes
Primary outcome
1. Functional outcomes including poor (mRS 4-6) versus favorable (mRS 0-3) functional outcomes, and actual scores of mRS which will be assessed at 3 and 7 days after starting EEG recording (recruitment), at discharge, 90 days, 6 months, 9 months, and 1 year.
2. ICU/in-hospital case fatality rate during hospitalization and crude annual mortality rate assessed at 1 year after hospital discharge
3. Cumulative incidences of each type of seizures i.e., pure NCS/NCSE, combined NCS/NCSE and CS/CSE, and pure CS/CSE in the intervention and control arms
Secondary outcome
1. ICU and hospital length of stay
2. Emergency visit and re-admission after hospital discharge assessed at 90 days, 6 months, 9 months, and 1 year
3. Health-related Quality of Life, assessed by Thai-version EQ-5D-5L at hospital discharge, 90 days, 6 months, 9 months, and 1 year
4. Costs assessed at hospital discharge, 90 days, 6 months, 9 months, and 1 year
5. Impact of change of medical decision making of the treating neurologists at study sites; a structured questionnaire will be assessed immediately after patient recruitment but prior to knowing the EEG results and then compared with the actual activities (investigations/treatment) after integrating the EEG findings with other clinical data
6. Health professional perceptions about Tele-cEEG implementation; a structured questionnaire will be evaluated by nurses and neurologists at study sites, assessed at 1 year after conducting the study

Abbreviations: mRS = modified Rankin Scale; NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; CS = convulsive seizure; CSE = convulsive status epilepticus

Sample size calculation

The primary outcome used for estimation of sample size is functional outcome measured by mRS. It is dichotomized into favorable (mRS 0-3) and poor outcomes (mRS 4-6). The formulae for the number of participants is estimated as follows [14]:

$$N = \left(z_{\alpha/2} + z_{\beta}\right)^2 \frac{\pi_0(1-\pi_0)+\pi_1(1-\pi_1)}{(\pi_0-\pi_1)^2}$$

N = total number of participants; $Z_{\alpha/2} = 1.96$; $Z_{\beta} = 0.84$; π_0 = the true proportions in the control populations; π_1 = the true proportions in the in intervention arm

As for previous study by Khawaja et al [15], which up until now it is the only one available study assessing functional outcomes in critically ill patients who received cEEG

monitoring (intervention) and also in those who did not receive the cEEG (controls) [15], proportions of patients with poor outcome (mRS 3-6) were 0.919 for intervention and 0.829 for control groups. If we plan to detect the difference of poor functional outcome of 0.1 (which should be clinically meaningful), with setting a ratio of intervention vs control, type I and II errors of 1:1, 0.05, and 0.2; the estimated sample size is as follows:

$$N = (1.96 + 0.84)^2 \frac{0.829\ (1 - 0.829) + 0.729(1 - 0.729)}{(0.829 - 0.729)^2}$$

$$= 7.84 \frac{(0.142 + 0.198)}{0.01}$$

$$= 267$$

Assuming a 20% loss to follow up, the total number of participants required in each arm is 270 + 54 = 324. In summary, in order to have 80% power to detect a 10% reduction of poor outcomes at a 5% level of significance (2-sided), we require 324 participants in each arm; this would result in 648 participants in total.

Patient recruitment

A pilot study will be performed to assess whether there will be any recruitment issues in the designated study hospitals. The initial recruitment plan is 10-15 patients per month from each hospital. After the formal pilot study, this plan may be changed according to actual recruitment rate of each hospital. However, PI and/or coordinator nurse at the central site (CCEC) recruitment centers will be continuously monitoring and encouraging patients to join the study via telephone reminder. In order to prevent bias related to predominant participant

recruiting from one particular study site, actual recruitment rates from the pilot study will be used to weight the quota for recruitment from each hospital.

Patient and public involvement

Neither patients nor public have been involved during the design of the Tele-cRCT study. The Tele-cRCT study results will be available at https:// clinicaltrials. in.th/ to both patients and general public. Assessment of the burden of the intervention has not been foreseen in the present study.

Data collection and data statement

Case record form (CRF) was created according to information of the study variables, intervention, and outcomes. These are divided into 9 parts and were created in paper-based forms, except for patient screening and EEG findings forms which both were created in web-based CRF (see Supplemental Table 1). Timing of data collection is shown in Supplemental Table 2. After ethics committee approval in each study hospital and obtaining written signed consent from patients or caregivers, principal investigators (PI) then asked for permission to access patient information to collect the patient data in respective study hospitals.

Participant neurologists assigned to be sub-PIs in each study hospital will help facilitate accessing archived raw data. Study variables and outcomes will be collected at enrollment period after randomization, then put in the CRFs. Independent outcome assessors (either sub-PIs or coordinator nurses at study hospitals) will assess the primary and secondary outcomes.

Data management

Conversion of the paper-and web-based CRF into an electronic database (EpiData Version 3.1, The EpiData Association, Odense, Denmark) is planned. Data entry will be assigned to two data entry staff. Patient database files will be kept in a personal computer at Rama CEB and also backed up in the PI's notebook. These two computers require passwords to access the database. Scheduled site visits for data audits will be arranged for each participant hospital every 1-2 months during the first 6 months and then every 3 months. In order to ensure appropriate intervention delivery, all completed competency assessment tools will be returned to the PI and will be included as a standard monitoring report to the Data and Safety Monitoring Board (DSMB). Manual, interactive, and batch checking methods will be used to ensure completeness and correctness of the data. In order to maintain high quality of the data, regular meetings to check for data correctness give feedback between data collectors and data entry staff will be arranged on a montly basis.

Data analysis plan

Descriptive statistics: Baseline characteristics between Tele-cEEG and Tele-rEEG arms are presented in mean with standard deviation (SD) or median with interquartile range (IQR) for continuous data depending on distribution of the data. For categorical data, frequency and percentage are presented. To compare characteristics of patients between groups, Pearson chi-square or Fisher exact test will be applied for categorical data; Student t-test or Mann-Whitney test for normal and non-normal distributed continuous data will be used.

Imputation: Imputations will be performed using STATA software version 15.0. Missing data will be explored to assess whether distribution of missing data is missing at random (MAR), if not this is said to be nonignorable. Multiple imputation (MI) will be applied. The number of imputation will be determined by percentage of missing values and MI performance [16], reflected by relative variance increased and fraction of missing information values.

Analytical statistics: Statistical methods will depend upon how the outcomes are being measured and the type of outcomes, either dichotomous or continuous, as summarized in Supplemental Table 3. Regarding time to event data analysis of functional outcome (mRS), the start date will be set as date of starting EEG recording. Patients will be initially stratified into having poor mRS 4-6) versus favorable outcome (mRS 0-3) at discharge. These two groups will be analyzed separately. A group with initial poor outcome, time to first ever favorable outcome analysis will be performed, whereas a group with initial favorable outcome time to first ever poor outcome will be estimated. Since death will be treated as competing risk thereby probabilities of developing interested events (poor or improved outcome) are not independent from probability of death, a cumulative incidence function (CIF)[17] will be used instead of KM method. The end date will be set as; date at end of study (1 year after hospital discharge), date of developing interested events; date of having competing risks, and date of loss to follow-up. Either cause-specific or subdistribution proportional hazard model will be used to estimate effect sizes and depends on whether or not the intervention (Tele-cEEG) has an effect on the hazards of competing risks (death) [18]. If it has no

effect, a cause-specific proportional hazard model with csHR will be reported. However, in the event of an effect, a subdistribution model with subHR will be reported.

Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE) will be applied to assess intervention effects [19] on functional outcome. A mixed effect model will be constructed as follows: First, intervention variable will be fitted as fixed-effect and random-effect in a multilevel equation with having poor/favorable function as the outcome variable. Second, a random-effect of intervention will be then constructed. A likelihood ratio will be applied to compare whether considering intervention effect as a random will improve model fitting. Adjusted odds ratio (OR) along with its 95% CI will be estimated.

Even if randomization is used, all of the prognostic factors may not be perfectly balanced. Covariate adjustment will be used in the analysis to minimize the effect of covariate imbalance. The following important covariates at baseline which may influence the study outcomes (i.e. functional outcome and mortality) will be adjusted; age (≥ 60 vs < 60 years) [20] [21], etiology of SE (acute vs chronic etiology) [21], and severity of the disease within 24 hours of admission (higher vs lower APACHE IV/SAPS II/GCS scores) [22]. The specific adjustment procedure depends on the type of covariate being adjusted for and the type of outcome being analyzed. In this study, both primary response variables (primary outcomes) and important covariates are categorical (i.e. age, etiology of SE, severity of disease), "a stratified analysis" taking the form of a Mantel-Haenszel (MH) statistic will be used. Study participants will be subdivided into smaller, more homogenous groups, or strata will be used. A comparison of

study groups will be made within each stratum and then averaged over all strata to achieve a summary result for the outcome.

Pre-specified subgroup analysis: We plan to perform a subgroup analysis on covariates which potential effect modifiers of the intervention effects. This may help identify the specific population most likely to benefit from or to be harmed by the Tele-cEEG. The following subgroup analysis will be assessed; Old age (≥ 60 years) vs younger (< 60 years); Patients with severe diseases (i.e. higher score) vs milder severity (i.e. lower score). This will be based on APACHE IV, SAPS II, GCS within 24 hours of enrolment; Indications for EEG study (prior clinical seizure/SE without recovery, coma, severely depressed LOC, intracranial hemorrhages, suspicious NCS/NSCE, CNS infection, and presence of epileptiform discharges or periodic pattern on initial EEG); Higher status epilepticus severity score vs lower scores (based on STESS and EMSE scores); and Type of SE (i.e. pure CSE vs pure NCSE vs combined CSE and NCSE).

Dealing with protocol violation: We will analyze with the following methods; 1) Intention-to-treat analysis: All participants and their outcomes will be included for primary analysis; 2) As-treated analysis: This will be used in cases as follows; a) patients who are initially randomized to receive Tele-rEEG but are subsequently switched to receive the Tele-cEEG as initial rEEG revealed seizure/epileptiform and/or periodic discharges, and b) patients with incorrect intervention allocation administration e.g. patients allocated to Tele-cEEG are incorrectly administered Tele-rEEG or vice versa; 3) Per-protocol analysis: This analysis refers to inclusion in the analysis of only those patients who strictly adhered to the protocol. Analysis flow is shown in Supplemental Figure 3.

Economic analysis

This is an economic analysis alongside the randomized controlled trial (trial-based economic evaluation). Costs and outcomes will be collected from all patients. We will perform cost-utility analysis (CUA) which enables the findings from our study to be compared with other healthcare interventions. This trial will evaluate economic analysis in view of societal perspectives including billing costs in order to assess whether the Tele-cEEG is economically feasible and worthwhile to implement in the context of Thailand.

Outline of interventions: By using TreeAge Pro 2016, a decision tree will be created using RCT-based data. This decision tree diagram will help depict choices of intervention, the logical structure of probabilities of conditions which could occur after applying the interventions, and values related to cost and utility associated with consequences related to each condition. Interested events discovered by the study interventions (Tele-cEEG and Tele-rEEG) are pure NCS/NCSE, combined CS/CSE and NCS/NCSE, pure CS/CSE, and no seizure. Decision tree diagram is shown in Supplemental Figure 4. Parameters and data sources for probabilities of interested events, cost, and utility are shown in Supplemental Table 4.

Cost analysis: Unit costs of services will be referenced on a price provided by the Center of Essential Information for All Health Officers, 2018. All costs will be converted to 2018 values using the Thai consumer price index (Bureau of Trade & Economic Indices, 2018). Lifetime time horizon is a cycle length of 1 year. All costs and outcomes occurring after 1

year will be discounted at a rate of 3%, as recommended in the Thai Health Technology Assessment guideline[23].

Determining cost-effectiveness: For primary economic analyses, with CUA cost per quality-adjusted life-year (QALY) gained based on EQ-5D-5L score will be examined. The EQ-5D-5L is a generic preference-based measure which a previous study in Thailand reported coefficients for converting to utility [24].

QALYs = number of years lived x utility

Utility can range from 0 as worst health state or death to 1 as best health state or healthy. To convert the EQ-5D-5L QoL score to utility, we use coefficients from a study by Pattanaphesaj J. (http://www.hitap.net/documents/89762) [24].

The Incremental Cost-Effectiveness Ratio (ICER) will be calculated as the formulation below [25]. The numerator will be the difference of mean total cost between intervention (Tele-cEEG) and controls (Tele-rEEG). Mean total cost is calculated by dividing the summation of all costs at discharge, 90 days, 6 months, 9 months, and 1 year in each patient (shown in Table 3.4) with total number of the patients. The denominator will be difference of QALY based on EQ-5D-5L score at 1 year between intervention and controls.

$$\text{ICER} = \frac{Mean\ (Total\ cost\ Tele-cEEG)\ -\ Mean\ (Total\ cost\ Tele-rEEG)}{Mean\ (QALY\ Tele-cEEG)\ -\ Mean\ (QALY\ Tele-rEEG)}$$

We will also derive 95% CI for the ICER. If the numerator (cost data) and denominator (QoL data) of the ICER follow a joint normal distribution, Fieller's method will be used [26]. However, if either data are non-normally distributed, a non-parametric bootstrap method will

be used [27]. The combination of 95% CIs for cost and effect differences will be shown in a graph to demonstrate a "confidence box" of the cost-effectiveness plane [27].

For the secondary economic analysis, ICER to represent additional cost per additional point on the mRS will be calculated as below. This will be separately assessed at 3 day and 7 days after starting EEG recording, at discharge, 90 days, 6 months, 9 months, and 1 year. In each time point, the numerator of the ICER will be the difference of mean total cost between intervention and controls. The denominator will be the difference of median mRS between intervention and controls at that time point. Cost-effectiveness plane and cost-effectiveness acceptability curves will be presented.

$$\text{ICER}= \frac{Mean\ (Total\ cost\ Tele-cEEG) - Mean\ (Total\ cost\ Tele-rEEG)}{Median\ (mRS\ score\ in\ Tele-cEEG) - Median\ (mRS\ score\ in\ Tele-rEEG)}$$

Uncertainty analysis: To handle cost analysis uncertainty, a Probabilistic Sensitivity Analysis (PSA) using Monte Carlo simulation with bootstrapping 1,000 replications will be used. One-way analysis will be applied using Tornado diagram.

Analytical statistics: In order to test the hypothesis regarding differences in costs between intervention and control arm, a linear regression where response variable is cost will be performed. Since this study has large sample size (> 50), even cost data are highly skewed, both linear regression relying on central limit theorem (CLT) and non-parametric bootstrap methods have been proved to be accurate to estimate the true standard errors (SEs) [28]. In this study, we will use linear regression for analysis since it is easier to implement. Complete-case-analysis will be also used to deal with missing data.

Ethical considerations

The Tele-cRCT study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University and also Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The ethical conduct of this study will be monitored by the independent DSMB which is a part of Faculty of Medicine, Chulalongkorn University Ethical Review Board. This is an investigator-generated study performed in full independence of the study sponsor from any other funding agencies. This study will comply with the commonly agreed international standards for good practice in research, the Belmont Report.

Contributorship statement

Dr. Limotai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Study concept or design: Limotai, Thakkinstian, Ingsathit

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Limotai, Thakkinstian, Pattanaprateep, Ingsathit

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Limotai, Thakkinstian

Administrative, technical, or material support: Limotai, Thakkinstian, Ingsathit

Study supervision: Thakkinstian, Ingsathit, Phanthumchinda, Suwanwela, Boonyapisit

Competing interests

None of the authors has associations with commercial entities that provided support for the work reported in the submitted manuscript. None of the authors has associations with

commercial entities that could be viewed as having an interest in the general area of the submitted manuscript. None of the authors has any similar financial associations involving their spouse or their children under 18 years of age. None of the authors has non-financial associations that may be relevant to the submitted manuscript.

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Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information. Data generated by our research that supports our article will be made available as soon as possible, wherever legally and ethically possible. Data will be made available upon reasonable request.

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Figure Legend

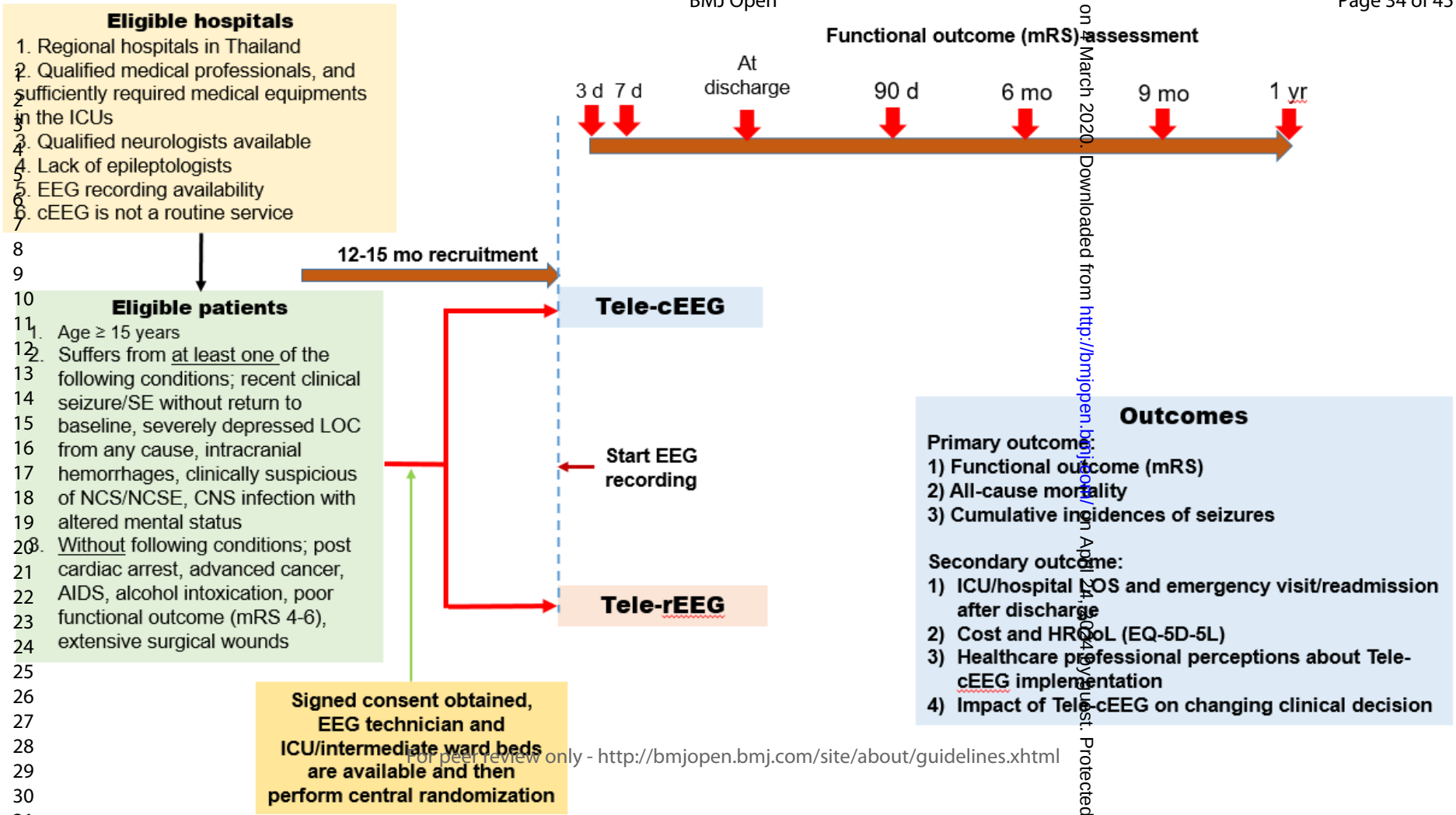
Figure 1: Study flow

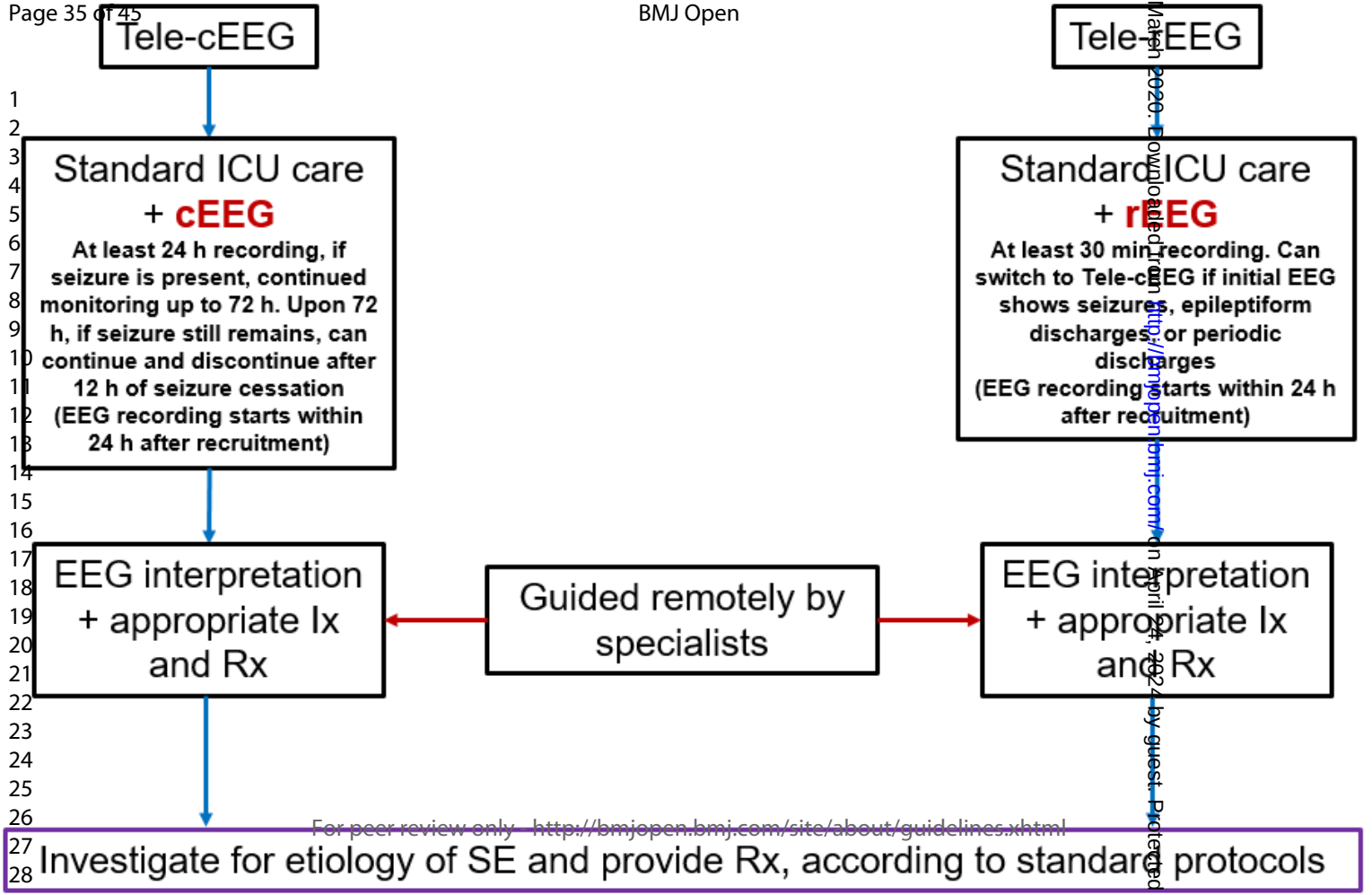
Abbreviations: cEEG = continuous EEG; SE = status epilepticus; LOC = loss of consciousness; NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; mRS = modified Rankin Scale; LOS = length of stay; HRQoL = health-related quality of life

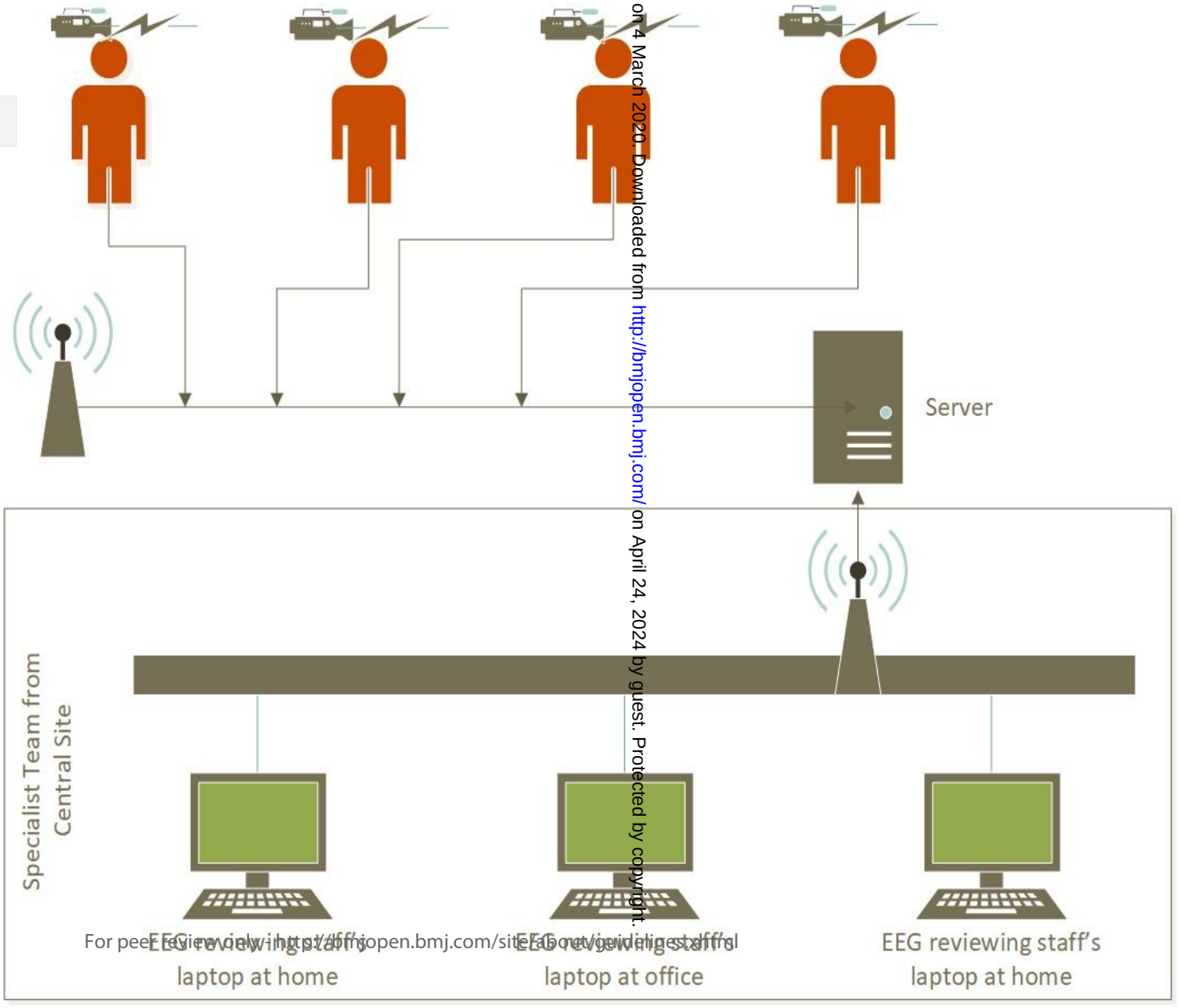
Figure 2: Implementation of study interventions

Abbreviations: cEEG = continuous EEG; rEEG = routine EEG; Ix = investigation; Rx = treatment; SE = status epilepticus

Figure 3: "De-centralized system" of the Tele-EEG







Supplementary files

Supplemental Figure 1: Study flow and investigator's role

Supplemental Figure 2: "Open communication architecture" of the Tele-EEG

Supplemental Table 1: Nine parts of case record form, type of data, and responsible operators

Supplemental Table 2: Timing of data collection

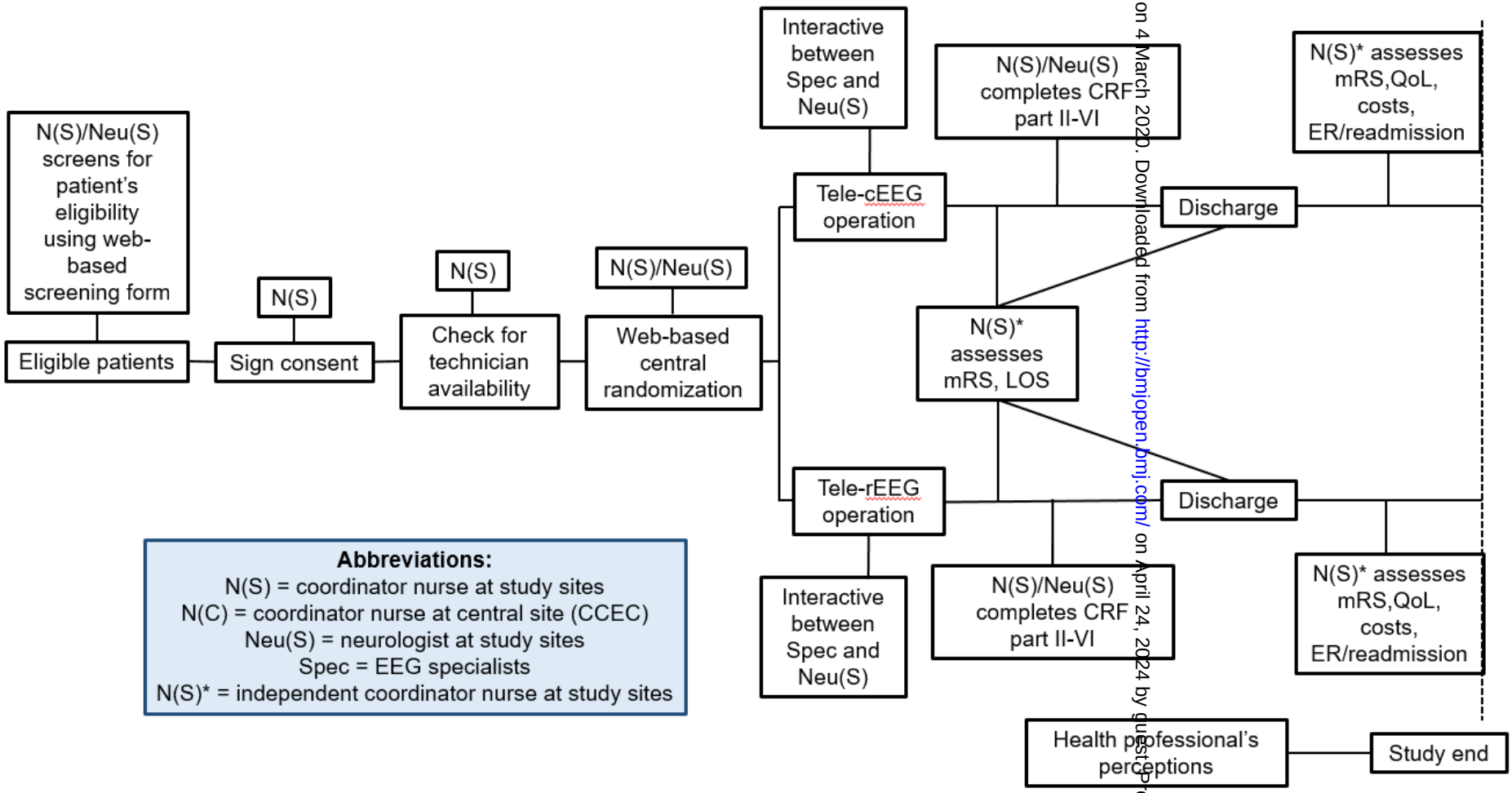
Supplemental Table 3: Statistical methods used for each study outcome

Supplemental Figure 3: Analysis flow

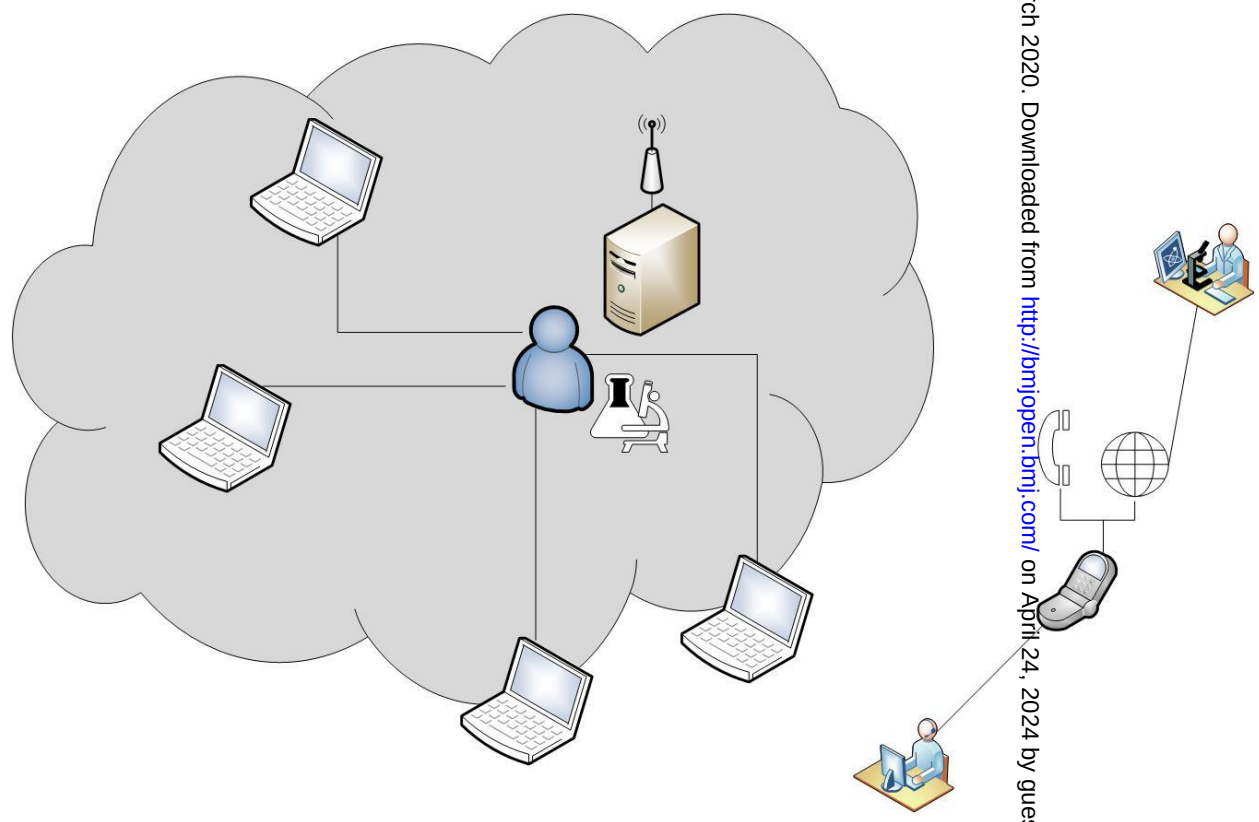
Supplemental Figure 4: Decision tree diagram

Supplemental Table 4: Parameters and data sources for probabilities of interested events, cost, and utility

Supplemental Figure 1: Study flow and investigator's role



Supplemental Figure 2: “Open communication architecture” of the Tele-EEG



Supplemental Table 1: **Nine parts of case record form, type of data, and responsible operators**

Forms	Data	Type of data	Responsible operators
Part I: **Inclusion and exclusion criteria**	Inclusion and exclusion criteria	Non-time dependent	Sub-PIs/ NS
Part II: **Hospital variables**	Hospital characteristics	Non-time dependent	NS
Part III: **Patient variables**	Patient characteristics	Non-time and time-dependent	Sub-PIs/ NS
Part IV: **Etiology of seizure/SE**	Etiology of SE	Non-time dependent	Sub-PIs
Part V: **Investigations**	Investigational data including EEG, imaging, blood and CSF test results	Time dependent	Sub-PIs
Part VI: **Treatment variables**	Information about treatment	Time dependent	Sub-PIs
Part VII: **Primary outcomes** (**i.e**. **functional outcomes, mortality, seizure/SE incidence**)	Assessment of functional outcomes, mortality, seizure/SE incidence	Time dependent and non-time dependent	Independent sub-PIs [1]/ Independent NS [2]
Part VIII: **Secondary outcomes** (**i.e**. **LOS, emergency visit/readmission, HRQoL, change of medical decision making, health professionals perceptions**)	Assessment of LOS HRQoL, emergency visit/readmission, HRQoL, assessment of changing of medical decision making, and health professional perceptions	Non-time dependent	Independent sub-PIs [1]/ Independent NS [2]
Part IX: **Costs**	All costs	Time dependent	Independent NS [2]

Abbreviations: Sub-PIs = neurologist at study sites; NS = coordinator nurses at study hospitals; SE = status epilepticus; CSF = cerebrospinal fluid; HRQoL = health-related quality of life

[1] Sub PIs who are not involved in patient screening and/or collecting the study independent variables

[2] NS who are not involved in patient screening and/or collecting the study independent variables

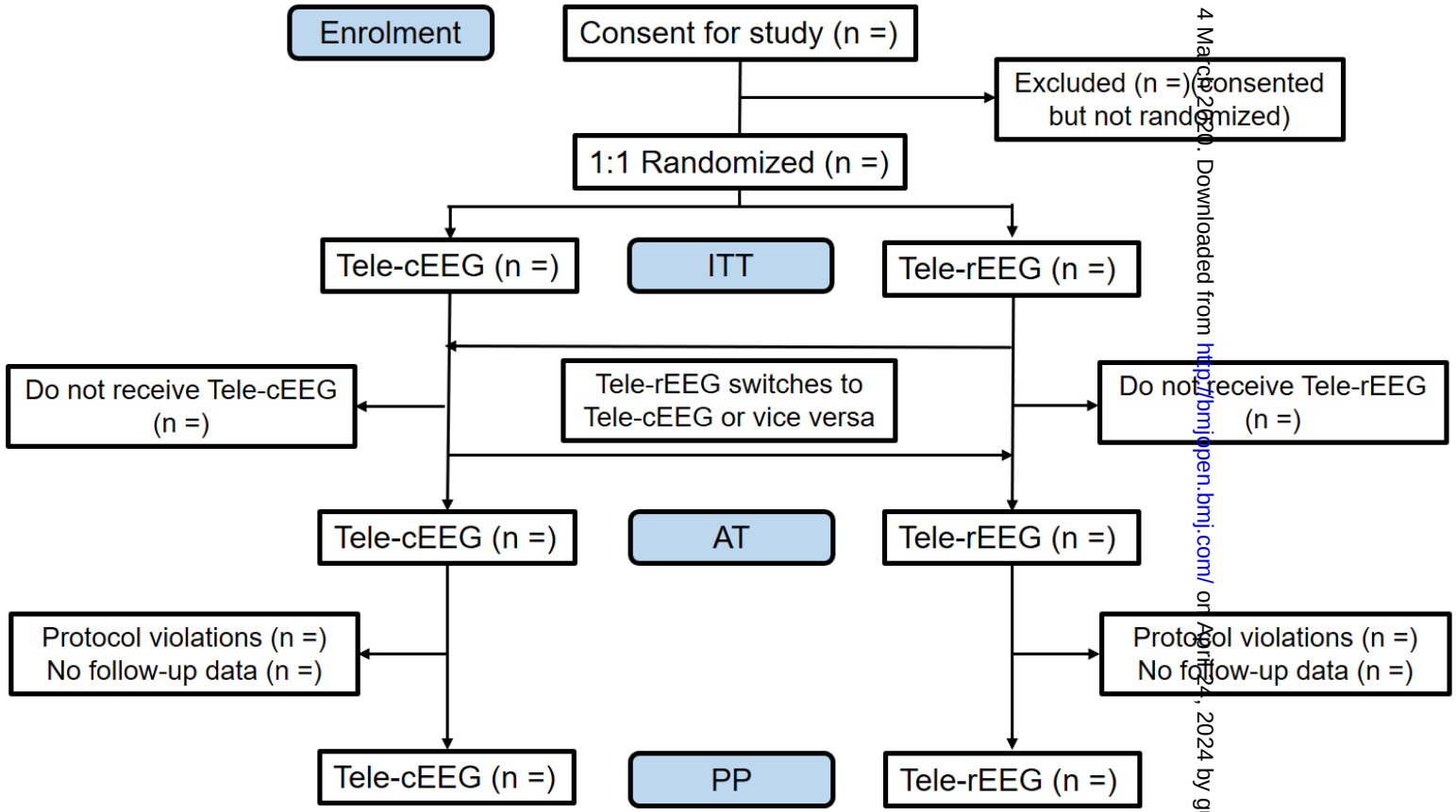
Supplemental Table 2: Timing of data collection

Variables	Time of data collection
Study independent variables (CRF part II – VI)	At enrollment period and during hospitalization
Primary outcome	
- Functional outcomes	At 3 and 7 days after starting EEG recording, at hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge
- Mortality	During hospitalization and 1 year
- Incidence of seizure/SE	During hospitalization
Secondary outcome	
- LOS	At hospital discharge
- Emergency visit/ readmission	At 90 days, 6 months, 9 months, and 1 year after discharge
- Change of medical decision-making	During hospitalization, immediately after patient recruitment
- HRQoL	At hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge
- Costs	At hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge

Supplemental Table 3: Statistical methods used for each study outcome

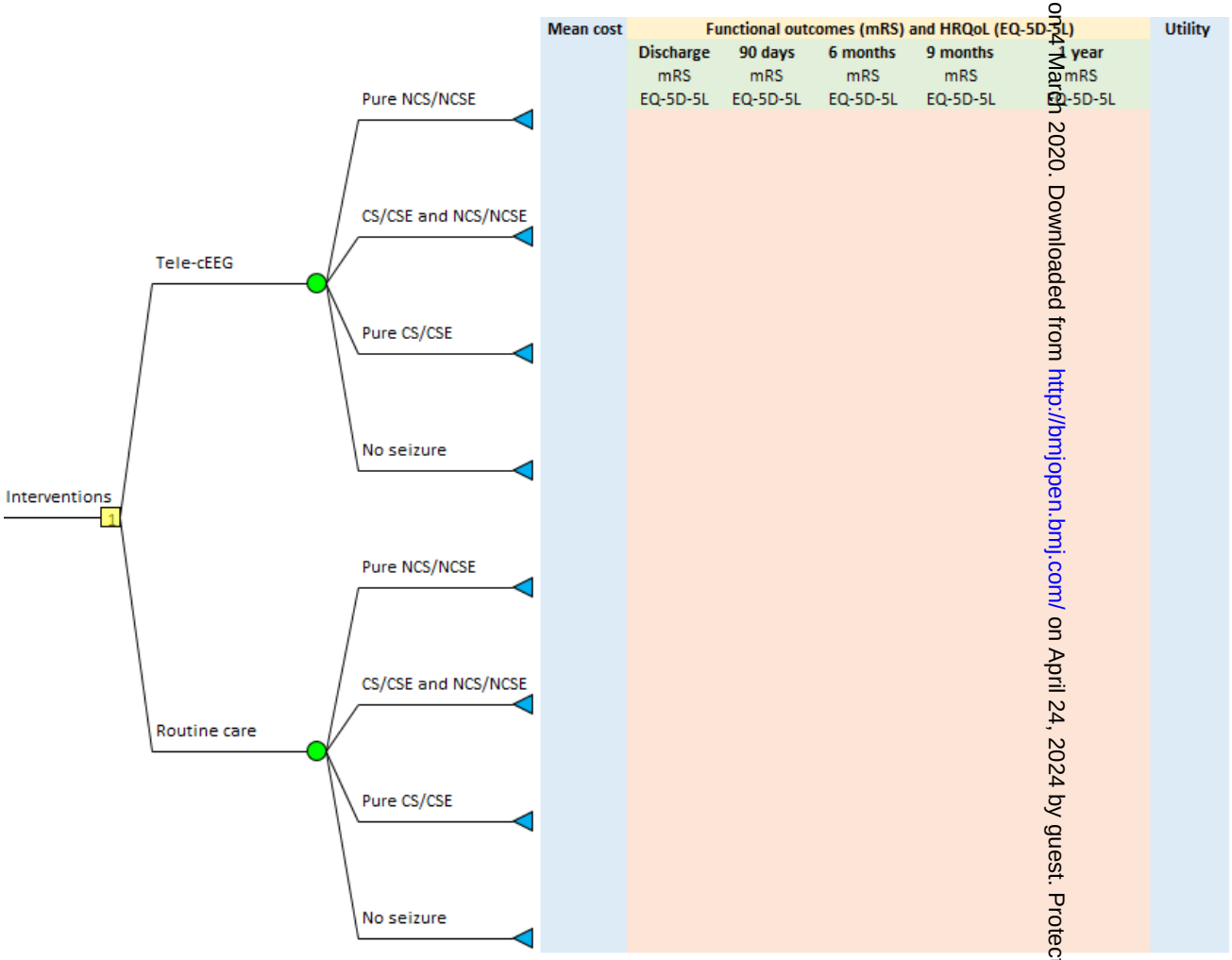
Outcomes	How is the outcome measured?		Type of outcome	Statistical methods
Functional outcome	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Dichotomous (poor vs favorable)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
	Once (at 1 year)		Time to develop poor outcome (mRS 4-6) in patients with initial favorable outcome (mRS 0-3) at discharge and Time to develop favorable outcome in patients with initial poor outcome at discharge	Survival analysis with cumulative incidence function (CIF) and Univariate and multivariate cause-specific or subdistribution proportional hazard model
All-cause mortality	ICU/ hospital Case fatality rate	Once (during hospitalization)	Dichotomous (death vs survived)	Univariate and multivariate logistic regression
	Crude annual mortality rate	Once (at 1 year)	Time to being dead	Survival analysis with Kaplan-Meier (KM) method and Univariate and multivariate Cox propotional hazard regression
Cumulative incidences of seizures	Once (during hospitalization)		Dichotomous (presence vs absence of NCS/NSCE; combined NCS/NCSE and CS/CSE; and CS/CSE)	Univariate and multivariate logistic regression
ICU and hospital LOS	Once (at discharge)		Continuous (days)	Univariate and multivariate linear regression
Emergency visit/readmission	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Dichotomous (Yes vs No)	Univariate and multivariate logistic regression
HRQoL	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Continuous (total score)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
Health professional perceptions about the Tele-cEEG implementation	Once at 1 year after conducting the study		Dichotomous (Yes vs No)	Univariate and multivariate linear regression
Changing of medical decision	Once (during hospitalization)		Dichotomous (Changing vs not changing)	Univariate and multivariate logistic regression
Costs	Once (summation of costs at discharge, 90 days, 6 months, 9 months, 1 year)		Continuous (total cost)	Univariate and multivariate linear regression

Supplemental Figure 3: Analysis flow



Abbreviations: ITT = intention-to-treat analysis; AT = As-treated analysis; PP = Per-protocol analysis

Supplemental Figure 4: Decision tree diagram



Supplemental Table 4: Parameters and data sources for probabilities of interested events, cost, and utility

	Parameters	Data sources
Probabilities of interested events		
Pure NCS/NCSE	Percentage of seizures detetced by EEG	CRF
Combined NCS/NCSE and CS/CSE	Percentage of seizures detetced by EEG	CRF
Pure CS/CSE	Percentage of seizures detetced by EEG	CRF
No seizure	Percentage of not having seizures	CRF
Cost		
At discharge		
Direct medical cost		
· Start-up cost for TM implementation	Sum up costs of internet connection set up; internet fee; and training for physicians and nurses; EEG monitoring cost	PI's budget management file
· Specialist cost	On-call stipends	PI's budget management file
· EEG technician cost	Stipends for electrode placement	PI's budget management file
· Total medical cost during admission	Sum up costs of variable costs	Hospital billing
Direct non-medical cost		
· Caregiver	Informal care cost[a]	Interview
Indirect cost		
· Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost		
At 90 days		
Direct medical cost		
· Home medication	Costs of medications used at home	Hospital billing; interview
· Outpatient visit	Costs during outpatient visit except for medications	Hospital billing; interview
· Re-admission	If any, costs during re-admission, EEG monitoring cost	Hospital billing
· Community health services	If any, costs related to district health promoting hospital care	Hospital billing
Direct non-medical cost		
· Caregiver	Informal care[a]	Interview
· Transportation	Cost per kilometer of running a car	Interview
· Ambulance	Cost per kilometer	Interview
· Out-of-pocket	Other expenses related to patient care	Interview
Indirect cost		
· Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost		
At 6 months		
Direct medical cost		
· Home medication	Costs of medications used at home	Hospital billing; interview
· Outpatient visit	Costs during outpatient visit except for medications	Hospital billing; interview
· Re-admission	If any, costs during re-admission	Hospital billing
· Community health services	If any, costs related to district health promoting hospital care	Hospital billing
Direct non-medical cost		
· Caregiver	Informal care[a]	Interview
· Transportation	Cost per kilometer of running a car	Interview
· Ambulance	Cost per kilometer	Interview
	Other expenses related to patient care	Interview

• Out-of-pocket ***Indirect cost*** • Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost **At 1 year** ***Direct medical cost*** • Home medication • Outpatient visit • Re-admission • Community health services ***Direct non-medical cost*** • Caregiver • Transportation • Ambulance • Out-of-pocket ***Indirect cost*** • Productivity loss	 Costs of medications used at home Costs during outpatient visit except for medications If any, costs during re-admission If any, costs related to district health promoting hospital care Informal care[a] Cost per kilometer of running a car Cost per kilometer Other expenses related to patient care Productivity loss (number of day × income/day)	 Hospital billing; interview Hospital billing; interview Hospital billing Hospital billing Interview Interview Interview Interview Interview
Clinical outcomes (utility) Functional outcomes (mRS) at discharge, 90 days, 6 months, 9 months, and 1 year HRQoL (EQ-5D-5L) at discharge, 90 days, 6 months, 9 months, and 1 year	 Scores; favorable or poor outcome Total scores	 CRF CRF

* Cases of patients who are re-admitted in other hospitals which are not our study hospitals; with approval by the patients (stated in the given signed consent) and permission from Ministry of Health investigators will archive hospital cost billing from the hospital where the patient is admitted.

[a]To identify and valuate informal care by caregiver, a market wage rates will be used

BMJ Open

Efficacy and economic evaluation of delivery of care with Tele-continuous EEG in critically ill patients: A multicenter randomized controlled trial (Tele-cRCT Study) study protocol

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Efficacy and economic evaluation of delivery of care with Tele-continuous EEG in critically ill patients: A multicenter randomized controlled trial (Tele-cRCT Study) study protocol

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Abstract

Introduction: Some critically ill patients are disclosed by continuous electroencephalography (cEEG) monitoring due to nonconvulsive seizure (NCS) and/or nonconvulsive status epilepticus (NCSE). Shortage of epilepsy specialists, especially in developing countries, is a major limiting factor to implement the cEEG in general practice. Delivery of care with the Tele-cEEG may be a potential solution as specialists from a central facility can remotely assist local neurologists in distant areas to interpret the EEG findings and suggest proper treatment. No Tele-cEEG program has been implemented to help improve quality of care. Therefore, this study is conducted to assess the efficacy and cost-utility of implementing the use of Tele-cEEG in critical care.

Methods and analysis: Tele-cRCT is a 3-year prospective, randomized, controlled, parallel, multicenter, superiority trial comparing delivery of care with "Tele-cEEG" intervention with "Tele-routine EEG (Tele-rEEG)" in patients with clinical suspicion of NCS/NCSE. A group of EEG specialists and Tele-EEG system were set up to remotely interpret the EEG in 6 regional government study hospitals across Thailand. Primary outcomes are functional neurological outcome [modified Rankin scale (mRS)]; mortality rates; and incidence of seizures. Secondary outcomes are cost-utility; length of stay; emergency visit/readmission; impact on changing medical decision-making; and health professional perceptions about Tele-cEEG implementation. Functional outcome (mRS) will be assessed at 3 and 7 days after recruitment and again at time of hospital discharge, 90 days, 6 months, 9 months, and 1 year. Costs and health-related quality of life using Thai-version 5-level EQ-5D (EQ-5D-5L) will be assessed at hospital discharge, 90 days, 6 months, 9 months, and 1 year.

Ethics and dissemination: This study has been approved by the Faculty of Medicine, Chulalongkorn University and Ramathibodi Hospital, Mahidol University Ethics Committees and registered on Thai Clinical Trials Registry. The results will be disseminated in a peer-reviewed journal.

Trial registration number: TCTR20181022002; Pre-results.

Strengths and limitations of this study

- This study is the first study assessing the efficacy and cost-utility of implementing the Tele-continuous electroencephalography (Tele-cEEG) in critical care
- This study is also among very few studies assessing efficacy of the cEEG on functional outcome and mortality
- This study is limited to implement the Tele-cEEG in only advanced level hospitals in distant areas. As a result, the results cannot be generalized to apply in the smaller scale hospitals where neurologists are not available and drug items and/or investigations are limited.
- Applying the study intervention [either Tele-routine EEG (Tele-rEEG) or Tele-cEEG] will not be able to blind due to its nature, so bias from outcome ascertainments might be present.

Introduction

Status epilepticus (SE) is a life-threatening medical and neurologic emergency requiring prompt recognition and treatment. A recent meta-analysis including 43 studies reported a pooled crude annual incidence rate of SE of 12.6/100,000 (95% CI 10.0-15.3) [1]. The pooled case fatality rate and the pooled crude annual mortality rate of SE were 14.9% (95% CI: 11.7-118.7) and 0.98/100,000 (95% CI: 0.74-1.22), respectively [1]. Based on the National Database of Thailand during the 2010 fiscal year, the SE rate in Thailand was 5.10/100,000 population, with a mortality rate of 0.6 death/100.000 population [2].

SE can manifest with either overt convulsive movements or subtle/no overt convulsion. The former and the latter have been known as "convulsive status epilepticus (CSE) and "nonconvulsive status epilepticus (NCSE)", respectively. In practice, electroencephalography (EEG) recording is required to help in diagnosis of nonconvulsive seizure (NCS)/NCSE, otherwise, it may be under-recognized and left untreated [3]. Our recent meta-analysis revealed that continuous EEG (cEEG) is significantly better than the routine EEG (rEEG) to help detect NCS/NCSE [4]. Overall prevalence of NCS/NCSE is 15.6% in critically ill patients, but higher in post convulsive SE (32.9%), central nervous system (CNS) infection (23.9%), and post cardiac arrest (22.6%)[4] patients. Evidences of systemic complications and neurological consequences have been clearly demonstrated in CSE [5], but remain unclear for NCS/NCSE. Previous observational studies did not address clear results as to whether the unfavorable outcome of study patients was a direct consequence of NCS/NCSE or the result of other potential confounding factors i.e. patient's characteristics, etiology, and treatment [6 7]. As a result, the

aggressiveness to treat patients with NCS/NCSE is unknown and varies among treating physicians [6].

Although EEG recording is necessary for helping in detection of NCS/NCSE, its routine use, particularly cEEG monitoring, has still been an issue because it is costly and requires specialists to interpret the findings [3]. Due to shortage of epilepsy specialists, especially in developing countries, cEEG implementation in general practice is therefore limited. Delivery of care with a telehealth system [8] may be a promising solution to this problem as specialists can remotely assist general physicians in distant areas to interpret EEG findings and suggest proper management. Until now, no one has implicated the Tele-cEEG system in helping improve quality of care particularly for SE patients. By doing this, at the same time we can assess prospectively both the benefit of Tele-cEEG and neurological consequences of the NCS/NCSE.

The Tele-cRCT study is a multicenter randomized controlled trial (RCT). With an RCT design, efficacy evidence of the Tele-cEEG implementation will be addressed with valid results since potential confounding factors will be balanced and adjusted between two groups of comparison. Alongside economic evaluation, cost-utility analysis of the Tele-cEEG will be also addressed and can be introduced to the community in order to initiate the adoption of this Tele-cEEG in routine practice.

Methods and analysis

This study protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), see SPIRIT checklist in Supplemental document 1.

Study design and setting

Tele-cRCT is a 3-year prospective, randomized, controlled, parallel, multicenter, superiority trial comparing delivery of care with "Tele-cEEG" intervention with "Tele-rEEG" in patients with clinical suspicion of NCS/NCSE. We have currently conducted a pilot study in some study hospitals in order to test the feasibility of the remote EEG monitoring, and the whole processes of data collection. A group of EEG specialists and Tele-EEG system were set up to remotely interpret the EEG in the study hospitals which are 6 regional government hospitals across Thailand. All six study hospitals have met our eligibility criteria which are 1) Regional hospitals defined according to Ministry of Public Health of Thailand as hospitals in service plan A (Advance-level hospital) with capability to treat patients who require advance and sophisticated technology; 2) Having surgical or medical ICUs which are run by qualified medical professionals, and sufficient requisite medical equipment in the ICUs, corresponding to any level of three-tiered system ICUs proposed by the American College of Critical Care Medicine (ACCM) [9]; 3) Having at least two portable EEG machines available and capability to operate the EEG recording in the ICUs or wards; 4) Having neurologists who are capable to treat status epilepticus with available necessary medications recommended by 2016 American Epilepsy Society (AES) guideline [10] and having capability to do etiology work up of status epilepticus, suggested by the 2012 Neurocritical Care Society [3], but 5) No qualified Epileptologists to interpret the EEG; and 6) cEEG monitoring is not part of the hospital's routine service.

Both intervention (Tele-cEEG) and control (Tele-rEEG) arms will be assisted by a specialist team to interpret the EEG findings and suggest appropriate treatment in order to standardize a "specialist factor" which might affect study outcomes. It should be noted that the EEG recording, even a rEEG, is under-utilized in Thailand due to a severe shortage of

epileptologists and neurologists who are comfortable and confident to interpret EEG findings. The study flow is shown in Figure 1.

Study objectives

Between intervention (Tele-cEEG) and control (Tele-rEEG) arm, our primary objective is to compare the efficacy in terms of functional outcomes (mRS) and mortality rate assessed at 3, 7 days after recruitment, at discharge, 90 days, 6 months, 9 months, and 1 year after hospital discharge, as well as detection rate of seizures during hospitalization. The secondary objective is to compare efficacy of ICU/hospital length of stay (LOS), emergency/readmission, cost-utility, and impact on changing of medical decision-making, and healthcare professional perceptions about the Tele-EEG implementation.

Screening and randomization

A dedicated nurse in each study hospital screens for eligible patients in every new admission or new neurology consultation from adult ICUs or medical or surgical wards to see whether or not potential study subjects fulfill one of the five conditions indicated in the inclusion criteria, listed in Box 1. Eligibility is then confirmed with a neurologist at the study site. In case of fulfilling eligibility, a nurse will provide study information to patients or relatives and then request for signed informed consent. A nurse will then log-in in order to fill out the study web-based screening form, and if the patient is eligible the system will automatically operate a central randomization and then assigning study intervention (Tele-cEEG vs Tele-rEEG) along with the patient's subject identification number for the study. A block randomization will be applied. Since this study is not double-blind where health care teams will not be blinded to the

intervention, in order to protect the integrity of the randomization process randomly selecting the block size will be performed prior to randomly select the patient. The block sizes will be 4, 6, 8, and 10. The ratio of intervention and control is 1:1. Statisticians at the central site will generate random sequences of assigned intervention using STATA version 15.0. Study flow and investigator's role are shown in Supplemental Figure 1.

Box 1: Inclusion and exclusion criteria for patient enrolment

Inclusion and exclusion criteria for enrolment
Inclusion criteria
1. Adult patients, aged ≥ 15 years, who are admitted in surgical or medical ICUs or wards
2. Suffering from at least one of the 5 conditions which are recommended by the 2012 Neurocritical Care Society[1] as well as corresponding with the results of our meta-analysis[2] to be highly associated with NCS/NCSE 2.1 Recent clinical seizure/status epilepticus without return to baseline (pre-status) with - In case of receiving sedative medication: at > 10 minutes after clinical seizure/SE ends, patient's GCS does not return to baseline - In case of not receiving sedative medication: at 2 hours after clinical seizure/SE ends, patient's GCS does not return to baseline 2.2 Severely depressed consciousness from any cause (except for TBI, SAH, ICH) with GCS ≤ 8 2.3 Intracranial hemorrhages with any of - TBI with GCS 6-12 - SAH with Hunt & Hess Classification grade ≤ IV or GCS > 5 - ICH with ICH score ≤ 3 2.4 Suspected NCS/NCSE in patients with altered mental status (cause indeterminate) 2.5 CNS infection with altered mental status
3. Patient and/or their relative is willing to participate with the study with given signed informed consent
4. Patients or caregivers which are defined as the main person, other than a health, social, or voluntary care provider can provide functional outcome data after discharge
Exclusion criteria
1. Patients with post cardiac arrest
2. Patients with advanced stage cancer (stage IV)
3. Patients with AIDs (CD4 count < 200 cells/mm^3 or with certain opportunistic infections)
4. Patients with alcoholic intoxication with/without delirium tremens*
5. Patients with poor functional outcome at pre-admission state (mRS 4-6)
6. Patients with extensive lacerations, skin lesions, or surgical wound where the electrode placement is not able to be applied

Abbreviations: NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; GCS = Glasgow Coma Scale; TBI = traumatic brain injury; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; CNS = central nervous system; mRS = modified Rankin Scale

[1] Brophy GM et.al., 2012; [2] Limotai C et.al., 2019

* These patients are excluded due to the fact that there are a large number of these types of patients in rural areas of Thailand who may significantly outweigh other types of patients included, where there has been no reported magnitude of its association with NCS/NCSE.

Allocation concealment

In order to prevent selection bias, the process of central randomization will be applied to conceal the allocation sequence from those assigning participants to intervention groups until the moment of assignment.

Blinding

As the nature of assigned intervention is different and easy to recognize (i.e. continuous (prolonged) versus rEEG (short) EEG recording), participants will not be blinded to the intervention assigned. Health care teams including physicians and nurse also will not be blinded because they will be involved in the patient care using either cEEG or rEEG. However, dedicated outcome assessors will be blinded to patient allocations.

Intervention

This study consists of two arms which apply two different interventions; one with Tele-cEEG (24-hr monitoring, intervention arm) and the other with Tele-rEEG (30-mins monitoring, control arm), see Figure 2. Since important study outcomes are functional outcomes and mortality after SE, a specialist team will assist the control arm (Tele-rEEG) to interpret EEG findings and suggest appropriate treatment in order to standardize a specialist factor which might affect the outcomes.

Tele-EEG system and database: Central facilities for the Tele-EEG system/EEG database and the patient's database were respectively set up at Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC) and the Section for Clinical Epidemiology and Biostatistics, Ramathibodi Hospital (Rama CEB). Two separate EEG review systems will be set up. One for real-time review with TeamViewer® software and the other for off-line review using EEG data uploaded on cloud storage. For off-line review, EEG data uploaded on cloud storage will be downloaded into EEG database server at CCEC on a daily basis. Upon being in charge, each EEG specialist can connect to the EEG machine at study sites and EEG server at CCEC for real-time and off-line review, respectively at anytime and from anywhere via internet ("De-centralized system"), see Figure 3. For both real-time and off-line review, password access control will be used.

Methods of conducting Tele-EEG: The EEG recording must be initiated within 24 hours after recruiting (randomization) patients in both arms (Tele-cEEG vs Tele-rEEG). Within working hours (8 am to 4 pm), an EEG technician will apply the EEG electrodes, where at the same time, an in-charge specialist on that day will be notified to prepare for EEG review. After completing internet connection set-up, Tele-EEG system integrity will be checked at both ends.

For the Tele-cEEG, a specialist will periodically report the EEG findings using standard case record form (CRF) every 2 or 6 or 12 hours, depending on clinical urgency determined by clinical data and initial 30-minute/prior EEG findings. EEG will be monitored for at least 24 hours. If seizures are detected, the Tele-cEEG will be continued and discontinued after 72 hours. However, if seizures are still present at 72 hours, the Tele-cEEG can be continued and then

discontinued after seizure cessation for 12 hours. Continuation of Tele-cEEG monitoring after 72 hours will be treated as co-intervention, see Figure 2.

For the Tele-rEEG, a specialist will interpret the EEG findings and feedback the results using the standard CRF to the treating neurologist at bedside within 2 hours after finishing the EEG study. EEG will be monitored and recorded for 30 minutes. Switching the Tele-rEEG to the Tele-cEEG is possible if the initial findings disclose seizures and/or epileptiform activity or periodic discharges. These specific EEG findings were reported by the 2012 Neurocrititical Care Society guideline to be highly associated with NCS/NCSE [3]. In this case, the Tele-cEEG will be treated as co-intervention, see Figure 2. Performing additional rEEG in case that a clinical concern for on-going seizure still remains is allowed; although once again this will be recorded and treated as co-intervention.

In both arms, standard consensus protocols for investigations and management of SE will be followed for all patients. An in-charge specialist will discuss the EEG findings with the treating neurologist at bedside and then appropriate management according to the consensus protocols. Flexible connectivity will be used where specialists who review the EEG can access patient medical information on cloud storage via internet ("Open communication architecture"), see Supplemental Figure 2. Communication between specialists and treating neurologists is limited to traditional telephonic modalities and are functionally outside the Tele-EEG system, see Supplemental Figure 2.

EEG reviewing organization: Nine EEG specialists included for this study are all certified Epileptologists with training in either Thailand and/or North America (US and Canada).

All EEG specialists will be assigned to be on-call for reviewing the EEG. Each on-call duration lasts for 24 hours (7 am to 7 am on the following day). EEG specialists are responsible to review both the cEEG and rEEG on that day. An EEG specialist will give his/her report to the other EEG specialist on the following day by verbal communication using a unified EEG finding and list of management report forms to ensure continuity of the appropriate management.

Standard consensus protocols for investigations and management of SE were developed using Modified Delphi method [11 12]. All nine EEG specialists were invited to perform on-line Google survey and then face-to-face discussion in order to standardize and make consensus protocols on how to report the EEG findings and manage SE. The terminology and definition of the EEG wave forms used in this study will be mainly based on the American Clinical Neurophysiology Society (ACNS) proposed standardized terminology 2012 version [13]. A unified EEG report form will be created as part of web-based CRF. Twenty-three and 5 EEG tracings with a variety of common EEG findings in critically ill and seizure/status epilepticus EEG patterns were prepared and then used to test inter-rater agreement [14] among 7 EEG specialists (see Supplemental Table 1). Percent level of agreements of these parts were respectively 79.3 and 79.1, with the Gwet's kappa coefficient (95% CI) of 0.7354 (0.5825, 0.8883) and 0.7373 (0.3409, 1.0000) indicating substantial agreements for both parts.

Study outcomes: Primary and secondary outcomes are listed in Box 2.

Box 2: Primary and secondary outcomes

Primary and secondary outcomes
Primary outcome
1. Functional outcomes including poor (mRS 4-6) versus favorable (mRS 0-3) functional outcomes and functional decline (i.e., mRS increases at least one score) of the actual scores, in which mRS will be assessed at 3 and 7 days after starting EEG recording (recruitment), at discharge, 90 days, 6 months, 9 months, and 1 year.
2. ICU/in-hospital case fatality rate during hospitalization and crude annual mortality rate assessed at 1 year after hospital discharge
3. Cumulative incidences of each type of seizures i.e., pure NCS/NCSE, combined NCS/NCSE and CS/CSE, and pure CS/CSE in the intervention and control arms
Secondary outcome
1. ICU and hospital length of stay
2. Emergency visit and re-admission after hospital discharge assessed at 90 days, 6 months, 9 months, and 1 year
3. Health-related Quality of Life, assessed by Thai-version EQ-5D-5L at hospital discharge, 90 days, 6 months, 9 months, and 1 year
4. Costs assessed at hospital discharge, 90 days, 6 months, 9 months, and 1 year
5. In order to assess the impact of change of medical decision making of the treating neurologists at study sites, a structured questionnaire will be assessed immediately after patient recruitment, but prior to knowing the EEG results and then compared with the actual activities (investigations/treatment) after integrating the EEG findings with other clinical data
6. In order to assess the health professional perceptions about Tele-cEEG implementation; a structured questionnaire will be evaluated by nurses and neurologists at study sites, assessed at 1 year after conducting the study, see Supplemental Table 2

Abbreviations: mRS = modified Rankin Scale; NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; CS = convulsive seizure; CSE = convulsive status epilepticus

Sample size calculation

The primary outcome used for estimation of sample size is functional outcome measured by mRS. It is dichotomized into favorable (mRS 0-3) and poor outcomes (mRS 4-6). The formulae for the number of participants is estimated as follows [15]:

$$N = \left(z_{\alpha/2} + z_{\beta}\right)^2 \frac{\pi_0(1-\pi_0)+\pi_1(1-\pi_1)}{(\pi_0-\pi_1)^2}$$

N = total number of participants; $Z_{\alpha/2} = 1.96$; $Z_{\beta} = 0.84$; π_0 = the true proportions in the control populations; π_1 = the true proportions in the in intervention arm

As for previous study by Khawaja et al [16], which up until now it is the only one available study assessing functional outcomes in critically ill patients who received cEEG monitoring (intervention) and also in those who did not receive the cEEG (controls) [16], the proportions of patients with poor outcome (mRS 3-6) was 0.829 for control groups. If we plan to detect the difference of poor functional outcome of 0.1 (which should be clinically meaningful), with setting a ratio of intervention vs control, type I and II errors of 1:1, 0.05, and 0.2; the estimated sample size is as follows:

$$N = (1.96 + 0.84)^2 \frac{0.829\ (1 - 0.829) + 0.729(1 - 0.729)}{(0.829 - 0.729)^2}$$

$$= 7.84 \frac{(0.142 + 0.198)}{0.01}$$

$$= 267$$

Assuming a 20% loss to follow up, the total number of participants required in each arm is 270 + 54 = 324. In summary, in order to have 80% power to detect a 10% reduction of poor outcomes at a 5% level of significance (2-sided), we require 324 participants in each arm; so this would result in 648 participants in total.

Patient recruitment

A pilot study will be performed to assess whether there will be any recruitment issues in the designated study hospitals. The initial recruitment plan is 10-15 patients per month from each hospital. After the formal pilot study, this plan may be changed according to actual recruitment rate of each hospital. However, PI and/or coordinator nurse at the central site (CCEC) recruitment centers will be continuously monitoring and encouraging patients to join the study via telephone reminder. In order to prevent bias related to predominant participant recruiting

from one particular study site, actual recruitment rates from the pilot study will be used to weight the quota for recruitment from each hospital.

Patient and public involvement

Neither patients nor public have been involved during the design of the Tele-cRCT study. The Tele-cRCT study results will be available at https://clinicaltrials.in.th/ to both patients and general public. Assessment of the burden of the intervention has not been foreseen in the present study.

Data collection and data statement

Case record form (CRF) was created according to information of the study variables, intervention, and outcomes. These are divided into 9 parts and were created in paper-based forms, except for patient screening and EEG findings forms which were both created in web-based CRF (see Supplemental Table 3). Timing of data collection is shown in Supplemental Table 4. After ethics committee approval in each study hospital and obtaining written signed consent from patients or caregivers, principal investigators (PI) then asked for permission to access patient information to collect the patient data in respective study hospitals.

Participant neurologists assigned to be sub-PIs in each study hospital will help facilitate accessing archived raw data. Study variables and outcomes will be collected at enrollment period after randomization, then fill in the CRFs. Independent outcome assessors (either sub-PIs or coordinator nurses at study hospitals) will assess the primary and secondary outcomes.

Data management

Conversion of the paper-and web-based CRF into an electronic database (EpiData Version 3.1, The EpiData Association, Odense, Denmark) is planned. Data entry will be assigned to two data entry staff. Patient database files will be kept in a personal computer at Rama CEB and also backed up in the PI's notebook. These two computers require passwords to access the database. Scheduled site visits for data audits will be arranged for each participant hospital every 1-2 months during the first 6 months and then every 3 months. In order to ensure appropriate intervention delivery, all completed competency assessment tools will be returned to the PI and will be included as a standard monitoring report to the Data and Safety Monitoring Board (DSMB). Manual, interactive, and batch checking methods will be used to ensure completeness and correctness of the data. In order to maintain high quality of the data, regular meetings to check for data correctness and give feedback between data collectors and data entry staff will be arranged on a monthly basis.

Data analysis plan

Descriptive statistics: Baseline characteristics between Tele-cEEG and Tele-rEEG arms are presented in mean with standard deviation (SD) or median with interquartile range (IQR) for continuous data depending on distribution of the data. For categorical data, frequency and percentage are presented. To compare characteristics of patients between groups, Pearson chi-square or Fisher exact test will be applied for categorical data; Student t-test or Mann-Whitney test for normal and non-normal distributed continuous data will be used.

Imputation: Imputations will be performed using STATA software version 15.0. Missing data will be explored to assess whether distribution of missing data is missing at random (MAR), if not this is said to be nonignorable. Multiple imputation (MI) will be applied. The number of imputations will be determined by percentage of missing values and MI performance [17], reflected by relative variance increase and fraction of missing information values.

Analytical statistics: Statistical methods will depend upon how the outcomes are being measured and the type of outcomes, either dichotomous or continuous, as summarized in Supplemental Table 5. Regarding time to event data analysis of functional outcome (mRS), the start date will be set as date of starting EEG recording. Patients will be initially stratified into having poor (mRS 4-6) versus favorable outcome (mRS 0-3) at discharge. These two groups will be analyzed separately. A group with initial poor outcome, time to first ever favorable outcome analysis will be performed, whereas a group with initial favorable outcome time to first ever poor outcome will be estimated. Since death will be treated as competing risk, so probabilities of developing interested events (poor or improved outcome) will not be independent from probability of death, in which cases a cumulative incidence function (CIF)[18] will be used instead of KM method. The end date will be set as; date at end of study (1 year after hospital discharge), date of developing interested events; date of having competing risks, and date of loss to follow-up. Either cause-specific or subdistribution proportional hazard model will be used to estimate effect sizes and depends on whether or not the intervention (Tele-cEEG) has an effect on the hazards of competing risks (death) [19]. If it has no effect, a cause-specific proportional hazard model with csHR will be reported. However, in the event of an effect, a subdistribution model with subHR will be reported.

Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE) will be applied to assess intervention effects [20] on functional outcome. A mixed effect model will be constructed as follows: First, intervention variable will be fitted as fixed-effect and random-effect in a multilevel equation with having poor/favorable function as the outcome variable. Second, a random-effect of intervention will be then constructed. A likelihood ratio will be applied to compare whether considering intervention effect as random will improve model fitting. Adjusted odds ratio (OR) along with its 95% CI will be estimated.

Even if randomization is used, all of the prognostic factors may not be perfectly balanced. Covariate adjustment will be used in the analysis of the primary and secondary outcomes to minimize the effect of covariate imbalance. The following important covariates at baseline which may influence the study outcomes (i.e. functional outcome and mortality) will be adjusted; age (≥ 60 vs < 60 years) [21 22], etiology of SE (acute vs chronic etiology) [22], severity of the disease within 24 hours of admission (higher vs lower APACHE IV/SAPS II/GCS scores) [23] and history of epilepsy/antiepileptic drug use. The specific adjustment procedure depends on the type of covariate being adjusted for and the type of outcome being analyzed. In this study, both primary response variables (primary outcomes) and important covariates are categorical (i.e. age, etiology of SE, severity of disease), so "a stratified analysis" taking the form of a Mantel-Haenszel (MH) statistic will be used. Study participants will be subdivided into smaller, more homogenous groups, or strata will be used. A comparison of study groups will be made within each stratum and then averaged over all strata to achieve a summary result for the outcome.

Pre-specified subgroup analysis: We plan to perform a subgroup analysis on covariates which potentially effect modifiers of the intervention effects. This may help identify the specific

population most likely to benefit from or to be harmed by the Tele-cEEG. The following subgroup analysis will be assessed; age (≥ 60 years) vs younger (< 60 years) and patients with severe diseases (i.e. higher score) vs milder severity (i.e. lower score). This will be based on APACHE IV, SAPS II, GCS within 24 hours of enrolment; indications for EEG study (prior clinical seizure/SE without recovery, coma, severely depressed LOC, intracranial hemorrhages, suspicious NCS/NSCE, CNS infection, and presence of epileptiform discharges or periodic pattern on initial EEG); higher status epilepticus severity score vs lower scores (based on STESS and EMSE scores); and Type of SE (i.e. pure CSE vs pure NCSE vs combined CSE and NCSE).

Dealing with protocol violation: We will analyze with the following methods; 1) Intention-to-treat analysis: All participants and their outcomes will be included for primary analysis; 2) As-treated analysis: This will be used in cases as follows; a) patients who are initially randomized to receive Tele-rEEG, but are subsequently switched to receive the Tele-cEEG as initial rEEG revealed seizure/epileptiform and/or periodic discharges, and b) patients with incorrect intervention allocation administration e.g. patients allocated to Tele-cEEG are incorrectly administered Tele-rEEG or vice versa; 3) Per-protocol analysis: This analysis refers to inclusion in the analysis of only those patients who strictly adhered to the protocol. Analysis flow is shown in Supplemental Figure 3.

Economic analysis

This is an economic analysis alongside the randomized controlled trial (trial-based economic evaluation). Costs and outcomes will be collected from all patients. We will perform cost-utility

analysis (CUA) which enables the findings from our study to be compared with other healthcare interventions. This trial will evaluate economic analysis in view of societal perspectives including billing costs in order to assess whether the Tele-cEEG is economically feasible and worthwhile to implement in the context of Thailand.

Outline of interventions: By using TreeAge Pro 2016, a decision tree will be created using RCT-based data. This decision tree diagram will help depict choices of intervention, the logical structure of probabilities of conditions which could occur after applying the interventions, and values related to cost and utility associated with consequences related to each condition. Interested events discovered by the study interventions (Tele-cEEG and Tele-rEEG) are pure NCS/NCSE, combined CS/CSE and NCS/NCSE, pure CS/CSE, and no seizure. Decision tree diagram is shown in Supplemental Figure 4. Parameters and data sources for probabilities of interested events, cost, and utility are shown in Supplemental Table 6.

Cost analysis: Unit costs of services will be referenced on a price provided by the Center of Essential Information for All Health Officers, 2018. All costs will be converted to 2018 values using the Thai consumer price index (Bureau of Trade & Economic Indices, 2018). Lifetime time horizon is a cycle length of 1 year. All costs and outcomes occurring after 1 year will be discounted at a rate of 3%, as recommended in the Thai Health Technology Assessment guideline[24].

Determining cost-effectiveness: For primary economic analyses, with CUA cost per quality-adjusted life-year (QALY) gained based on EQ-5D-5L score will be examined. The EQ-5D-5L is a generic preference-based measure for which a previous study in Thailand reported coefficients for converting to utility [25].

QALYs = number of years lived x utility

Utility can range from 0 as worst health state or death to 1 as best health state or healthy. To convert the EQ-5D-5L QoL score to utility, we use coefficients from a study by Pattanaphesaj J. (http://www.hitap.net/documents/89762) [25].

The Incremental Cost-Effectiveness Ratio (ICER) will be calculated by the formula below [26]. The numerator will be the difference of mean total cost between intervention (Tele-cEEG) and controls (Tele-rEEG). Mean total cost will be calculated by dividing the summation of all costs at discharge, 90 days, 6 months, 9 months, and 1 year in each patient with total number of the patients. The denominator will be difference of QALY based on EQ-5D-5L score at 1 year between intervention and controls.

$$\text{ICER} = \frac{Mean\ (Total\ cost\ Tele-cEEG)\ -\ Mean\ (Total\ cost\ Tele-rEEG)}{Mean\ (QALY\ Tele-cEEG)\ -\ Mean\ (QALY\ Tele-rEEG)}$$

We will also derive 95% CI for the ICER. If the numerator (cost data) and denominator (QoL data) of the ICER follow a joint normal distribution, Fieller's method will be used [27]. However, if either data are non-normally distributed, a non-parametric bootstrap method will be used [28]. The combination of 95% CIs for cost and effect differences will be shown in a graph to demonstrate a "confidence box" of the cost-effectiveness plane [28].

For the secondary economic analysis, ICER to represent additional cost per additional point on the mRS will be calculated as below. This will be separately assessed at 3 day and 7 days after starting EEG recording, at discharge, 90 days, 6 months, 9 months, and 1 year. In each time point, the numerator of the ICER will be the difference of mean total cost between intervention and controls. The denominator will be the difference of median mRS between

intervention and controls at that time point. Cost-effectiveness plane and cost-effectiveness acceptability curves will be presented.

$$\text{ICER} = \frac{Mean\ (Total\ cost\ Tele{-}cEEG) - Mean\ (Total\ cost\ Tele{-}rEEG)}{Median\ (mRS\ score\ in\ Tele{-}cEEG) - Median\ (mRS\ score\ in\ Tele{-}rEEG)}$$

Uncertainty analysis: To handle cost analysis uncertainty, a Probabilistic Sensitivity Analysis (PSA) using Monte Carlo simulation with bootstrapping 1,000 replications will be used. One-way analysis will be applied using Tornado diagram.

Analytical statistics: In order to test the hypothesis regarding differences in costs between intervention and control arm, a linear regression where response variable is cost will be performed. Since this study has large sample size (> 50), even cost data are highly skewed.,, Both linear regression relying on central limit theorem (CLT) and non-parametric bootstrap methods have been proved to be accurate to estimate the true standard errors (SEs) [29]. In this study, we will use linear regression for analysis since it is easier to implement. Complete-case-analysis will be also used to deal with missing data.

Ethical considerations

The Tele-cRCT study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University and also Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The ethical conduct of this study will be monitored by the independent DSMB which is a part of the Faculty of Medicine, Chulalongkorn University Ethical Review Board. This is an investigator-generated study performed in full independence of study sponsor from any other funding agencies. This study will comply with the commonly agreed international standards for good practice in research, the Belmont Report. Any important

protocol modifications will be reported to the Ethics Committee of both institutions and the trial registries. English language examples of the patient consent form is shown in Supplemental document 2.

Contributorship statement

Dr. Chusak Limotai (C.L.) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and contributed to study concept or design, acquisition/analysis/interpretation of data, drafting the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative/ technical/material support.

Dr. Atiporn Ingsathit (A.I.) contributed to study concept or design, critical revision of the manuscript for important intellectual content, and is a study supervision.

Dr. Kunlawat Thadanipon (K.T.) contributed to critical revision of the manuscript for important intellectual content, and is a study supervision.

Dr. Oraluck Pattanaprateep (O.P.) contributed to study concept or design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and is a study supervision.

Anuchate Pattanateepapon (A.P.) contributed to study concept or design, critical revision of the manuscript for important intellectual content, administrative/ technical/material support, and is a study supervision.

Dr. Kammant Phanthumchinda (K.P.) contributed to critical revision of the manuscript for important intellectual content, and is a study supervision.

Dr. Nijasri C. Suwanwela (N.S.) contributed to critical revision of the manuscript for important intellectual content, and is a study supervision.

Dr. Iyavut Thaipisuttikul (I.T.) contributed to critical revision of the manuscript for important intellectual content, and administrative/ technical/material support.

Dr. Kanokwan Boonyapisit (K.B.) contributed to critical revision of the manuscript for important intellectual content, and is a study supervision.

Dr. Ammarin Thakkinstian (A.T.) contributed to study concept or design, acquisition/analysis/interpretation of data, drafting the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and is a study supervision.

Competing interests

None of the authors has associations with commercial entities that provided support for the work reported in the submitted manuscript. None of the authors has associations with commercial entities that could be viewed as having an interest in the general area of the submitted manuscript. None of the authors has any similar financial associations involving their spouse or their children under 18 years of age. None of the authors has non-financial associations that may be relevant to the submitted manuscript.

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the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information. Data generated by our research that supports our article will be made available as soon as possible, wherever legally and ethically possible. Data will be made available upon reasonable request.

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Figure Legend

Figure 1: Study flow

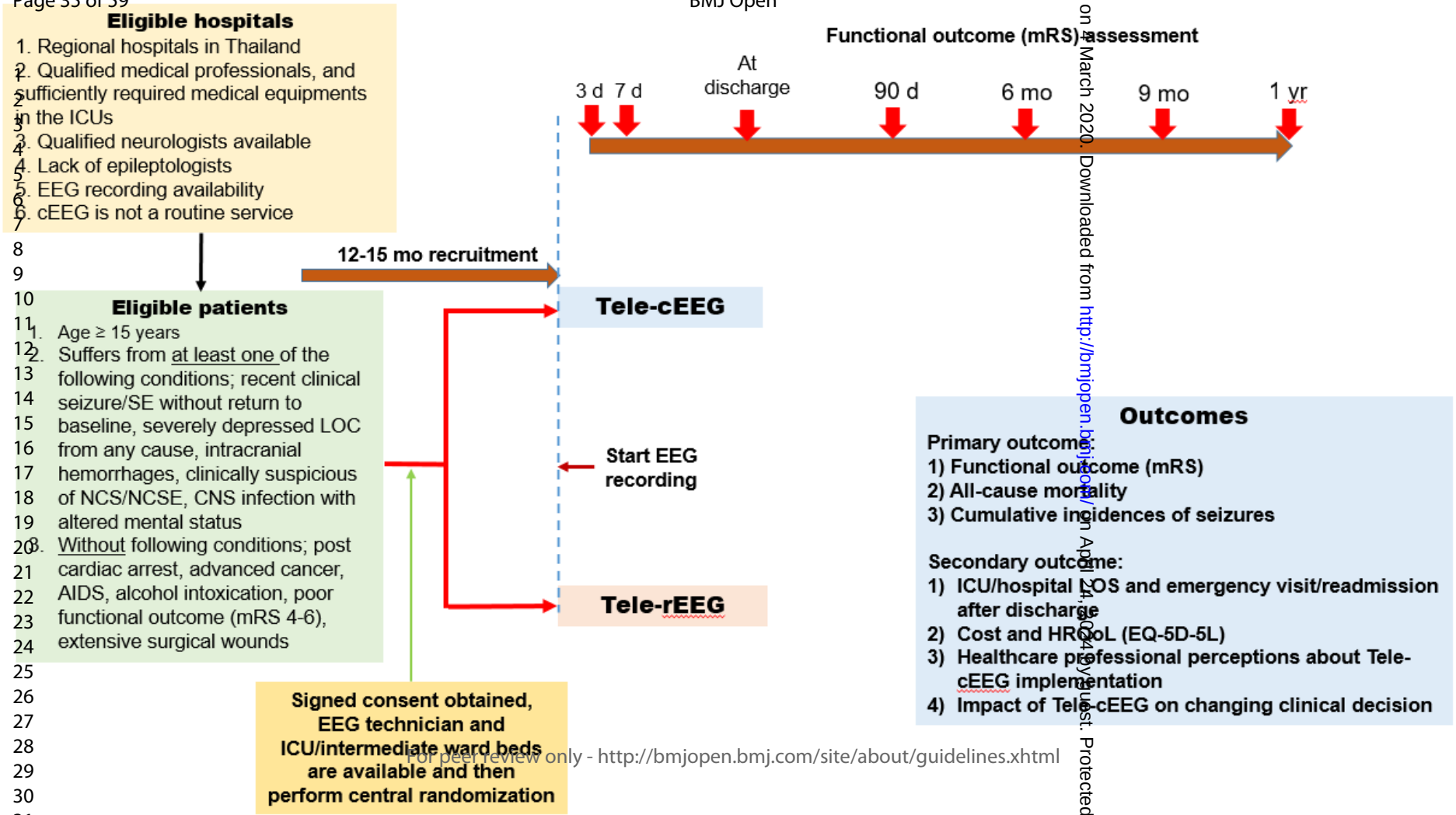
Abbreviations: cEEG = continuous EEG; SE = status epilepticus; LOC = loss of consciousness; NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; mRS = modified Rankin Scale; LOS = length of stay; HRQoL = health-related quality of life

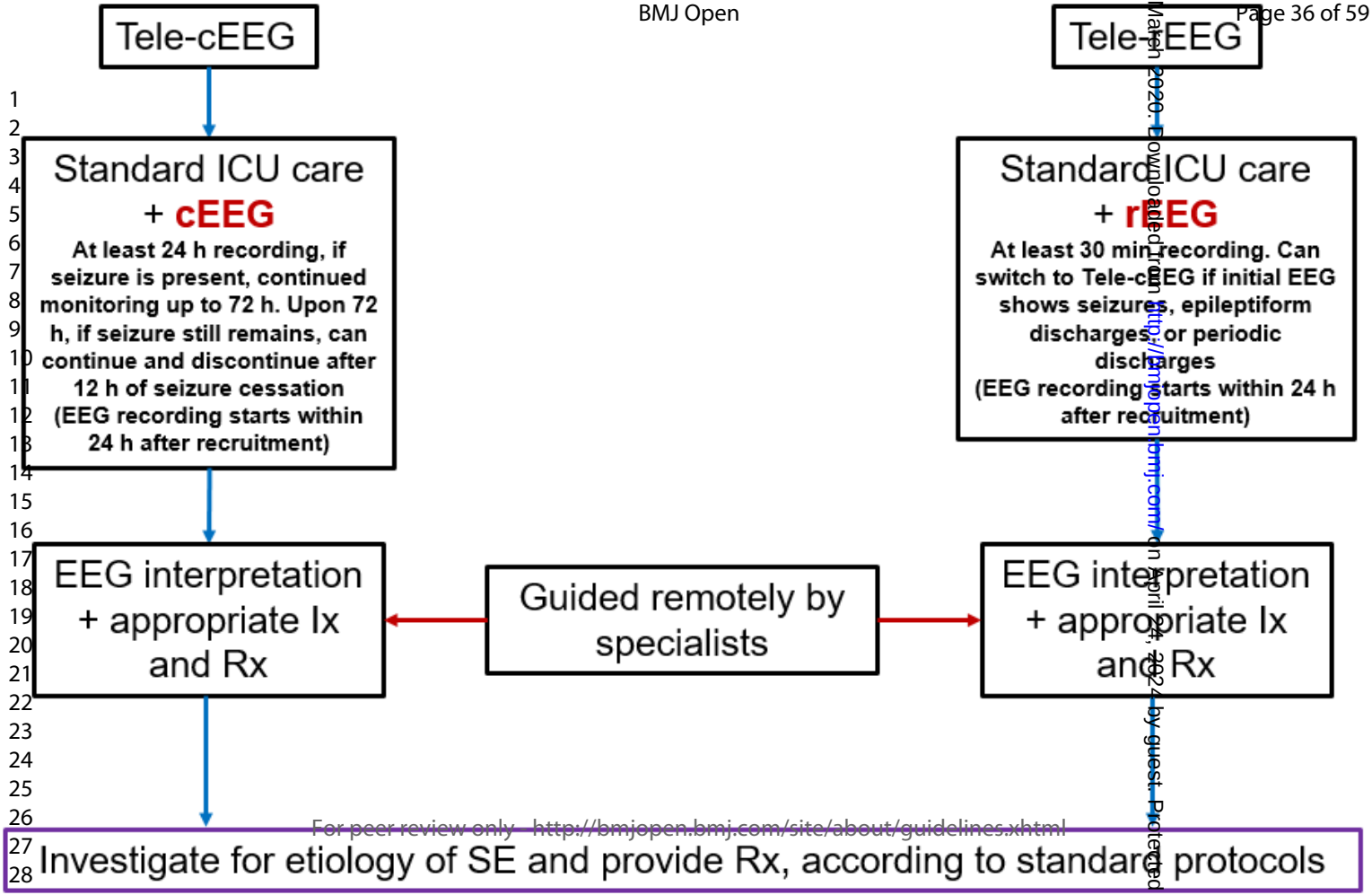
Figure 2: Implementation of study interventions

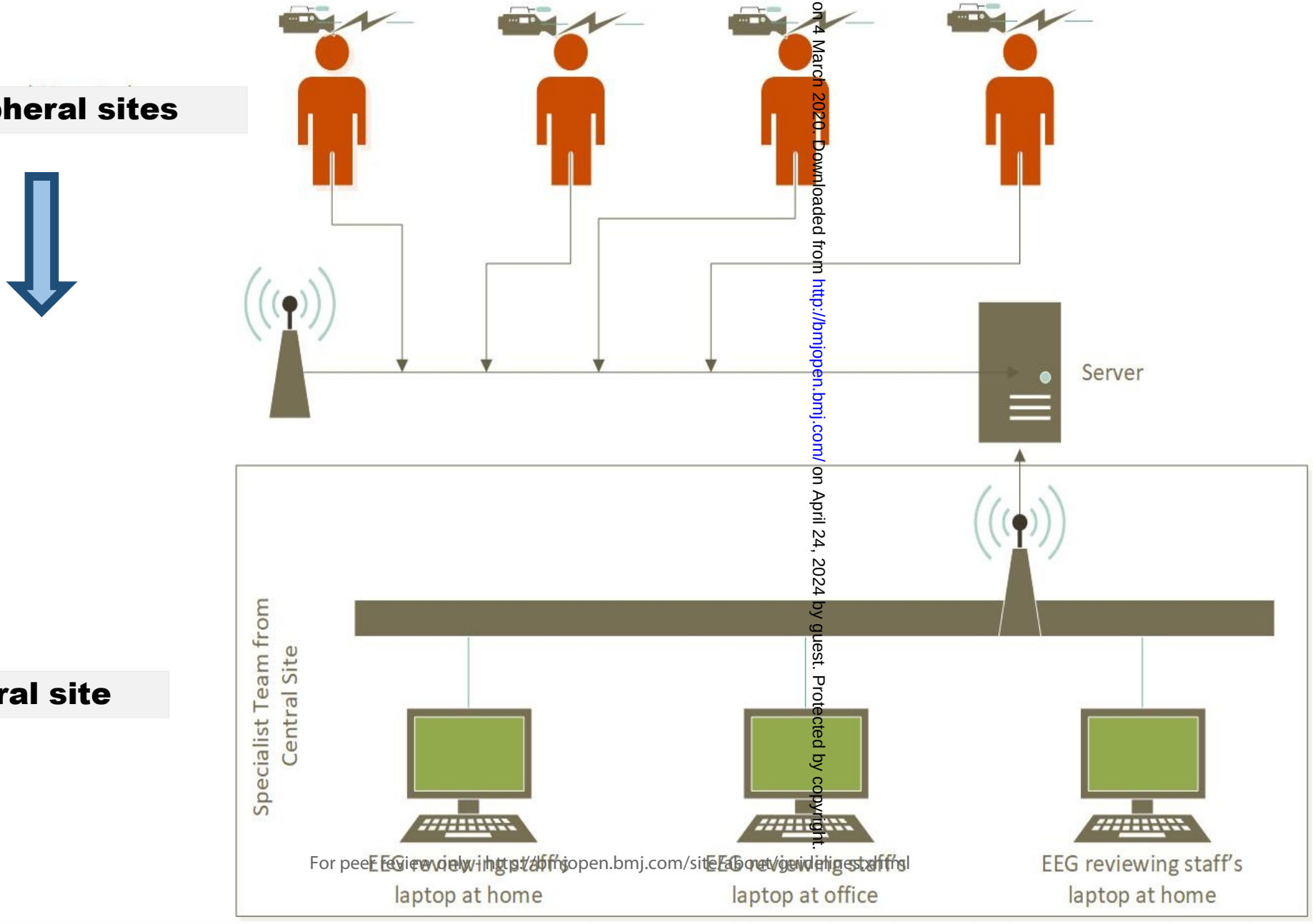
Abbreviations: cEEG = continuous EEG; rEEG = routine EEG; Ix = investigation; Rx = treatment; SE = status epilepticus

Figure 3: "De-centralized system" of the Tele-EEG

Upon being in charge, each EEG specialist can connect to the EEG machine at study sites and EEG server at the Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC) for real-time and off-line review, respectively at anytime and from anywhere via internet.







Supplementary files

Supplemental Figure 1: Study flow and investigator's role

Supplemental Figure 2: "Open communication architecture" of the Tele-EEG

"Flexible connectivity where specialists who review the EEG can access patient medical information on cloud storage via internet. Communication between specialists and treating neurologists is limited to traditional telephonic modalities and are functionally outside the Tele-EEG system."

Supplemental Figure 3: Analysis flow

Supplemental Figure 4: Decision tree diagram

Supplemental Table 1: Inter-rater agreement of the EEG interpretations among EEG specialists

Supplemental Table 2: The survey questionnaire to gauze the perceptions about Tele-cEEG implementation

Supplemental Table 3: Nine parts of case record form, type of data, and responsible operators

Supplemental Table 4: Timing of data collection

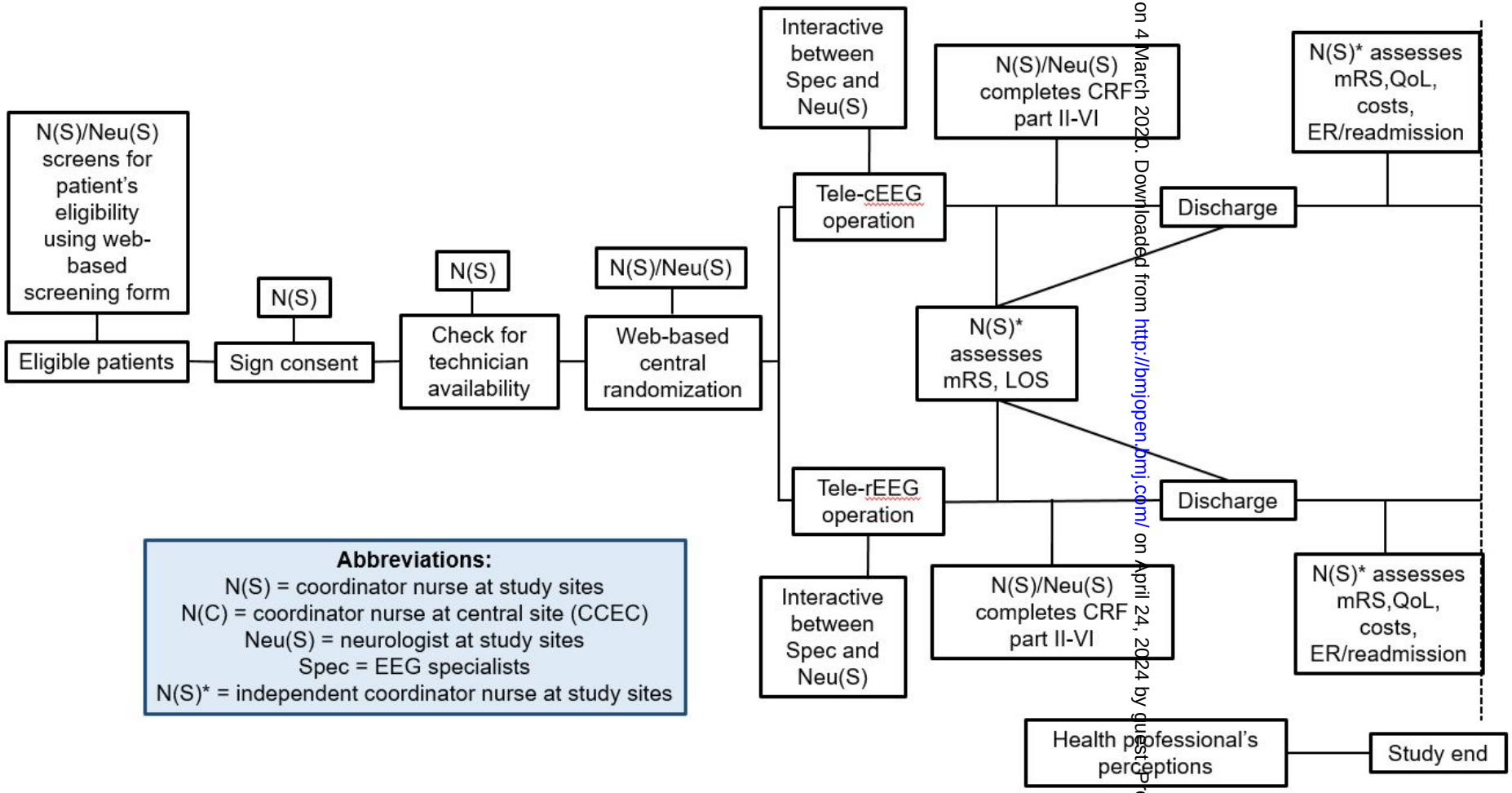
Supplemental Table 5: Statistical methods used for each study outcome

Supplemental Table 6: Parameters and data sources for probabilities of interested events, cost, and utility

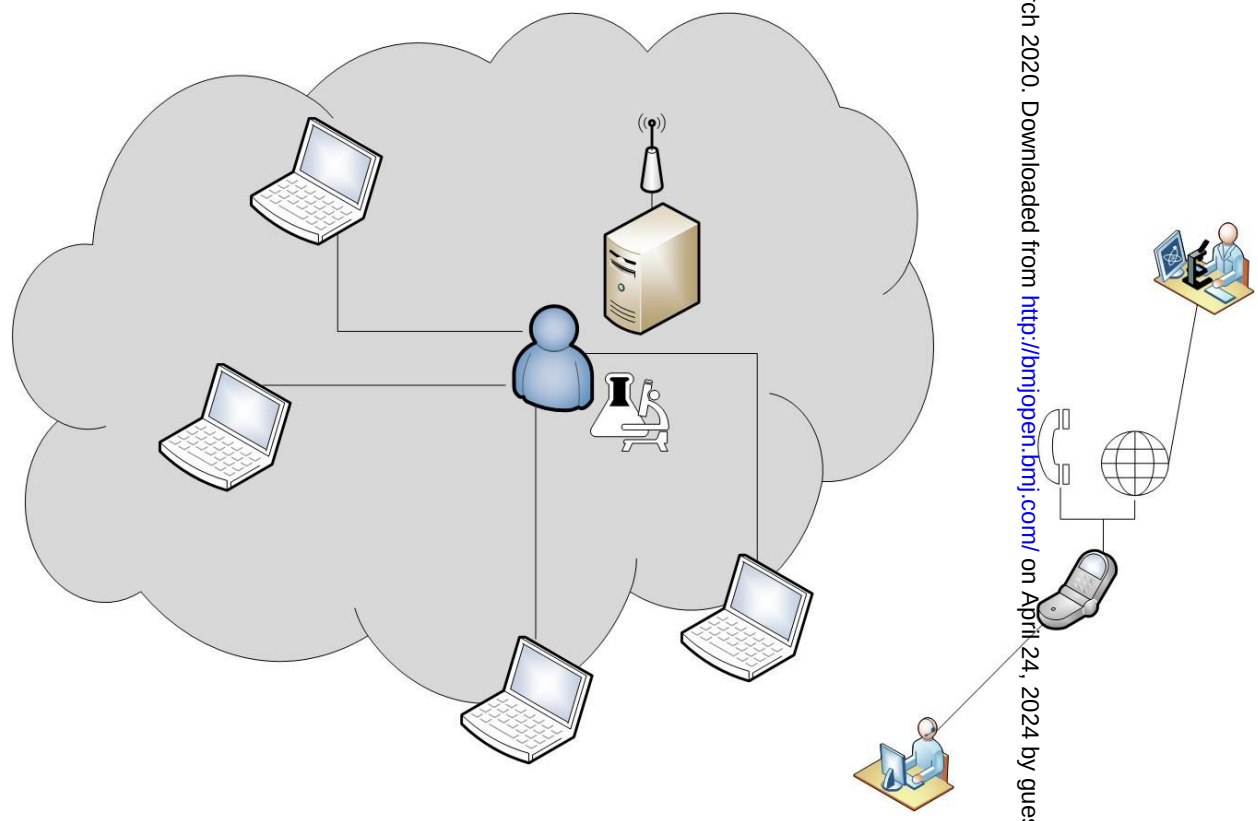
Supplemental document 1: SPIRIT checklist

Supplemental document 2: English language examples of the patient consent form

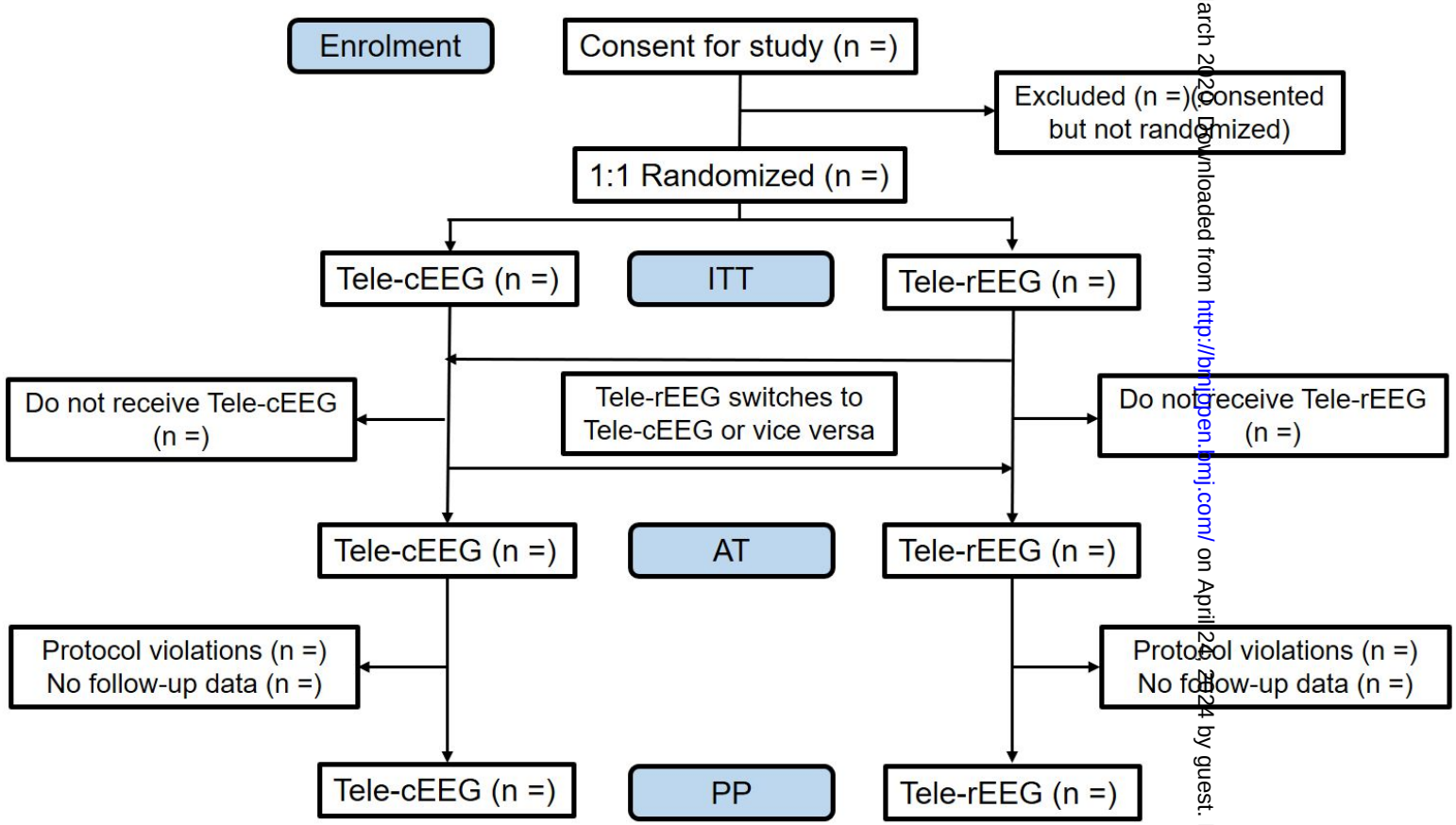
Supplemental Figure 1: Study flow and investigator's role



Supplemental Figure 2: "Open communication architecture" of the Tele-EEG

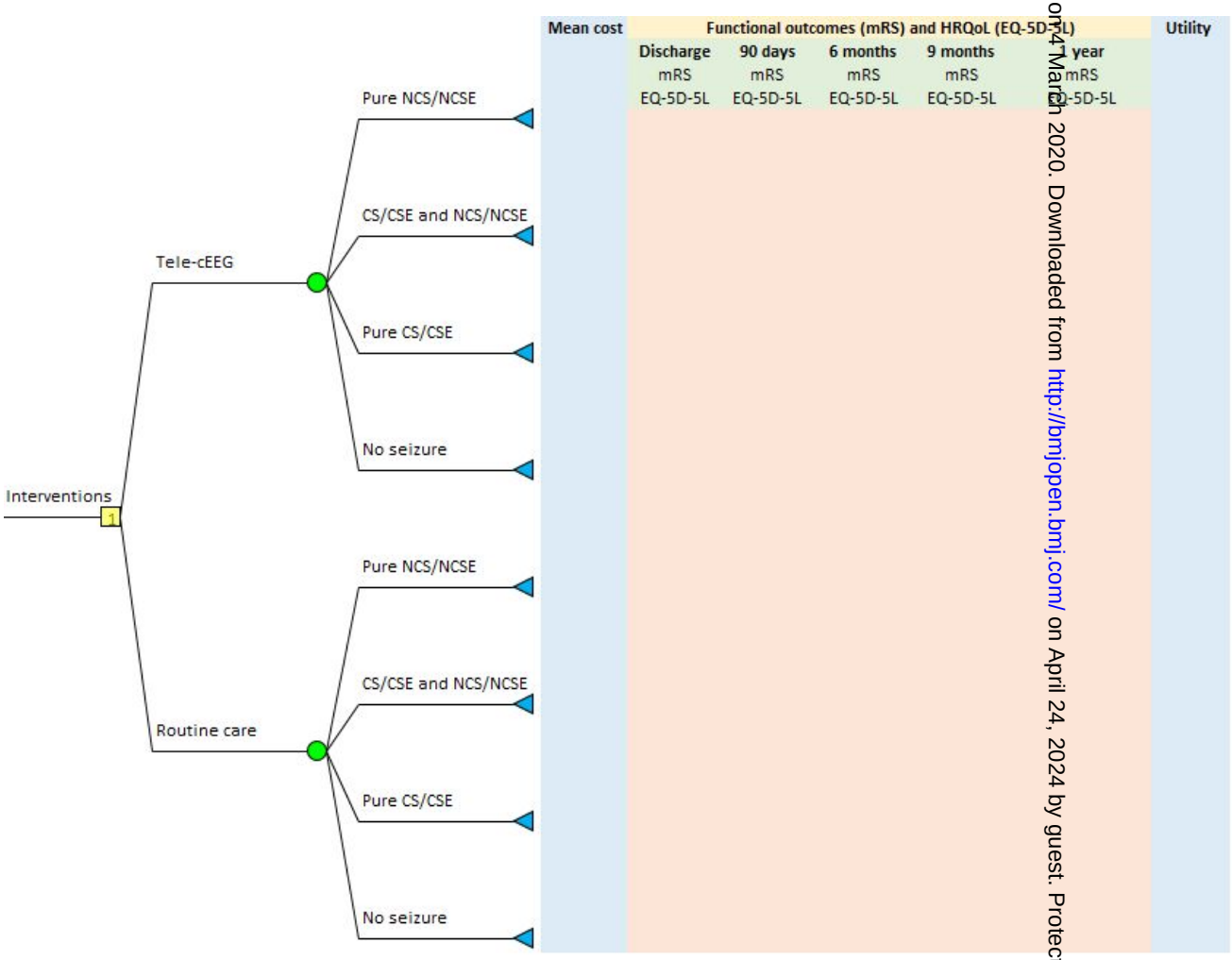


Supplemental Figure 3: Analysis flow



Abbreviations: ITT = intention-to-treat analysis; AT = As-treated analysis; PP = Per-protocol analysis

Supplemental Figure 4: Decision tree diagram



Supplemental Table 1: Inter-rater agreement of the EEG interpretations among EEG specialists

A) 23 tracings of common EEG findings in critically ills

EEG tracing items	Rater 1 score	Rater 2 score	Rater 3 score	Rater 4 score	Rater 5 score	Rater 6 score	Rater 7 score
1	1	1	1	1	1	1	1
2	1	0	1	1	0	1	1
3	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1
6	1	0	1	1	1	1	1
7	1	0	0	1	0	1	1
8	0	0	1	1	1	1	0
9	1	1	1	1	1	1	1
10	1	1	1	1	1	1	1
11	1	1	0	1	1	1	1
12	1	1	1	1	1	1	1
13	1	1	1	0	1	1	0
14	1	1	1	1	1	1	1
15	1	1	1	0	1	1	1
16	0	1	1	1	1	1	0
17	0	1	1	1	1	1	1
18	1	1	1	1	1	1	1
19	1	0	1	0	1	1	0
20	1	1	1	1	1	1	1
21	1	1	1	1	1	1	0
22	1	1	1	1	1	1	1
23	1	0	1	1	1	1	1

Score 1 = EEG findings described by most raters and being a correct answer according to the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version; Score 0 = otherwise EEG findings.

B) 5 tracings of seizures/status epilepticus

EEG tracing items	Rater 1 score	Rater 2 score	Rater 3 score	Rater 4 score	Rater 5 score	Rater 6 score	Rater 7 score
1	1	1	1	1	1	1	1
2	1	1	1	0	1	0	1
3	1	0	1	1	1	1	1
4	1	1	1	1	1	0	1
5	1	1	1	1	1	1	1

Score 1 = EEG findings described by most raters and being a correct answer to be "a seizure" or "not a seizure" according to the Salzburg EEG criteria; Score 0 = otherwise rating

Rater = epileptologist; There are 9 epileptologists participating this study. One epileptologist and Dr. Chusak Limotai who prepared the EEG tracing did not rate the EEG findings; as a result, there were only 7 epileptologists included for this inter-rater assessment.

Supplemental Table 2: The survey questionnaire for assessing perceptions of Tele-cEEG implementation

Part I: Neurologist perceptions about the Tele-EEG system, assessed at 1 year after the Tele-EEG implementation	
1. Assessment date	☐☐/☐☐/25☐☐
2. Name of neurologist	_____
3. Tele-EEG system of both Tele-cEEG and Tele-rEEG can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
4. Tele-cEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
5. Tele-rEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
6. Tele-EEG system helps the treating neurologist be able to provide appropriate treatment to the patients on a timely fashion.	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
7. EEG reporting system by the specialists is effective.	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
8. If the government supports adequate budget and personnel for the Tele-EEG system, would you like to implement the Tele-EEG system in your practice?	☐ 1. Yes; please specify reason _____ _____ ☐ 2. No; please specify reason _____ _____

Part II: Nurse perceptions about the Tele-EEG system, assessed at 1 year after the Tele-EEG implementation	
1. Assessment date	☐☐/☐☐/25☐☐
2. Name of nurse	_____
3. Tele-EEG system of both Tele-cEEG and Tele-rEEG can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
4. Tele-cEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
5. Tele-rEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
6. Tele-EEG system helps improve the quality of treatment	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
7. Cooperation between specialists and treating neurologists is effective	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
8. With the Tele-EEG system, cooperation between nurses and treating neurologists is effective	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
8. If the government supports adequate budget and personnel for the Tele-EEG system, would you like to implement the Tele-EEG system in your practice?	☐ 1. Yes; please specify reason _____ _____ ☐ 2. No; please specify reason _____ _____

Supplemental Table 3: Describe characteristics of case record form, type of data, and responsible operators

Forms	Data	Type of data	Responsible operators
Part I: **Inclusion and exclusion criteria**	Inclusion and exclusion criteria	Non-time dependent	Sub-PIs/ NS
Part II: **Hospital variables**	Hospital characteristics	Non-time dependent	NS
Part III: **Patient variables**	Patient characteristics	Non-time and time-dependent	Sub-PIs/ NS
Part IV: **Etiology of seizure/SE**	Etiology of SE	Non-time dependent	Sub-PIs
Part V: **Investigations**	Investigational data including EEG, imaging, blood and CSF test results	Time dependent	Sub-PIs
Part VI: **Treatment variables**	Information about treatment	Time dependent	Sub-PIs
Part VII: **Primary outcomes (i.e. functional outcomes, mortality, seizure/SE incidence)**	Assessment of functional outcomes, mortality, seizure/SE incidence	Time dependent and non-time dependent	Independent sub-PIs [1]/ Independent NS [2]
Part VIII: **Secondary outcomes (i.e. LOS, emergency visit/readmission, HRQoL, change of medical decision making, health professionals perceptions)**	Assessment of LOS HRQoL, emergency visit/readmission, HRQoL, assessment of changing of medical decision making, and health professional perceptions	Non-time dependent	Independent sub-PIs [1]/ Independent NS [2]
Part IX: **Costs**	All costs	Time dependent	Independent NS [2]

Abbreviations: Sub-PIs = neurologist at study sites; NS = coordinator nurses at study hospitals; SE = status epilepticus; CSF = cerebrospinal fluid; HRQoL = health-related quality of life

[1] Sub PIs who are not involved in patient screening and/or collecting the study independent variables

[2] NS who are not involved in patient screening and/or collecting the study independent variables

Supplemental Table 4: Timing of data collection

Variables	Time of data collection
Study independent variables (CRF part II – VI)	At enrollment period and during hospitalization
Primary outcome	
- Functional outcomes	At 3 and 7 days after starting EEG recording, at hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge
- Mortality	During hospitalization and 1 year
- Incidence of seizure/SE	During hospitalization
Secondary outcome	
- LOS	At hospital discharge
- Emergency visit/ readmission	At 90 days, 6 months, 9 months, and 1 year after discharge
- Change of medical decision-making	During hospitalization, immediately after patient recruitment
- HRQoL	At hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge
- Costs	At hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge

Supplemental Table 5: Statistical methods used for each study outcome

Outcomes	How is the outcome measured?		Type of outcome	Statistical methods
Functional outcome	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Dichotomous (poor vs favorable)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
	Once (at discharge)		Dichotomous (functional decline vs unchanged/improved)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
	Once (at 1 year)		Time to develop poor outcome (mRS 4-6) in patients with initial favorable outcome (mRS 0-3) at discharge and Time to develop favorable outcome in patients with initial poor outcome at discharge	Survival analysis with cumulative incidence function (CIF) and Univariate and multivariate cause-specific or subdistribution proportional hazard model
All-cause mortality	ICU/ hospital Case fatality rate	Once (during hospitalization)	Dichotomous (death vs survived)	Univariate and multivariate logistic regression
	Crude annual mortality rate	Once (at 1 year)	Time to being dead	Survival analysis with Kaplan-Meier (KM) method and Univariate and multivariate Cox propotional hazard regression
Cumulative incidences of seizures	Once (during hospitalization)		Dichotomous (presence vs absence of NCS/NSCE; combined NCS/NCSE and CS/CSE; and CS/CSE)	Univariate and multivariate logistic regression
ICU and hospital LOS	Once (at discharge)		Continuous (days)	Univariate and multivariate linear regression
Emergency visit/readmission	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Dichotomous (Yes vs No)	Univariate and multivariate logistic regression
HRQoL	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Continuous (total score)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
Health professional perceptions about the Tele-cEEG implementation	Once at 1 year after conducting the study		Dichotomous (Yes vs No)	Univariate and multivariate linear regression
Changing of medical decision	Once (during hospitalization)		Dichotomous (Changing vs not changing)	Univariate and multivariate logistic regression
Costs	Once		Continuous (total cost)	Univariate and multivariate linear regression

	(summation of costs at discharge, 90 days, 6 months, 9 months, 1 year)		

Supplemental Table 6: Parameters and data sources for probabilities of interested events, cost, and utility

	Parameters	Data sources
Probabilities of interested events		
Pure NCS/NCSE	Percentage of seizures detetced by EEG	CRF
Combined NCS/NCSE and CS/CSE	Percentage of seizures detetced by EEG	CRF
Pure CS/CSE	Percentage of seizures detetced by EEG	CRF
No seizure	Percentage of not having seizures	CRF
Cost		
At discharge		
Direct medical cost		
• Start-up cost for TM implementation	Sum up costs of internet connection set up; internet fee; and training for physicians and nurses; EEG monitoring cost	PI's budget management file
• Specialist cost	On-call stipends	PI's budget management file
• EEG technician cost	Stipends for electrode placement	PI's budget management file
• Total medical cost during admission	Sum up costs of variable costs	Hospital billing
Direct non-medical cost		
• Caregiver	Informal care cost[a]	Interview
Indirect cost		
• Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost		
At 90 days		
Direct medical cost		
• Home medication	Costs of medications used at home	Hospital billing; interview
• Outpatient visit	Costs during outpatient visit except for medications	Hospital billing; interview
• Re-admission	If any, costs during re-admission, EEG monitoring cost	Hospital billing
• Community health services	If any, costs related to district health promoting hospital care	Hospital billing
Direct non-medical cost		
• Caregiver	Informal care[a]	Interview
• Transportation	Cost per kilometer of running a car	Interview
• Ambulance	Cost per kilometer	Interview
• Out-of-pocket	Other expenses related to patient care	Interview
Indirect cost		
• Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost		
At 6 months		
Direct medical cost		
• Home medication	Costs of medications used at home	Hospital billing; interview
• Outpatient visit	Costs during outpatient visit except for medications	Hospital billing; interview
• Re-admission	If any, costs during re-admission	Hospital billing
• Community health services	If any, costs related to district health promoting hospital care	Hospital billing
Direct non-medical cost		
• Caregiver	Informal care[a]	Interview
• Transportation	Cost per kilometer of running a car	Interview
• Ambulance	Cost per kilometer	Interview
• Out-of-pocket	Other expenses related to patient care	Interview
Indirect cost		

• Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost **At 1 year** ***Direct medical cost*** • Home medication • Outpatient visit • Re-admission • Community health services ***Direct non-medical cost*** • Caregiver • Transportation • Ambulance • Out-of-pocket ***Indirect cost*** • Productivity loss	 Costs of medications used at home Costs during outpatient visit except for medications If any, costs during re-admission If any, costs related to district health promoting hospital care Informal care[a] Cost per kilometer of running a car Cost per kilometer Other expenses related to patient care Productivity loss (number of day × income/day)	 Hospital billing; interview Hospital billing; interview Hospital billing Hospital billing Interview Interview Interview Interview Interview
Clinical outcomes (utility) Functional outcomes (mRS) at discharge, 90 days, 6 months, 9 months, and 1 year HRQoL (EQ-5D-5L) at discharge, 90 days, 6 months, 9 months, and 1 year	 Scores; favorable or poor outcome Total scores	 CRF CRF

* Cases of patients who are re-admitted in other hospitals which are not our study hospitals; with approval by the patients (stated in the given signed consent) and permission from Ministry of Health investigators will archive hospital cost billing from the hospital where the patient is admitted.

[a]To identify and valuate informal care by caregiver, a market wage rates will be used

Supplemental document 1: SPIRIT checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1/ Line 1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4/ Line 5
	2b	All items from the World Health Organization Trial Registration Data Set	Page 4/ Line 5
Protocol version	3	Date and version identifier	Page 2/ Line 21
Funding	4	Sources and types of financial, material, and other support	Page 24/ Line 4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 23/ Line 10
	5b	Name and contact information for the trial sponsor	Page 24/ Line 5-7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 24/ Line 7-9

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 17/ Line 3
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 6-7
	6b	Explanation for choice of comparators	Page 11/ Line 13
Objectives	7	Specific objectives or hypotheses	Page 9/ Line 1
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 7/ Line 18-19
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7/ Line 22-24
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 10/ Box 1 Page 7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 12-13

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 9/ Line 11-14 Page 16/ Line 5-7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 12/ Line 18-19; Page 13/ Line 1-4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 14/ Box 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 16/ Line 1-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 16/ Line 1-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 9/ Line 10-23
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 9/ Line 16-18 Page 11/ Line 1-4

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 9/ Line 16-19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 11/ Line 6-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 11/ Line 6-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 16/ Line 15-22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 16/ Line 5-7
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17/ Line 4-6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 19/ Line 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 17/ Line 23 Page 20/ Line 3
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 17/ Line 9-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	None
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 17/ Line 9-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 17/ Line 8-15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 23/ Line 1-8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 23/ Line 8-10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9/ Line 14-16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	None
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17/ Line 5-8 Page 24/ Line 13-17

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 23/ Line 23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 24/ Line 13-17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	None
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 16/ Line 10-14
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 23/ Line 12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 24/ Line 13-17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental document 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	None

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

Supplemental document 2: English language examples of the patient consent form

	Faculty of Medicine **Chulalongkorn University**	**Informed Consent Form**	**AF 09-05/5.0** **Page 1/3**

INFORMED CONSENT FORM

NAME OF STUDY: Efficacy and economic evaluation of delivery of care with Tele-continuous EEG in critically ill patients: a multicenter randomized controlled trial (Tele-cRCT Study)

STUDY DOCTOR: Chusak Limotai, MD, Atiporn Ingsathit, MD, PhD, Kunlawat Thadanipon, MD, Oraluck Pattanaprateep, PhD, Anuchate Pattanateepapon, MSc, Kammant Phanthumchinda, MD, Nijasri C. Suwanwela, MD, Iyavut Thaipisuttikul, MD, Kanokwan Boonyapisit, MD, Ammarin Thakkinstian, PhD

DATE OF CONSENT: Date..... Month..... Year.....

Study number	
Subject's Name	
Subject's Identification Number	
Subject's Date of Birth	

SIGNATURES

I,.....Address.....
.....have read the information in the attached subject information sheet version date:.....
..... By personally signing and dating this informed consent form, you affirm that you have read and understood this informed consent form; the study has been explained to you, your questions have been answered, and you agree to take part in this study; or you as the Guardian or Legally Authorized Representative give your permission for the adult who lacks capacity to provide this informed consent to participate in this study. You do not give up any of your legal rights by signing this informed consent form. You will receive a signed copy of this Informed Consent Form and Authorization for Use and Disclosure of Health Information for Research Purposes.

Participant

..... Signature of person giving consent

(.....) Printed Name of person giving consent

Date.....Month.....Year.....

	**Faculty of Medicine** **Chulalongkorn University**	**Informed Consent Form**	**AF 09-05/5.0** **Page 2/3**

I Agree

Not Agree

to have my leftover biological samples (such as blood) to be stored for the purpose of study test

..... Signature of person giving consent (.....)

Printed Name of person giving consent Date.....Month.....Year.....

I certify that I have the legal authority under applicable law to make this request on behalf of the patient identified above:

Guardian or Legally Authorized Representative (if applicable)

..... Signature of Guardian or Legally Authorized Representative

(.....) Name of Signature of Guardian or Legally Authorized Representative (Print Name)

.....

Relationship to Participant (e.g. guardian, power of attorney, etc.)

Date.....Month.....Year.....

Person Obtaining Consent

..... Signature of Person Obtaining Consent (.....)

Name of Person Obtaining Consent (Print Name) Date.....Month.....Year.....

Witness

..... Signature of Witness (if applicable)

(.....) Printed Name of Witness (if applicable)

Date.....Month.....Year.....

	Faculty of Medicine **Chulalongkorn University**	**Informed Consent Form**	AF 09-05/5.0 Page 3/3

INVESTIGATOR STATEMENT

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions raised have been answered to the individual's satisfaction.

..... Signature of Investigator (.....) Printed Name of Investigator Date.....Month.....Year.....

Thank you for your help.

BMJ Open

Efficacy and economic evaluation of delivery of care with Tele-continuous EEG in critically ill patients: A multicenter randomized controlled trial (Tele-cRCT Study) study protocol

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Intensive care
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Epilepsy < NEUROLOGY

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Efficacy and economic evaluation of delivery of care with Tele-continuous EEG in critically ill patients: A multicenter randomized controlled trial (Tele-cRCT Study) study protocol

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Dr. Limotai reports no disclosures; Dr. Ingsathit reports no disclosures

Dr. Thadanipon reports no disclosures; Dr. Pattanaprateep reports no disclosures

Mr. Pattanateepapon reports no disclosures; Dr. Phanthumchinda reports no disclosures

Dr. Suwanwela reports no disclosures; Dr. Thaipisuttikul reports no disclosures

Dr. Boonyapisit reports no disclosures; Dr. Thakkinstian reports no disclosures

Version 2_Date 27 October 2019

Abstract

Introduction: Some critically ill patients are disclosed by continuous electroencephalography (cEEG) monitoring due to nonconvulsive seizure (NCS) and/or nonconvulsive status epilepticus (NCSE). Shortage of epilepsy specialists, especially in developing countries, is a major limiting factor to implement the cEEG in general practice. Delivery of care with the Tele-cEEG may be a potential solution as specialists from a central facility can remotely assist local neurologists in distant areas to interpret the EEG findings and suggest proper treatment. No Tele-cEEG program has been implemented to help improve quality of care. Therefore, this study is conducted to assess the efficacy and cost-utility of implementing the use of Tele-cEEG in critical care.

Methods and analysis: Tele-cRCT is a 3-year prospective, randomized, controlled, parallel, multicenter, superiority trial comparing delivery of care with "Tele-cEEG" intervention with "Tele-routine EEG (Tele-rEEG)" in patients with clinical suspicion of NCS/NCSE. A group of EEG specialists and Tele-EEG system were set up to remotely interpret the EEG in 6 regional government study hospitals across Thailand. Primary outcomes are functional neurological outcome [modified Rankin scale (mRS)]; mortality rates; and incidence of seizures. Secondary outcomes are cost-utility; length of stay; emergency visit/readmission; impact on changing medical decision-making; and health professional perceptions about Tele-cEEG implementation. Functional outcome (mRS) will be assessed at 3 and 7 days after recruitment and again at time of hospital discharge, 90 days, 6 months, 9 months, and 1 year. Costs and health-related quality of life using Thai-version 5-level EQ-5D (EQ-5D-5L) will be assessed at hospital discharge, 90 days, 6 months, 9 months, and 1 year.

Ethics and dissemination: This study has been approved by the Faculty of Medicine, Chulalongkorn University and Ramathibodi Hospital, Mahidol University Ethics Committees and registered on Thai Clinical Trials Registry. The results will be disseminated in a peer-reviewed journal.

Trial registration number: TCTR20181022002; Pre-results.

Strengths and limitations of this study

- This study is the first study assessing the efficacy and cost-utility of implementing the Tele-continuous electroencephalography (Tele-cEEG) in critical care
- This study is also among very few studies assessing efficacy of the cEEG on functional outcome and mortality
- This study is limited to implement the Tele-cEEG in only advanced level hospitals in distant areas. As a result, the results cannot be generalized to apply in the smaller scale hospitals where neurologists are not available and drug items and/or investigations are limited.
- Applying the study intervention [either Tele-routine EEG (Tele-rEEG) or Tele-cEEG] will not be able to blind due to its nature, so bias from outcome ascertainments might be present.

Introduction

Status epilepticus (SE) is a life-threatening medical and neurologic emergency requiring prompt recognition and treatment. A recent meta-analysis including 43 studies reported a pooled crude annual incidence rate of SE of 12.6/100,000 (95% CI 10.0-15.3) [1]. The pooled case fatality rate and the pooled crude annual mortality rate of SE were 14.9% (95% CI: 11.7-118.7) and 0.98/100,000 (95% CI: 0.74-1.22), respectively [1]. Based on the National Database of Thailand during the 2010 fiscal year, the SE rate in Thailand was 5.10/100,000 population, with a mortality rate of 0.6 death/100.000 population [2].

SE can manifest with either overt convulsive movements or subtle/no overt convulsion. The former and the latter have been known as "convulsive status epilepticus (CSE) and "nonconvulsive status epilepticus (NCSE)", respectively. In practice, electroencephalography (EEG) recording is required to help in diagnosis of nonconvulsive seizure (NCS)/NCSE, otherwise, it may be under-recognized and left untreated [3]. Our recent meta-analysis revealed that continuous EEG (cEEG) is significantly better than the routine EEG (rEEG) to help detect NCS/NCSE [4]. Overall prevalence of NCS/NCSE is 15.6% in critically ill patients, but higher in post convulsive SE (32.9%), central nervous system (CNS) infection (23.9%), and post cardiac arrest (22.6%)[4] patients. Evidences of systemic complications and neurological consequences have been clearly demonstrated in CSE [5], but remain unclear for NCS/NCSE. Previous observational studies did not address clear results as to whether the unfavorable outcome of study patients was a direct consequence of NCS/NCSE or the result of other potential confounding factors i.e. patient's characteristics, etiology, and treatment [6 7]. As a result, the

aggressiveness to treat patients with NCS/NCSE is unknown and varies among treating physicians [6].

Although EEG recording is necessary for helping in detection of NCS/NCSE, its routine use, particularly cEEG monitoring, has still been an issue because it is costly and requires specialists to interpret the findings [3]. Due to shortage of epilepsy specialists, especially in developing countries, cEEG implementation in general practice is therefore limited. Delivery of care with a telehealth system [8] may be a promising solution to this problem as specialists can remotely assist general physicians in distant areas to interpret EEG findings and suggest proper management. Until now, no one has implicated the Tele-cEEG system in helping improve quality of care particularly for SE patients. By doing this, at the same time we can assess prospectively both the benefit of Tele-cEEG and neurological consequences of the NCS/NCSE.

The Tele-cRCT study is a multicenter randomized controlled trial (RCT). With an RCT design, efficacy evidence of the Tele-cEEG implementation will be addressed with valid results since potential confounding factors will be balanced and adjusted between two groups of comparison. Alongside economic evaluation, cost-utility analysis of the Tele-cEEG will be also addressed and can be introduced to the community in order to initiate the adoption of this Tele-cEEG in routine practice.

Methods and analysis

This study protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), see SPIRIT checklist in Supplemental document 1.

Study design and setting

Tele-cRCT is a 3-year prospective, randomized, controlled, parallel, multicenter, superiority trial comparing delivery of care with "Tele-cEEG" intervention with "Tele-rEEG" in patients with clinical suspicion of NCS/NCSE. We have currently conducted a pilot study in some study hospitals in order to test the feasibility of the remote EEG monitoring, and the whole processes of data collection. A group of EEG specialists and Tele-EEG system were set up to remotely interpret the EEG in the study hospitals which are 6 regional government hospitals across Thailand. All six study hospitals have met our eligibility criteria which are 1) Regional hospitals defined according to Ministry of Public Health of Thailand as hospitals in service plan A (Advance-level hospital) with capability to treat patients who require advance and sophisticated technology; 2) Having surgical or medical ICUs which are run by qualified medical professionals, and sufficient requisite medical equipment in the ICUs, corresponding to any level of three-tiered system ICUs proposed by the American College of Critical Care Medicine (ACCM) [9]; 3) Having at least two portable EEG machines available and capability to operate the EEG recording in the ICUs or wards; 4) Having neurologists who are capable to treat status epilepticus with available necessary medications recommended by 2016 American Epilepsy Society (AES) guideline [10] and having capability to do etiology work up of status epilepticus, suggested by the 2012 Neurocritical Care Society [3], but 5) No qualified Epileptologists to interpret the EEG; and 6) cEEG monitoring is not part of the hospital's routine service.

Both intervention (Tele-cEEG) and control (Tele-rEEG) arms will be assisted by a specialist team to interpret the EEG findings and suggest appropriate treatment in order to standardize a "specialist factor" which might affect study outcomes. It should be noted that the EEG recording, even a rEEG, is under-utilized in Thailand due to a severe shortage of

epileptologists and neurologists who are comfortable and confident to interpret EEG findings. The study flow is shown in Figure 1.

Study objectives

Between intervention (Tele-cEEG) and control (Tele-rEEG) arm, our primary objective is to compare the efficacy in terms of functional outcomes (mRS) and mortality rate assessed at 3, 7 days after recruitment, at discharge, 90 days, 6 months, 9 months, and 1 year after hospital discharge, as well as detection rate of seizures during hospitalization. The secondary objective is to compare efficacy of ICU/hospital length of stay (LOS), emergency/readmission, cost-utility, and impact on changing of medical decision-making, and healthcare professional perceptions about the Tele-EEG implementation.

Screening and randomization

A dedicated nurse in each study hospital screens for eligible patients in every new admission or new neurology consultation from adult ICUs or medical or surgical wards to see whether or not potential study subjects fulfill one of the five conditions indicated in the inclusion criteria, listed in Box 1. Eligibility is then confirmed with a neurologist at the study site. In case of fulfilling eligibility, a nurse will provide study information to patients or relatives and then request for signed informed consent. A nurse will then log-in in order to fill out the study web-based screening form, and if the patient is eligible the system will automatically operate a central randomization and then assigning study intervention (Tele-cEEG vs Tele-rEEG) along with the patient's subject identification number for the study. A block randomization will be applied. Since this study is not double-blind where health care teams will not be blinded to the

intervention, in order to protect the integrity of the randomization process randomly selecting the block size will be performed prior to randomly select the patient. The block sizes will be 4, 6, 8, and 10. The ratio of intervention and control is 1:1. Statisticians at the central site will generate random sequences of assigned intervention using STATA version 15.0. Study flow and investigator's role are shown in Supplemental Figure 1.

Box 1: Inclusion and exclusion criteria for patient enrolment

Inclusion and exclusion criteria for enrolment
Inclusion criteria
1. Adult patients, aged ≥ 15 years, who are admitted in surgical or medical ICUs or wards
2. Suffering from at least one of the 5 conditions which are recommended by the 2012 Neurocritical Care Society[1] as well as corresponding with the results of our meta-analysis[2] to be highly associated with NCS/NCSE 2.1 Recent clinical seizure/status epilepticus without return to baseline (pre-status) with - In case of receiving sedative medication: at > 10 minutes after clinical seizure/SE ends, patient's GCS does not return to baseline - In case of not receiving sedative medication: at 2 hours after clinical seizure/SE ends, patient's GCS does not return to baseline 2.2 Severely depressed consciousness from any cause (except for TBI, SAH, ICH) with GCS ≤ 8 2.3 Intracranial hemorrhages with any of - TBI with GCS 6-12 - SAH with Hunt & Hess Classification grade ≤ IV or GCS > 5 - ICH with ICH score ≤ 3 2.4 Suspected NCS/NCSE in patients with altered mental status (cause indeterminate) 2.5 CNS infection with altered mental status
3. Patient and/or their relative is willing to participate with the study with given signed informed consent
4. Patients or caregivers which are defined as the main person, other than a health, social, or voluntary care provider can provide functional outcome data after discharge
Exclusion criteria
1. Patients with post cardiac arrest
2. Patients with advanced stage cancer (stage IV)
3. Patients with AIDs (CD4 count < 200 cells/mm^3 or with certain opportunistic infections)
4. Patients with alcoholic intoxication with/without delirium tremens*
5. Patients with poor functional outcome at pre-admission state (mRS 4-6)
6. Patients with extensive lacerations, skin lesions, or surgical wound where the electrode placement is not able to be applied

Abbreviations: NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; GCS = Glasgow Coma Scale; TBI = traumatic brain injury; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; CNS = central nervous system; mRS = modified Rankin Scale

[1] Brophy GM et.al., 2012; [2] Limotai C et.al., 2019

* These patients are excluded due to the fact that there are a large number of these types of patients in rural areas of Thailand who may significantly outweigh other types of patients included, where there has been no reported magnitude of its association with NCS/NCSE.

Allocation concealment

In order to prevent selection bias, the process of central randomization will be applied to conceal the allocation sequence from those assigning participants to intervention groups until the moment of assignment.

Blinding

As the nature of assigned intervention is different and easy to recognize (i.e. continuous (prolonged) versus rEEG (short) EEG recording), participants will not be blinded to the intervention assigned. Health care teams including physicians and nurse also will not be blinded because they will be involved in the patient care using either cEEG or rEEG. However, dedicated outcome assessors will be blinded to patient allocations.

Intervention

This study consists of two arms which apply two different interventions; one with Tele-cEEG (24-hr monitoring, intervention arm) and the other with Tele-rEEG (30-mins monitoring, control arm), see Figure 2. Since important study outcomes are functional outcomes and mortality after SE, a specialist team will assist the control arm (Tele-rEEG) to interpret EEG findings and suggest appropriate treatment in order to standardize a specialist factor which might affect the outcomes.

Tele-EEG system and database: Central facilities for the Tele-EEG system/EEG database and the patient's database were respectively set up at Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC) and the Section for Clinical Epidemiology and Biostatistics, Ramathibodi Hospital (Rama CEB). Two separate EEG review systems will be set up. One for real-time review with TeamViewer® software and the other for off-line review using EEG data uploaded on cloud storage. For off-line review, EEG data uploaded on cloud storage will be downloaded into EEG database server at CCEC on a daily basis. Upon being in charge, each EEG specialist can connect to the EEG machine at study sites and EEG server at CCEC for real-time and off-line review, respectively at anytime and from anywhere via internet ("De-centralized system"), see Figure 3. For both real-time and off-line review, password access control will be used.

Methods of conducting Tele-EEG: The EEG recording must be initiated within 24 hours after recruiting (randomization) patients in both arms (Tele-cEEG vs Tele-rEEG). Within working hours (8 am to 4 pm), an EEG technician will apply the EEG electrodes, where at the same time, an in-charge specialist on that day will be notified to prepare for EEG review. After completing internet connection set-up, Tele-EEG system integrity will be checked at both ends.

For the Tele-cEEG, a specialist will periodically report the EEG findings using standard case record form (CRF) every 2 or 6 or 12 hours, depending on clinical urgency determined by clinical data and initial 30-minute/prior EEG findings. EEG will be monitored for at least 24 hours. If seizures are detected, the Tele-cEEG will be continued and discontinued after 72 hours. However, if seizures are still present at 72 hours, the Tele-cEEG can be continued and then

discontinued after seizure cessation for 12 hours. Continuation of Tele-cEEG monitoring after 72 hours will be treated as co-intervention, see Figure 2.

For the Tele-rEEG, a specialist will interpret the EEG findings and feedback the results using the standard CRF to the treating neurologist at bedside within 2 hours after finishing the EEG study. EEG will be monitored and recorded for 30 minutes. Switching the Tele-rEEG to the Tele-cEEG is possible if the initial findings disclose seizures and/or epileptiform activity or periodic discharges. These specific EEG findings were reported by the 2012 Neurocrititical Care Society guideline to be highly associated with NCS/NCSE [3]. In this case, the Tele-cEEG will be treated as co-intervention, see Figure 2. Performing additional rEEG in case that a clinical concern for on-going seizure still remains is allowed; although once again this will be recorded and treated as co-intervention.

In both arms, standard consensus protocols for investigations and management of SE will be followed for all patients. An in-charge specialist will discuss the EEG findings with the treating neurologist at bedside and then appropriate management according to the consensus protocols. Flexible connectivity will be used where specialists who review the EEG can access patient medical information on cloud storage via internet ("Open communication architecture"), see Supplemental Figure 2. Communication between specialists and treating neurologists is limited to traditional telephonic modalities and are functionally outside the Tele-EEG system, see Supplemental Figure 2.

EEG reviewing organization: Nine EEG specialists included for this study are all certified Epileptologists with training in either Thailand and/or North America (US and Canada).

All EEG specialists will be assigned to be on-call for reviewing the EEG. Each on-call duration lasts for 24 hours (7 am to 7 am on the following day). EEG specialists are responsible to review both the cEEG and rEEG on that day. An EEG specialist will give his/her report to the other EEG specialist on the following day by verbal communication using a unified EEG finding and list of management report forms to ensure continuity of the appropriate management.

Standard consensus protocols for investigations and management of SE were developed using Modified Delphi method [11 12]. All nine EEG specialists were invited to perform on-line Google survey and then face-to-face discussion in order to standardize and make consensus protocols on how to report the EEG findings and manage SE. The terminology and definition of the EEG wave forms used in this study will be mainly based on the American Clinical Neurophysiology Society (ACNS) proposed standardized terminology 2012 version [13]. A unified EEG report form will be created as part of web-based CRF. Twenty-three and 5 EEG tracings with a variety of common EEG findings in critically ill and seizure/status epilepticus EEG patterns were prepared and then used to test inter-rater agreement [14] among 7 EEG specialists (see Supplemental Table 1). Percent level of agreements of these parts were respectively 79.3 and 79.1, with the Gwet's kappa coefficient (95% CI) of 0.7354 (0.5825, 0.8883) and 0.7373 (0.3409, 1.0000) indicating substantial agreements for both parts.

Study outcomes: Primary and secondary outcomes are listed in Box 2.

Box 2: Primary and secondary outcomes

Primary and secondary outcomes
Primary outcome
1. Functional outcomes including poor (mRS 4-6) versus favorable (mRS 0-3) functional outcomes and functional decline (i.e., mRS increases at least one score) of the actual scores, in which mRS will be assessed at 3 and 7 days after starting EEG recording (recruitment), at discharge, 90 days, 6 months, 9 months, and 1 year.
2. ICU/in-hospital case fatality rate during hospitalization and crude annual mortality rate assessed at 1 year after hospital discharge
3. Cumulative incidences of each type of seizures i.e., pure NCS/NCSE, combined NCS/NCSE and CS/CSE, and pure CS/CSE in the intervention and control arms
Secondary outcome
1. ICU and hospital length of stay
2. Emergency visit and re-admission after hospital discharge assessed at 90 days, 6 months, 9 months, and 1 year
3. Health-related Quality of Life, assessed by Thai-version EQ-5D-5L at hospital discharge, 90 days, 6 months, 9 months, and 1 year
4. Costs assessed at hospital discharge, 90 days, 6 months, 9 months, and 1 year
5. In order to assess the impact of change of medical decision making of the treating neurologists at study sites, a structured questionnaire will be assessed immediately after patient recruitment, but prior to knowing the EEG results and then compared with the actual activities (investigations/treatment) after integrating the EEG findings with other clinical data
6. In order to assess the health professional perceptions about Tele-cEEG implementation; a structured questionnaire will be evaluated by nurses and neurologists at study sites, assessed at 1 year after conducting the study, see Supplemental Table 2

Abbreviations: mRS = modified Rankin Scale; NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; CS = convulsive seizure; CSE = convulsive status epilepticus

Sample size calculation

The primary outcome used for estimation of sample size is functional outcome measured by mRS. It is dichotomized into favorable (mRS 0-3) and poor outcomes (mRS 4-6). The formulae for the number of participants is estimated as follows [15]:

$$N = \left(z_{\alpha/2} + z_{\beta}\right)^2 \frac{\pi_0(1-\pi_0)+\pi_1(1-\pi_1)}{(\pi_0-\pi_1)^2}$$

N = total number of participants; $Z_{\alpha/2} = 1.96$; $Z_{\beta} = 0.84$; π_0 = the true proportions in the control populations; π_1 = the true proportions in the in intervention arm

As for previous study by Khawaja et al [16], which up until now it is the only one available study assessing functional outcomes in critically ill patients who received cEEG monitoring (intervention) and also in those who did not receive the cEEG (controls) [16], the proportions of patients with poor outcome (mRS 3-6) was 0.829 for control groups. If we plan to detect the difference of poor functional outcome of 0.1 (which should be clinically meaningful), with setting a ratio of intervention vs control, type I and II errors of 1:1, 0.05, and 0.2; the estimated sample size is as follows:

$$N = (1.96 + 0.84)^2 \frac{0.829\ (1 - 0.829) + 0.729(1 - 0.729)}{(0.829 - 0.729)^2}$$

$$= 7.84 \frac{(0.142 + 0.198)}{0.01}$$

$$= 267$$

Assuming a 20% loss to follow up, the total number of participants required in each arm is 270 + 54 = 324. In summary, in order to have 80% power to detect a 10% reduction of poor outcomes at a 5% level of significance (2-sided), we require 324 participants in each arm; so this would result in 648 participants in total.

Patient recruitment

A pilot study will be performed to assess whether there will be any recruitment issues in the designated study hospitals. The initial recruitment plan is 10-15 patients per month from each hospital. After the formal pilot study, this plan may be changed according to actual recruitment rate of each hospital. However, PI and/or coordinator nurse at the central site (CCEC) recruitment centers will be continuously monitoring and encouraging patients to join the study via telephone reminder. In order to prevent bias related to predominant participant recruiting

from one particular study site, actual recruitment rates from the pilot study will be used to weight the quota for recruitment from each hospital.

Patient and public involvement

Neither patients nor public have been involved during the design of the Tele-cRCT study. The Tele-cRCT study results will be available at https://clinicaltrials.in.th/ to both patients and general public. Assessment of the burden of the intervention has not been foreseen in the present study.

Data collection and data statement

Case record form (CRF) was created according to information of the study variables, intervention, and outcomes. These are divided into 9 parts and were created in paper-based forms, except for patient screening and EEG findings forms which were both created in web-based CRF (see Supplemental Table 3). Timing of data collection is shown in Supplemental Table 4. After ethics committee approval in each study hospital and obtaining written signed consent from patients or caregivers, principal investigators (PI) then asked for permission to access patient information to collect the patient data in respective study hospitals.

Participant neurologists assigned to be sub-PIs in each study hospital will help facilitate accessing archived raw data. Study variables and outcomes will be collected at enrollment period after randomization, then fill in the CRFs. Independent outcome assessors (either sub-PIs or coordinator nurses at study hospitals) will assess the primary and secondary outcomes.

Data management

Conversion of the paper-and web-based CRF into an electronic database (EpiData Version 3.1, The EpiData Association, Odense, Denmark) is planned. Data entry will be assigned to two data entry staff. Patient database files will be kept in a personal computer at Rama CEB and also backed up in the PI's notebook. These two computers require passwords to access the database. Scheduled site visits for data audits will be arranged for each participant hospital every 1-2 months during the first 6 months and then every 3 months. In order to ensure appropriate intervention delivery, all completed competency assessment tools will be returned to the PI and will be included as a standard monitoring report to the Data and Safety Monitoring Board (DSMB). Manual, interactive, and batch checking methods will be used to ensure completeness and correctness of the data. In order to maintain high quality of the data, regular meetings to check for data correctness and give feedback between data collectors and data entry staff will be arranged on a monthly basis.

Data analysis plan

Descriptive statistics: Baseline characteristics between Tele-cEEG and Tele-rEEG arms are presented in mean with standard deviation (SD) or median with interquartile range (IQR) for continuous data depending on distribution of the data. For categorical data, frequency and percentage are presented. To compare characteristics of patients between groups, Pearson chi-square or Fisher exact test will be applied for categorical data; Student t-test or Mann-Whitney test for normal and non-normal distributed continuous data will be used.

Imputation: Imputations will be performed using STATA software version 15.0. Missing data will be explored to assess whether distribution of missing data is missing at random (MAR), if not this is said to be nonignorable. Multiple imputation (MI) will be applied. The number of imputations will be determined by percentage of missing values and MI performance [17], reflected by relative variance increase and fraction of missing information values.

Analytical statistics: Statistical methods will depend upon how the outcomes are being measured and the type of outcomes, either dichotomous or continuous, as summarized in Supplemental Table 5. Regarding time to event data analysis of functional outcome (mRS), the start date will be set as date of starting EEG recording. Patients will be initially stratified into having poor (mRS 4-6) versus favorable outcome (mRS 0-3) at discharge. These two groups will be analyzed separately. A group with initial poor outcome, time to first ever favorable outcome analysis will be performed, whereas a group with initial favorable outcome time to first ever poor outcome will be estimated. Since death will be treated as competing risk, so probabilities of developing interested events (poor or improved outcome) will not be independent from probability of death, in which cases a cumulative incidence function (CIF)[18] will be used instead of KM method. The end date will be set as; date at end of study (1 year after hospital discharge), date of developing interested events; date of having competing risks, and date of loss to follow-up. Either cause-specific or subdistribution proportional hazard model will be used to estimate effect sizes and depends on whether or not the intervention (Tele-cEEG) has an effect on the hazards of competing risks (death) [19]. If it has no effect, a cause-specific proportional hazard model with csHR will be reported. However, in the event of an effect, a subdistribution model with subHR will be reported.

Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE) will be applied to assess intervention effects [20] on functional outcome. A mixed effect model will be constructed as follows: First, intervention variable will be fitted as fixed-effect and random-effect in a multilevel equation with having poor/favorable function as the outcome variable. Second, a random-effect of intervention will be then constructed. A likelihood ratio will be applied to compare whether considering intervention effect as random will improve model fitting. Adjusted odds ratio (OR) along with its 95% CI will be estimated.

Even if randomization is used, all of the prognostic factors may not be perfectly balanced. Covariate adjustment will be used in the analysis of the primary and secondary outcomes to minimize the effect of covariate imbalance. The following important covariates at baseline which may influence the study outcomes (i.e. functional outcome and mortality) will be adjusted; age (≥ 60 vs < 60 years) [21 22], etiology of SE (acute vs chronic etiology) [22], severity of the disease within 24 hours of admission (higher vs lower APACHE IV/SAPS II/GCS scores) [23] and history of epilepsy/antiepileptic drug use. The specific adjustment procedure depends on the type of covariate being adjusted for and the type of outcome being analyzed. In this study, both primary response variables (primary outcomes) and important covariates are categorical (i.e. age, etiology of SE, severity of disease), so "a stratified analysis" taking the form of a Mantel-Haenszel (MH) statistic will be used. Study participants will be subdivided into smaller, more homogenous groups, or strata will be used. A comparison of study groups will be made within each stratum and then averaged over all strata to achieve a summary result for the outcome.

Pre-specified subgroup analysis: We plan to perform a subgroup analysis on covariates which potentially effect modifiers of the intervention effects. This may help identify the specific

population most likely to benefit from or to be harmed by the Tele-cEEG. The following subgroup analysis will be assessed; age (≥ 60 years) vs younger (< 60 years) and patients with severe diseases (i.e. higher score) vs milder severity (i.e. lower score). This will be based on APACHE IV, SAPS II, GCS within 24 hours of enrolment; indications for EEG study (prior clinical seizure/SE without recovery, coma, severely depressed LOC, intracranial hemorrhages, suspicious NCS/NSCE, CNS infection, and presence of epileptiform discharges or periodic pattern on initial EEG); higher status epilepticus severity score vs lower scores (based on STESS and EMSE scores); and Type of SE (i.e. pure CSE vs pure NCSE vs combined CSE and NCSE).

Dealing with protocol violation: We will analyze with the following methods; 1) Intention-to-treat analysis: All participants and their outcomes will be included for primary analysis; 2) As-treated analysis: This will be used in cases as follows; a) patients who are initially randomized to receive Tele-rEEG, but are subsequently switched to receive the Tele-cEEG as initial rEEG revealed seizure/epileptiform and/or periodic discharges, and b) patients with incorrect intervention allocation administration e.g. patients allocated to Tele-cEEG are incorrectly administered Tele-rEEG or vice versa; 3) Per-protocol analysis: This analysis refers to inclusion in the analysis of only those patients who strictly adhered to the protocol. Analysis flow is shown in Supplemental Figure 3.

Economic analysis

This is an economic analysis alongside the randomized controlled trial (trial-based economic evaluation). Costs and outcomes will be collected from all patients. We will perform cost-utility

analysis (CUA) which enables the findings from our study to be compared with other healthcare interventions. This trial will evaluate economic analysis in view of societal perspectives including billing costs in order to assess whether the Tele-cEEG is economically feasible and worthwhile to implement in the context of Thailand.

Outline of interventions: By using TreeAge Pro 2016, a decision tree will be created using RCT-based data. This decision tree diagram will help depict choices of intervention, the logical structure of probabilities of conditions which could occur after applying the interventions, and values related to cost and utility associated with consequences related to each condition. Interested events discovered by the study interventions (Tele-cEEG and Tele-rEEG) are pure NCS/NCSE, combined CS/CSE and NCS/NCSE, pure CS/CSE, and no seizure. Decision tree diagram is shown in Supplemental Figure 4. Parameters and data sources for probabilities of interested events, cost, and utility are shown in Supplemental Table 6.

Cost analysis: Unit costs of services will be referenced on a price provided by the Center of Essential Information for All Health Officers, 2018. All costs will be converted to 2018 values using the Thai consumer price index (Bureau of Trade & Economic Indices, 2018). Lifetime time horizon is a cycle length of 1 year. All costs and outcomes occurring after 1 year will be discounted at a rate of 3%, as recommended in the Thai Health Technology Assessment guideline[24].

Determining cost-effectiveness: For primary economic analyses, with CUA cost per quality-adjusted life-year (QALY) gained based on EQ-5D-5L score will be examined. The EQ-5D-5L is a generic preference-based measure for which a previous study in Thailand reported coefficients for converting to utility [25].

QALYs = number of years lived x utility

Utility can range from 0 as worst health state or death to 1 as best health state or healthy. To convert the EQ-5D-5L QoL score to utility, we use coefficients from a study by Pattanaphesaj J. (http://www.hitap.net/documents/89762) [25].

The Incremental Cost-Effectiveness Ratio (ICER) will be calculated by the formula below [26]. The numerator will be the difference of mean total cost between intervention (Tele-cEEG) and controls (Tele-rEEG). Mean total cost will be calculated by dividing the summation of all costs at discharge, 90 days, 6 months, 9 months, and 1 year in each patient with total number of the patients. The denominator will be difference of QALY based on EQ-5D-5L score at 1 year between intervention and controls.

$$\text{ICER} = \frac{Mean\ (Total\ cost\ Tele-cEEG)\ -\ Mean\ (Total\ cost\ Tele-rEEG)}{Mean\ (QALY\ Tele-cEEG)\ -\ Mean\ (QALY\ Tele-rEEG)}$$

We will also derive 95% CI for the ICER. If the numerator (cost data) and denominator (QoL data) of the ICER follow a joint normal distribution, Fieller's method will be used [27]. However, if either data are non-normally distributed, a non-parametric bootstrap method will be used [28]. The combination of 95% CIs for cost and effect differences will be shown in a graph to demonstrate a "confidence box" of the cost-effectiveness plane [28].

For the secondary economic analysis, ICER to represent additional cost per additional point on the mRS will be calculated as below. This will be separately assessed at 3 day and 7 days after starting EEG recording, at discharge, 90 days, 6 months, 9 months, and 1 year. In each time point, the numerator of the ICER will be the difference of mean total cost between intervention and controls. The denominator will be the difference of median mRS between

intervention and controls at that time point. Cost-effectiveness plane and cost-effectiveness acceptability curves will be presented.

$$\text{ICER} = \frac{Mean\ (Total\ cost\ Tele{-}cEEG) - Mean\ (Total\ cost\ Tele{-}rEEG)}{Median\ (mRS\ score\ in\ Tele{-}cEEG) - Median\ (mRS\ score\ in\ Tele{-}rEEG)}$$

Uncertainty analysis: To handle cost analysis uncertainty, a Probabilistic Sensitivity Analysis (PSA) using Monte Carlo simulation with bootstrapping 1,000 replications will be used. One-way analysis will be applied using Tornado diagram.

Analytical statistics: In order to test the hypothesis regarding differences in costs between intervention and control arm, a linear regression where response variable is cost will be performed. Since this study has large sample size (> 50), even cost data are highly skewed.,, Both linear regression relying on central limit theorem (CLT) and non-parametric bootstrap methods have been proved to be accurate to estimate the true standard errors (SEs) [29]. In this study, we will use linear regression for analysis since it is easier to implement. Complete-case-analysis will be also used to deal with missing data.

Ethical considerations

The Tele-cRCT study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University and also Faculty of Medicine, Ramathibodi Hospital, Mahidol University. The ethical conduct of this study will be monitored by the independent DSMB which is a part of the Faculty of Medicine, Chulalongkorn University Ethical Review Board. This is an investigator-generated study performed in full independence of study sponsor from any other funding agencies. This study will comply with the commonly agreed international standards for good practice in research, the Belmont Report. Any important

protocol modifications will be reported to the Ethics Committee of both institutions and the trial registries. English language examples of the patient consent form is shown in Supplemental document 2.

Contributorship statement

Dr. Chusak Limotai (C.L.) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and contributed to study concept or design, acquisition/analysis/interpretation of data, drafting the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative/ technical/material support.

Dr. Atiporn Ingsathit (A.I.) contributed to study concept or design, critical revision of the manuscript for important intellectual content, and is a study supervision.

Dr. Kunlawat Thadanipon (K.T.) contributed to critical revision of the manuscript for important intellectual content, and is a study supervision.

Dr. Oraluck Pattanaprateep (O.P.) contributed to study concept or design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and is a study supervision.

Anuchate Pattanateepapon (A.P.) contributed to study concept or design, critical revision of the manuscript for important intellectual content, administrative/ technical/material support, and is a study supervision.

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Competing interests

None of the authors has associations with commercial entities that provided support for the work reported in the submitted manuscript. None of the authors has associations with commercial entities that could be viewed as having an interest in the general area of the submitted manuscript. None of the authors has any similar financial associations involving their spouse or their children under 18 years of age. None of the authors has non-financial associations that may be relevant to the submitted manuscript.

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Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information. Data generated by our research that supports our article will be made available as soon as possible, wherever legally and ethically possible. Data will be made available upon reasonable request.

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Figure Legend

Figure 1: Study flow

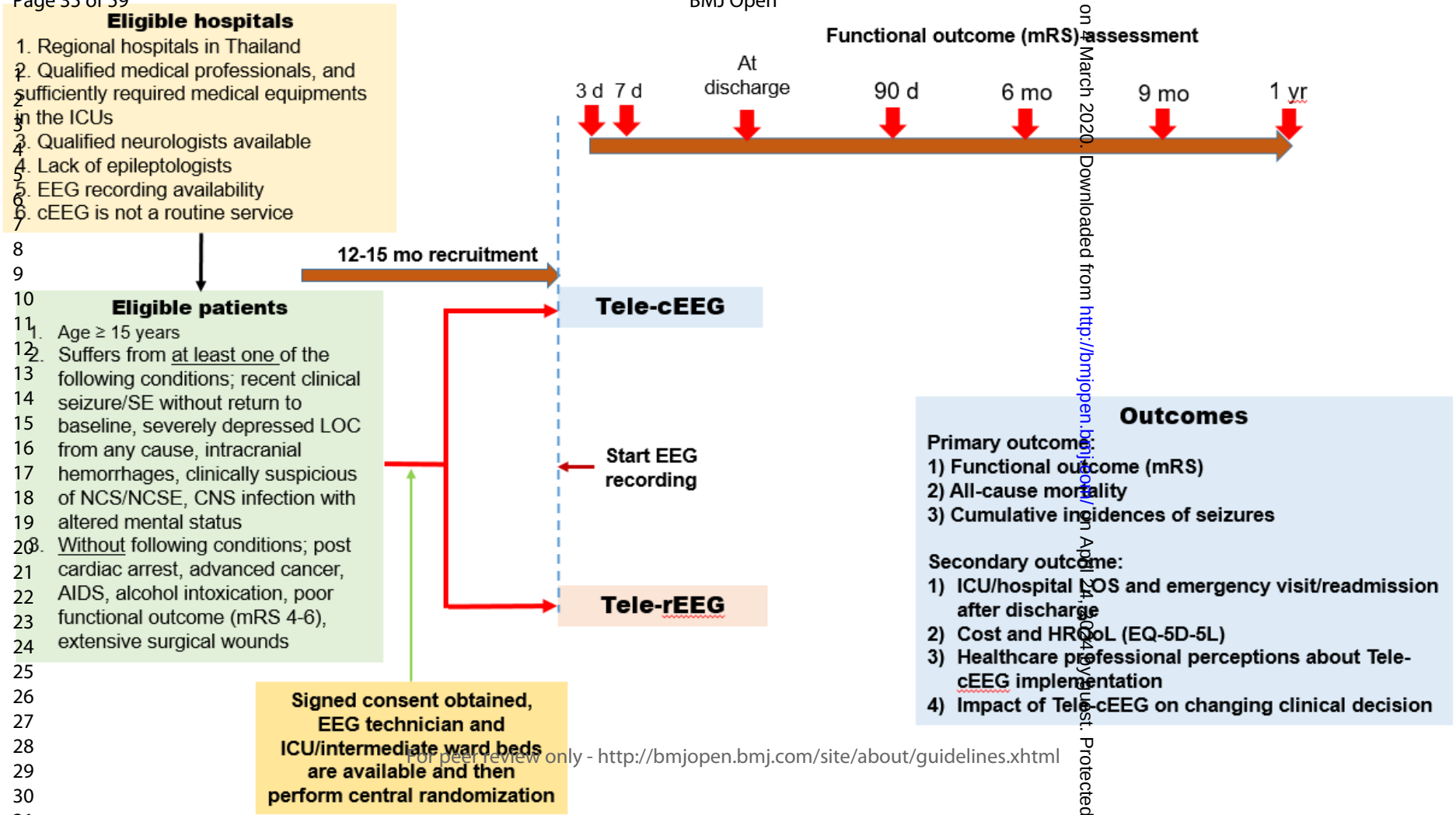
Abbreviations: cEEG = continuous EEG; SE = status epilepticus; LOC = loss of consciousness; NCS = nonconvulsive seizure; NCSE = nonconvulsive status epilepticus; mRS = modified Rankin Scale; LOS = length of stay; HRQoL = health-related quality of life

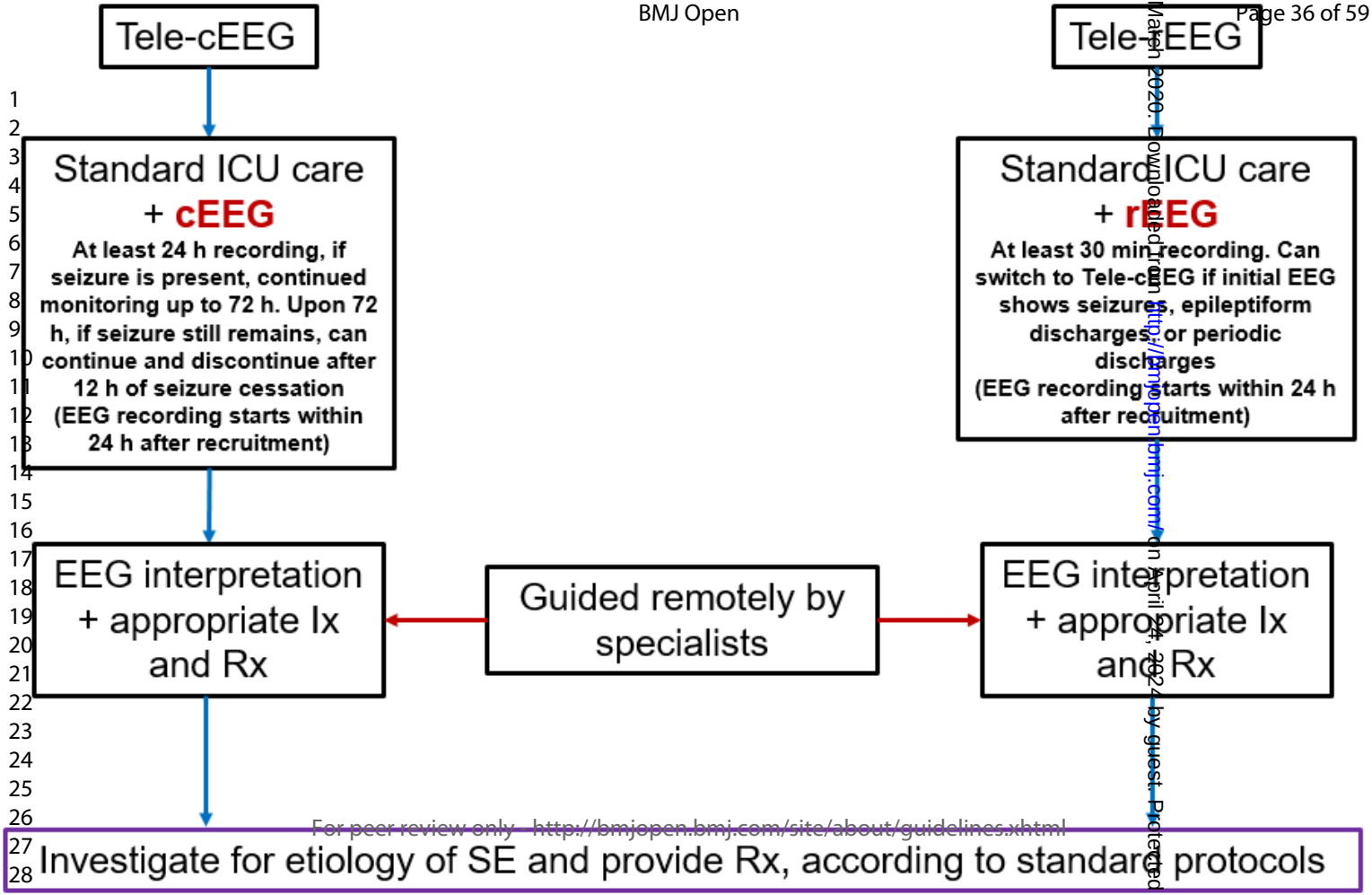
Figure 2: Implementation of study interventions

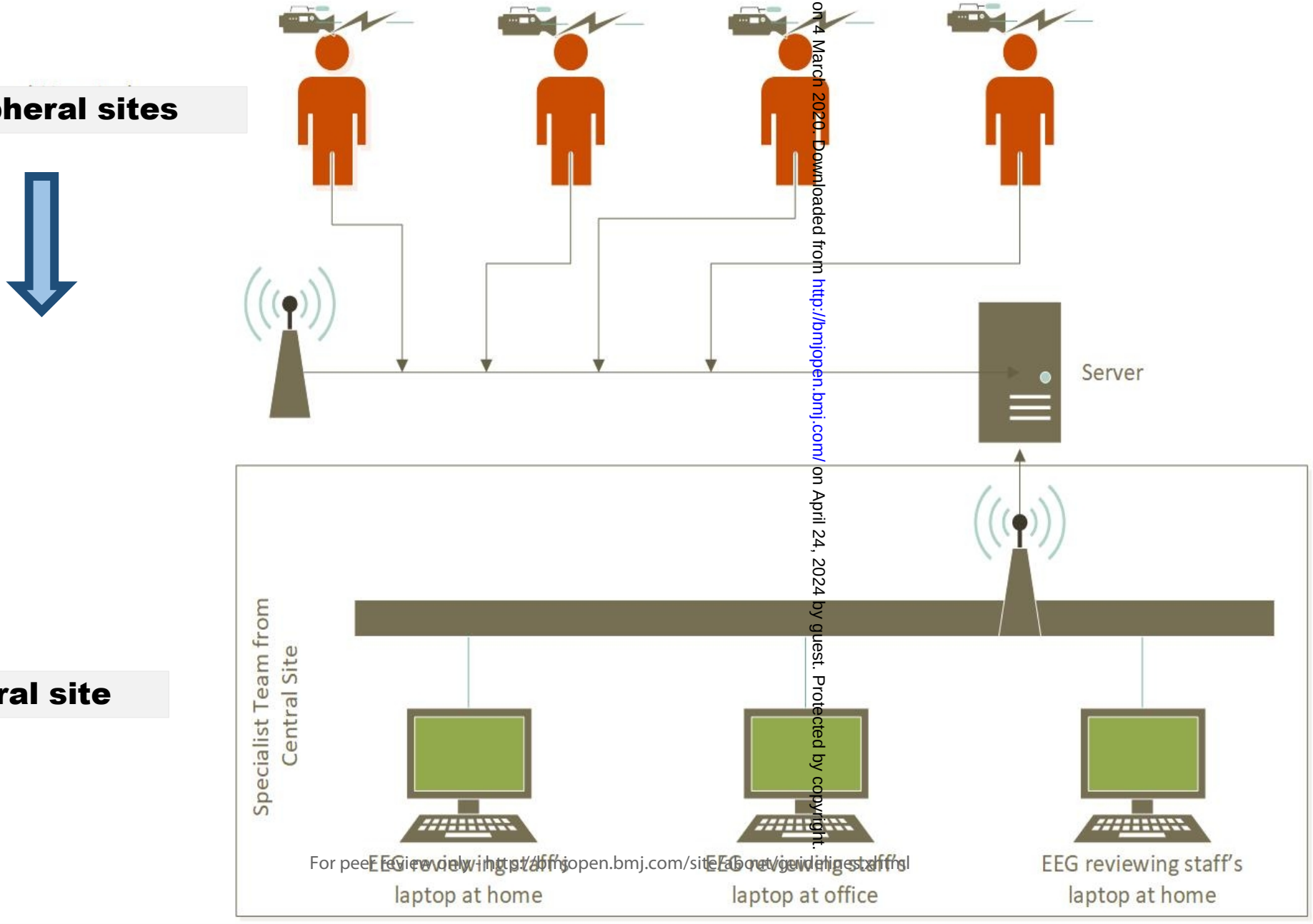
Abbreviations: cEEG = continuous EEG; rEEG = routine EEG; Ix = investigation; Rx = treatment; SE = status epilepticus

Figure 3: "De-centralized system" of the Tele-EEG

Upon being in charge, each EEG specialist can connect to the EEG machine at study sites and EEG server at the Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC) for real-time and off-line review, respectively at anytime and from anywhere via internet.







Supplementary files

Supplemental Figure 1: Study flow and investigator's role

Supplemental Figure 2: "Open communication architecture" of the Tele-EEG

"Flexible connectivity where specialists who review the EEG can access patient medical information on cloud storage via internet. Communication between specialists and treating neurologists is limited to traditional telephonic modalities and are functionally outside the Tele-EEG system."

Supplemental Figure 3: Analysis flow

Supplemental Figure 4: Decision tree diagram

Supplemental Table 1: Inter-rater agreement of the EEG interpretations among EEG specialists

Supplemental Table 2: The survey questionnaire to gauze the perceptions about Tele-cEEG implementation

Supplemental Table 3: Nine parts of case record form, type of data, and responsible operators

Supplemental Table 4: Timing of data collection

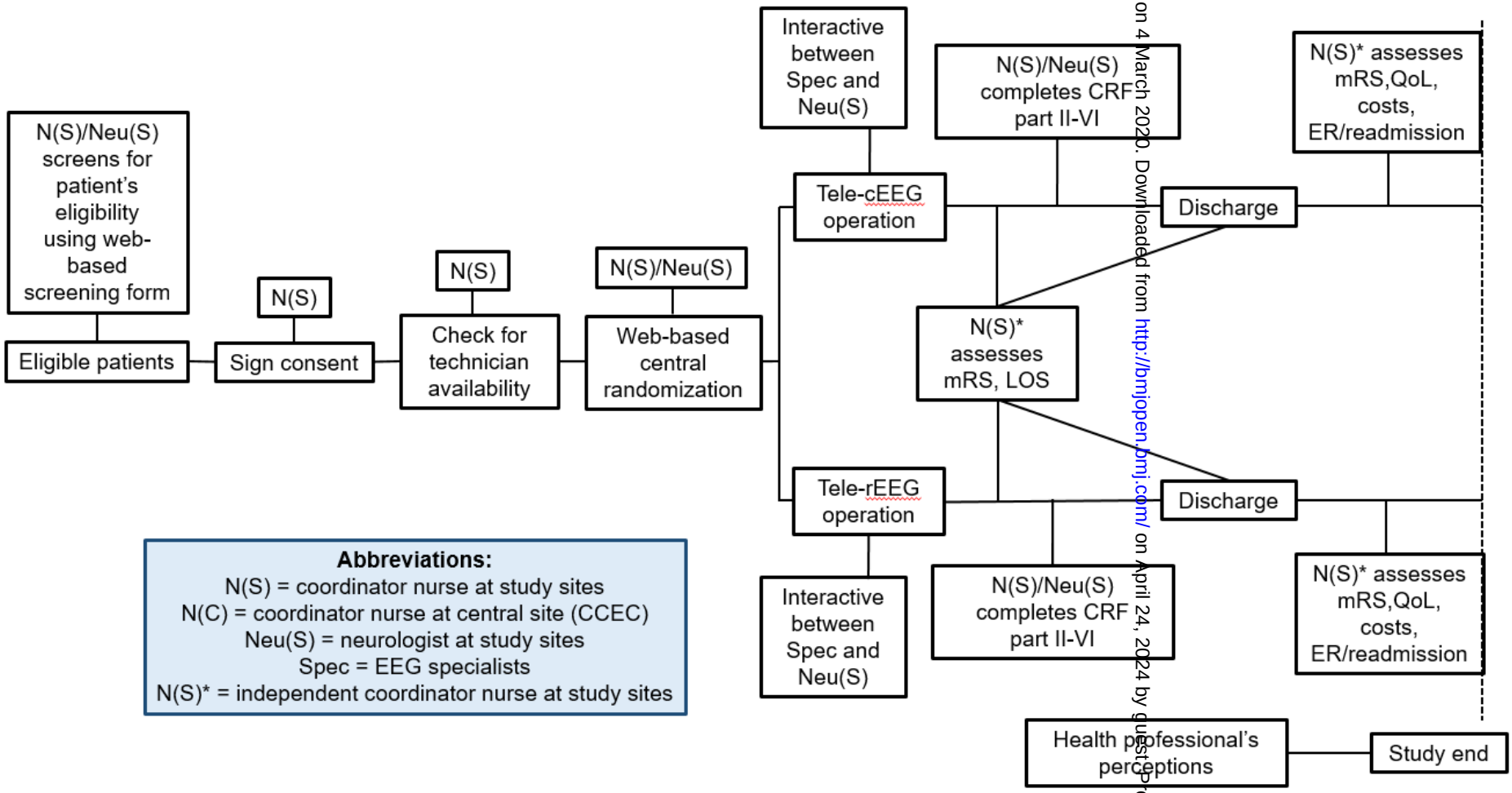
Supplemental Table 5: Statistical methods used for each study outcome

Supplemental Table 6: Parameters and data sources for probabilities of interested events, cost, and utility

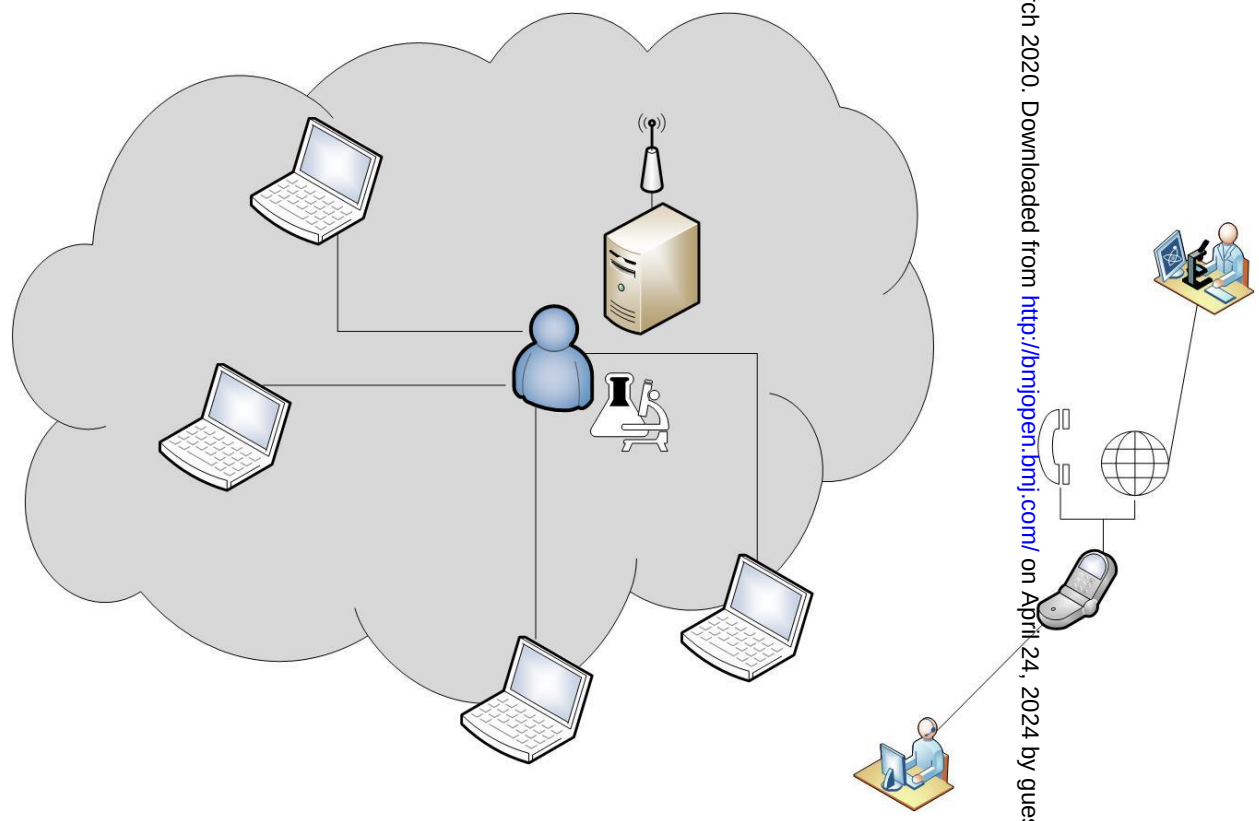
Supplemental document 1: SPIRIT checklist

Supplemental document 2: English language examples of the patient consent form

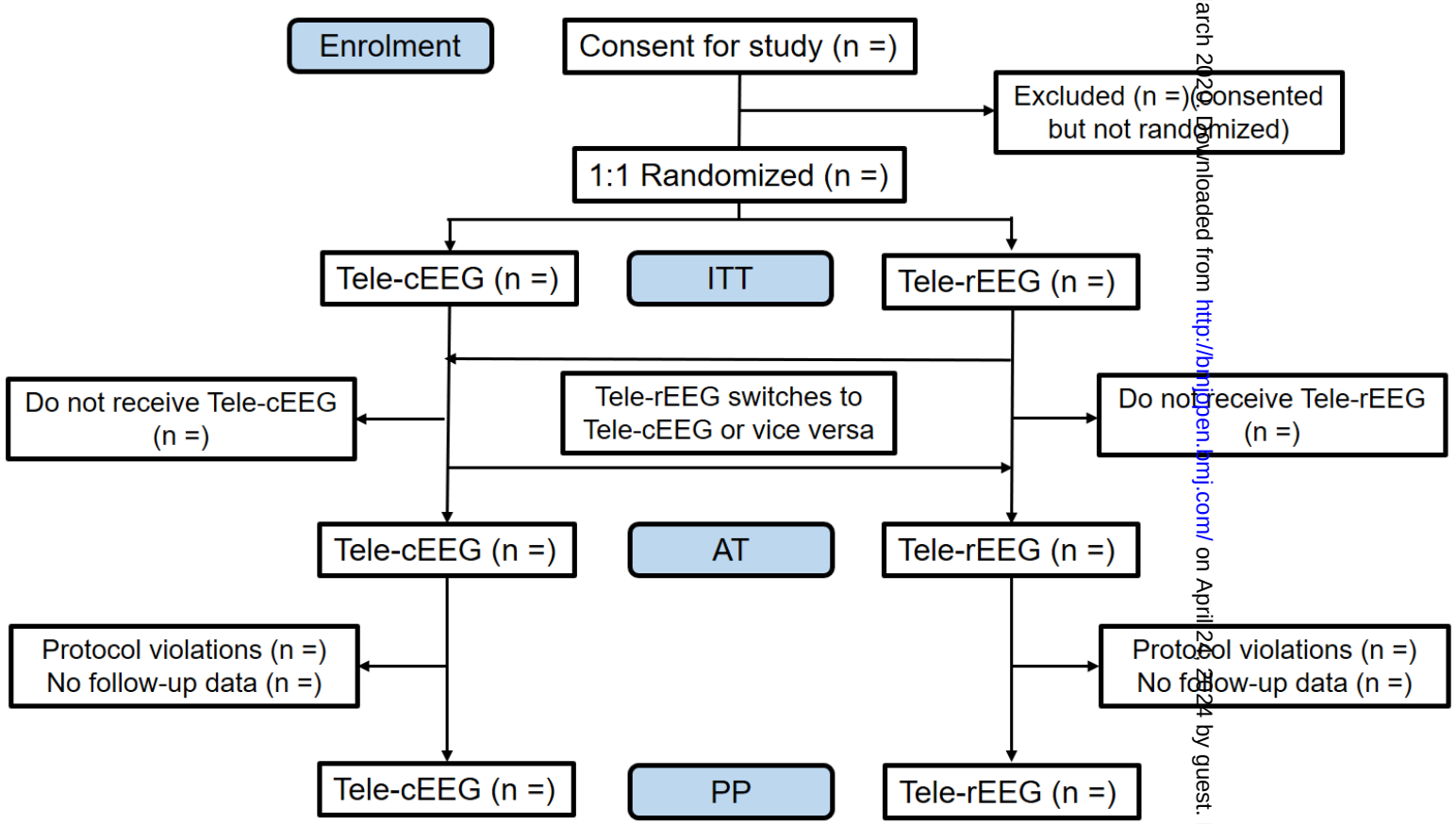
Supplemental Figure 1: Study flow and investigator's role



Supplemental Figure 2: “Open communication architecture” of the Tele-EEG

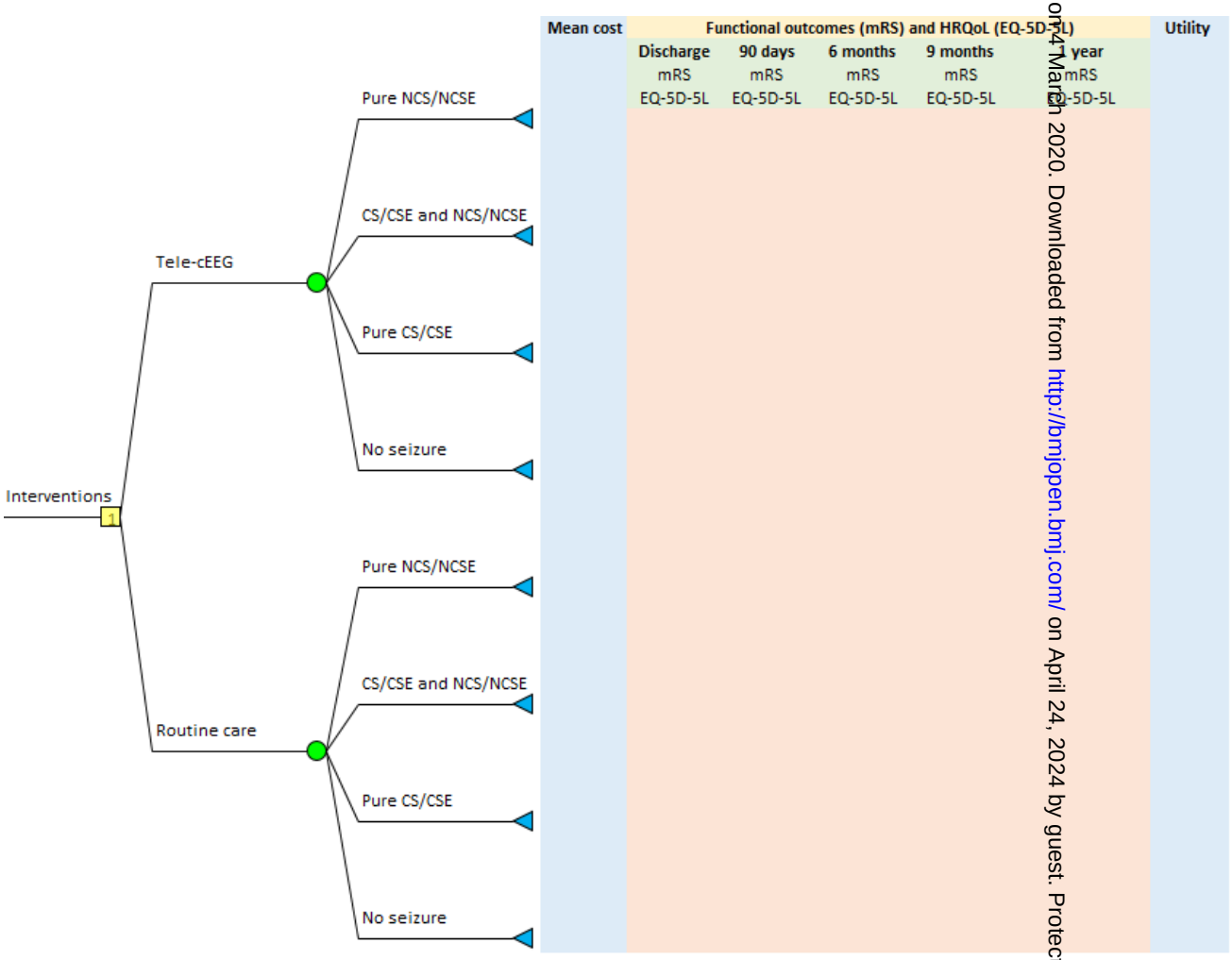


Supplemental Figure 3: Analysis flow



Abbreviations: ITT = intention-to-treat analysis; AT = As-treated analysis; PP = Per-protocol analysis

Supplemental Figure 4: Decision tree diagram



Supplemental Table 1: Inter-rater agreement of the EEG interpretations among EEG specialists

A) 23 tracings of common EEG findings in critically ills

EEG tracing items	Rater 1 score	Rater 2 score	Rater 3 score	Rater 4 score	Rater 5 score	Rater 6 score	Rater 7 score
1	1	1	1	1	1	1	1
2	1	0	1	1	0	1	1
3	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1
6	1	0	1	1	1	1	1
7	1	0	0	1	0	1	1
8	0	0	1	1	1	1	0
9	1	1	1	1	1	1	1
10	1	1	1	1	1	1	1
11	1	1	0	1	1	1	1
12	1	1	1	1	1	1	1
13	1	1	1	0	1	1	0
14	1	1	1	1	1	1	1
15	1	1	1	0	1	1	1
16	0	1	1	1	1	1	0
17	0	1	1	1	1	1	1
18	1	1	1	1	1	1	1
19	1	0	1	0	1	1	0
20	1	1	1	1	1	1	1
21	1	1	1	1	1	1	0
22	1	1	1	1	1	1	1
23	1	0	1	1	1	1	1

Score 1 = EEG findings described by most raters and being a correct answer according to the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version; Score 0 = otherwise EEG findings.

B) 5 tracings of seizures/status epilepticus

EEG tracing items	Rater 1 score	Rater 2 score	Rater 3 score	Rater 4 score	Rater 5 score	Rater 6 score	Rater 7 score
1	1	1	1	1	1	1	1
2	1	1	1	0	1	0	1
3	1	0	1	1	1	1	1
4	1	1	1	1	1	0	1
5	1	1	1	1	1	1	1

Score 1 = EEG findings described by most raters and being a correct answer to be "a seizure" or "not a seizure" according to the Salzburg EEG criteria; Score 0 = otherwise rating

Rater = epileptologist; There are 9 epileptologists participating this study. One epileptologist and Dr. Chusak Limotai who prepared the EEG tracing did not rate the EEG findings; as a result, there were only 7 epileptologists included for this inter-rater assessment.

Supplemental Table 2: The survey questionnaire for assessing perceptions of Tele-cEEG implementation

Part I: Neurologist perceptions about the Tele-EEG system, assessed at 1 year after the Tele-EEG implementation	
1. Assessment date	☐☐/☐☐/25☐☐
2. Name of neurologist	_____
3. Tele-EEG system of both Tele-cEEG and Tele-rEEG can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
4. Tele-cEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
5. Tele-rEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
6. Tele-EEG system helps the treating neurologist be able to provide appropriate treatment to the patients on a timely fashion.	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
7. EEG reporting system by the specialists is effective.	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
8. If the government supports adequate budget and personnel for the Tele-EEG system, would you like to implement the Tele-EEG system in your practice?	☐ 1. Yes; please specify reason _____ _____ ☐ 2. No; please specify reason _____ _____

Part II: Nurse perceptions about the Tele-EEG system, assessed at 1 year after the Tele-EEG implementation	
1. Assessment date	☐☐/☐☐/25☐☐
2. Name of nurse	_____
3. Tele-EEG system of both Tele-cEEG and Tele-rEEG can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
4. Tele-cEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
5. Tele-rEEG system can be implemented in real clinical practice	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
6. Tele-EEG system helps improve the quality of treatment	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
7. Cooperation between specialists and treating neurologists is effective	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
8. With the Tele-EEG system, cooperation between nurses and treating neurologists is effective	☐ 1. Very strongly agree ☐ 2. Strongly agree ☐ 3. Agree ☐ 4. Disagree ☐ 5. Strongly disagree ☐ 6. Very strongly disagree
8. If the government supports adequate budget and personnel for the Tele-EEG system, would you like to implement the Tele-EEG system in your practice?	☐ 1. Yes; please specify reason _____ _____ ☐ 2. No; please specify reason _____ _____

Supplemental Table 3: Describe characteristics of case record form, type of data, and responsible operators

Forms	Data	Type of data	Responsible operators
Part I: **Inclusion and exclusion criteria**	Inclusion and exclusion criteria	Non-time dependent	Sub-PIs/ NS
Part II: **Hospital variables**	Hospital characteristics	Non-time dependent	NS
Part III: **Patient variables**	Patient characteristics	Non-time and time-dependent	Sub-PIs/ NS
Part IV: **Etiology of seizure/SE**	Etiology of SE	Non-time dependent	Sub-PIs
Part V: **Investigations**	Investigational data including EEG, imaging, blood and CSF test results	Time dependent	Sub-PIs
Part VI: **Treatment variables**	Information about treatment	Time dependent	Sub-PIs
Part VII: **Primary outcomes** (**i.e. functional outcomes, mortality, seizure/SE incidence**)	Assessment of functional outcomes, mortality, seizure/SE incidence	Time dependent and non-time dependent	Independent sub-PIs [1]/ Independent NS [2]
Part VIII: **Secondary outcomes** (**i.e. LOS, emergency visit/readmission, HRQoL, change of medical decision making, health professionals perceptions**)	Assessment of LOS HRQoL, emergency visit/readmission, HRQoL, assessment of changing of medical decision making, and health professional perceptions	Non-time dependent	Independent sub-PIs [1]/ Independent NS [2]
Part IX: **Costs**	All costs	Time dependent	Independent NS [2]

Abbreviations: Sub-PIs = neurologist at study sites; NS = coordinator nurses at study hospitals; SE = status epilepticus; CSF = cerebrospinal fluid; HRQoL = health-related quality of life

[1] Sub PIs who are not involved in patient screening and/or collecting the study independent variables

[2] NS who are not involved in patient screening and/or collecting the study independent variables

Supplemental Table 4: Timing of data collection

Variables	Time of data collection
Study independent variables (CRF part II – VI)	At enrollment period and during hospitalization
Primary outcome	
- Functional outcomes	At 3 and 7 days after starting EEG recording, at hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge
- Mortality	During hospitalization and 1 year
- Incidence of seizure/SE	During hospitalization
Secondary outcome	
- LOS	At hospital discharge
- Emergency visit/ readmission	At 90 days, 6 months, 9 months, and 1 year after discharge
- Change of medical decision-making	During hospitalization, immediately after patient recruitment
- HRQoL	At hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge
- Costs	At hospital discharge, and 90 days, 6 months, 9 months, and 1 year after discharge

Supplemental Table 5: Statistical methods used for each study outcome

Outcomes	How is the outcome measured?		Type of outcome	Statistical methods
Functional outcome	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Dichotomous (poor vs favorable)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
	Once (at discharge)		Dichotomous (functional decline vs unchanged/improved)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
	Once (at 1 year)		Time to develop poor outcome (mRS 4-6) in patients with initial favorable outcome (mRS 0-3) at discharge and Time to develop favorable outcome in patients with initial poor outcome at discharge	Survival analysis with cumulative incidence function (CIF) and Univariate and multivariate cause-specific or subdistribution proportional hazard model
All-cause mortality	ICU/ hospital Case fatality rate	Once (during hospitalization)	Dichotomous (death vs survived)	Univariate and multivariate logistic regression
	Crude annual mortality rate	Once (at 1 year)	Time to being dead	Survival analysis with Kaplan-Meier (KM) method and Univariate and multivariate Cox propotional hazard regression
Cumulative incidences of seizures	Once (during hospitalization)		Dichotomous (presence vs absence of NCS/NSCE; combined NCS/NCSE and CS/CSE; and CS/CSE)	Univariate and multivariate logistic regression
ICU and hospital LOS	Once (at discharge)		Continuous (days)	Univariate and multivariate linear regression
Emergency visit/readmission	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Dichotomous (Yes vs No)	Univariate and multivariate logistic regression
HRQoL	Repeatedly (at discharge, 90 days, 6 months, 9 months, 1 year)		Continuous (total score)	Multilevel analysis with mixed effects models using maximum likelihood estimation (MLE)
Health professional perceptions about the Tele-cEEG implementation	Once at 1 year after conducting the study		Dichotomous (Yes vs No)	Univariate and multivariate linear regression
Changing of medical decision	Once (during hospitalization)		Dichotomous (Changing vs not changing)	Univariate and multivariate logistic regression
Costs	Once		Continuous (total cost)	Univariate and multivariate linear regression

	(summation of costs at discharge, 90 days, 6 months, 9 months, 1 year)		

Supplemental Table 6: Parameters and data sources for probabilities of interested events, cost, and utility

	Parameters	Data sources
Probabilities of interested events		
Pure NCS/NCSE	Percentage of seizures detetced by EEG	CRF
Combined NCS/NCSE and CS/CSE	Percentage of seizures detetced by EEG	CRF
Pure CS/CSE	Percentage of seizures detetced by EEG	CRF
No seizure	Percentage of not having seizures	CRF
Cost		
At discharge		
Direct medical cost		
• Start-up cost for TM implementation	Sum up costs of internet connection set up; internet fee; and training for physicians and nurses; EEG monitoring cost	PI's budget management file
• Specialist cost	On-call stipends	PI's budget management file
• EEG technician cost	Stipends for electrode placement	PI's budget management file
• Total medical cost during admission	Sum up costs of variable costs	Hospital billing
Direct non-medical cost		
• Caregiver	Informal care cost[a]	Interview
Indirect cost		
• Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost		
At 90 days		
Direct medical cost		
• Home medication	Costs of medications used at home	Hospital billing; interview
• Outpatient visit	Costs during outpatient visit except for medications	Hospital billing; interview
• Re-admission	If any, costs during re-admission, EEG monitoring cost	Hospital billing
• Community health services	If any, costs related to district health promoting hospital care	Hospital billing
Direct non-medical cost		
• Caregiver	Informal care[a]	Interview
• Transportation	Cost per kilometer of running a car	Interview
• Ambulance	Cost per kilometer	Interview
• Out-of-pocket	Other expenses related to patient care	Interview
Indirect cost		
• Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost		
At 6 months		
Direct medical cost		
• Home medication	Costs of medications used at home	Hospital billing; interview
• Outpatient visit	Costs during outpatient visit except for medications	Hospital billing; interview
• Re-admission	If any, costs during re-admission	Hospital billing
• Community health services	If any, costs related to district health promoting hospital care	Hospital billing
Direct non-medical cost		
• Caregiver	Informal care[a]	Interview
• Transportation	Cost per kilometer of running a car	Interview
• Ambulance	Cost per kilometer	Interview
• Out-of-pocket	Other expenses related to patient care	Interview
Indirect cost		

• Productivity loss	Productivity loss (number of day × income/day)	Interview
Cost **At 1 year** ***Direct medical cost*** • Home medication • Outpatient visit • Re-admission • Community health services ***Direct non-medical cost*** • Caregiver • Transportation • Ambulance • Out-of-pocket ***Indirect cost*** • Productivity loss	 Costs of medications used at home Costs during outpatient visit except for medications If any, costs during re-admission If any, costs related to district health promoting hospital care Informal care[a] Cost per kilometer of running a car Cost per kilometer Other expenses related to patient care Productivity loss (number of day × income/day)	 Hospital billing; interview Hospital billing; interview Hospital billing Hospital billing Interview Interview Interview Interview Interview
Clinical outcomes (utility) Functional outcomes (mRS) at discharge, 90 days, 6 months, 9 months, and 1 year HRQoL (EQ-5D-5L) at discharge, 90 days, 6 months, 9 months, and 1 year	 Scores; favorable or poor outcome Total scores	 CRF CRF

* Cases of patients who are re-admitted in other hospitals which are not our study hospitals; with approval by the patients (stated in the given signed consent) and permission from Ministry of Health investigators will archive hospital cost billing from the hospital where the patient is admitted.

[a]To identify and valuate informal care by caregiver, a market wage rates will be used

Supplemental document 1: SPIRIT checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1/ Line 1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4/ Line 5
	2b	All items from the World Health Organization Trial Registration Data Set	Page 4/ Line 5
Protocol version	3	Date and version identifier	Page 2/ Line 21
Funding	4	Sources and types of financial, material, and other support	Page 24/ Line 4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 23/ Line 10
	5b	Name and contact information for the trial sponsor	Page 24/ Line 5-7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 24/ Line 7-9

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 17/ Line 3
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 6-7
	6b	Explanation for choice of comparators	Page 11/ Line 13
Objectives	7	Specific objectives or hypotheses	Page 9/ Line 1
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 7/ Line 18-19
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7/ Line 22-24
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 10/ Box 1 Page 7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 12-13

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 9/ Line 11-14 Page 16/ Line 5-7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 12/ Line 18-19; Page 13/ Line 1-4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 14/ Box 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 16/ Line 1-9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 16/ Line 1-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 9/ Line 10-23
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 9/ Line 16-18 Page 11/ Line 1-4

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 9/ Line 16-19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 11/ Line 6-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 11/ Line 6-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 16/ Line 15-22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 16/ Line 5-7
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17/ Line 4-6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 17-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 19/ Line 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 17/ Line 23 Page 20/ Line 3
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 17/ Line 9-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	None
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 17/ Line 9-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 17/ Line 8-15
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 23/ Line 1-8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 23/ Line 8-10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 9/ Line 14-16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	None
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17/ Line 5-8 Page 24/ Line 13-17

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 23/ Line 23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 24/ Line 13-17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	None
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 16/ Line 10-14
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 23/ Line 12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 24/ Line 13-17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental document 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	None

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

Supplemental document 2: English language examples of the patient consent form

	Faculty of Medicine **Chulalongkorn University**	**Informed Consent Form**	AF 09- Page 1/3

INFORMED CONSENT FORM

NAME OF STUDY: Efficacy and economic evaluation of delivery of care with Tele-continuous EEG in critically ill patients: a multicenter randomized controlled trial (Tele-cRCT Study)

STUDY DOCTOR: Chusak Limotai, MD, Atiporn Ingsathit, MD, PhD, Kunlawat Thadanipon, MD, Oraluck Pattanaprateep, PhD, Anuchate Pattanateepapon, MSc, Kammant Phanthumchinda, MD, Nijasri C. Suwanwela, MD, Iyavut Thaipisuttikul, MD, Kanokwan Boonyapisit, MD, Ammarin Thakkinstian, PhD

DATE OF CONSENT: Date..... Month..... Year.....

Study number	
Subject's Name	
Subject's Identification Number	
Subject's Date of Birth	

SIGNATURES

I,.....Address.....
.....have read the information in the attached subject information sheet version date:.....
..... By personally signing and dating this informed consent form, you affirm that you have read and understood this informed consent form; the study has been explained to you, your questions have been answered, and you agree to take part in this study; or you as the Guardian or Legally Authorized Representative give your permission for the adult who lacks capacity to provide this informed consent to participate in this study. You do not give up any of your legal rights by signing this informed consent form. You will receive a signed copy of this Informed Consent Form and Authorization for Use and Disclosure of Health Information for Research Purposes.

Participant

..... Signature of person giving consent

(.....) Printed Name of person giving consent

Date.....Month.....Year.....

	**Faculty of Medicine** **Chulalongkorn University**	**Informed Consent Form**	AF 09- Page 2/3

I Agree

Not Agree

to have my leftover biological samples (such as blood) to be stored for the purpose of study test

..... Signature of person giving consent (.....)

Printed Name of person giving consent Date.....Month.....Year.....

I certify that I have the legal authority under applicable law to make this request on behalf of the patient identified above:

Guardian or Legally Authorized Representative (if applicable)

..... Signature of Guardian or Legally Authorized Representative

(.....) Name of Signature of Guardian or Legally Authorized Representative (Print Name)

.....

Relationship to Participant (e.g. guardian, power of attorney, etc.)

Date.....Month.....Year.....

Person Obtaining Consent

..... Signature of Person Obtaining Consent (.....)

Name of Person Obtaining Consent (Print Name) Date.....Month.....Year.....

Witness

..... Signature of Witness (if applicable)

(.....) Printed Name of Witness (if applicable)

Date.....Month.....Year.....

	Faculty of Medicine **Chulalongkorn University**	**Informed Consent Form**	AF 09-05/5.0 Page 3/3

INVESTIGATOR STATEMENT

I certify that the research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in this research study. Any questions raised have been answered to the individual's satisfaction.

..... Signature of Investigator (.....) Printed Name of Investigator Date.....Month.....Year.....

Thank you for your help.