PROTOCOL

*Efficacy of neurostimulation with the **EASEE**® System to treat patients with medically refractory focal epilepsy: protocol for a prospective **m**eta-**a**nalysis*

EASEE Meta-Analysis

CV08-027

Version 01, 19 July 2021

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Approval of the Meta-Analysis Protocol

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Synopsis

STUDY TITLE	Efficacy of neurostimulation with the **EASEE**® System to treat patients with medically refractory focal epilepsy: protocol for a prospective **m**eta-**a**nalysis	
ABBREVIATED TITLE	**EASEE** meta-analysis	
STUDY NUMBER/ PROSPERO	**CV-08-027** / Prospero ID 266440	
INTENDED USE / MAIN DIAGNOSIS	Treatment of medically refractory focal epilepsy	
OBJECTIVES	The primary objective of this meta-analysis is to report on the efficacy, safety and performance of the EASEE® System for transcranial, subgaleal neurostimulation in subjects with medically refractory focal epilepsy, by analysing the data collected in two clinical studies (EASEE II, PIMIDES I).	
DESIGN	Meta-analysis of safety and performance data collected in EASEE II and PIMIDES I, two clinical studies which are homogeneous in terms of participants, interventions and outcomes.	
KEY ENDPOINTS	Primary endpoint (efficacy): - Responder rate, defined as at least 50 % reduction of seizure frequency between month 6 and baseline month Safety: - device or procedure related Serious Adverse Events - all SAEs - all AEs Performance: - device implant duration - deficiency rate per device For details on endpoints see section 4.	
TIMETABLE	Study conduct:	EASEE II: August 2018 – May 2023 PIMIDES I: January 2020 – December 2023
	First statistical evaluation:	EASEE II (4-month safety): April 2021 EASEE II: August 2021 PIMIDES I: August 2021
	Results of meta-analysis:	August 2021
SAMPLE SIZE	30	
STATISTICAL ANALYSIS	<u>Primary efficacy analysis</u> The primary efficacy meta-analysis will be performed on the full analysis set (FAS), including all patients from both studies who underwent implantation with the device. Responder rate (defined as at least 50 % reduction in seizure rate from baseline) at 7 months post-implant (6 months of active stimulation) will be analysed as a repeated binary variable via generalised estimating equations. <u>Safety</u> Safety analyses will be performed on the safety set, including all patients who underwent implantation with the device. Adverse events will be coded using MedDRA and summarized by body system. The incidence of device/procedure related serious adverse events (SAE) for the surgical implantation procedure and the following 4 months will be summarized with corresponding exact one-sided 95 % confidence intervals based on a binominal distribution.	
ELIGIBILITY CRITERIA	All available clinical data from studies on the safety and performance of the EASEE® System (Precisis AG, Germany). Two clinical studies were identified as eligible: EASEE II and PIMIDES I. These two studies are homogeneous in terms of participants, interventions and outcomes. No further clinical studies will be considered for this prospective meta-analysis.	
INFORMATION SOURCES	No further information sources will be consulted.	
SEARCH STRATEGY	No specific search strategy will be applied for identifying published research.	

Revision History

Lists details of all protocol amendments whenever a new version of the protocol is produced.

Protocol Version No.	Date	Author(s) of changes	Modification Description
1.0	19-JUL-2021	Prof. Dr. med. A. Schulze-Bonhage	Initial Protocol Version

Terms and abbreviations

Term or Abbreviation	Description
AC	Alternating Current
ASM	Anti-Seizure Medication
CA	Competent Authority
EC	Ethics Committee
EEG	Electroencephalography
QOLIE-31-P	Quality of Life in Epilepsy Inventory
(S)AE	(Serious) Adverse Event
SAP	Statistical Analysis Plan
SSQ	Seizure severity Questionnaire
ULFA	Ultra-low frequency asymmetric

References

Document identification	Description
CV08-006 v6	EASEE II Clinical Investigation Plan
CV08-017 v7	PIMIDES I Clinical Investigation Plan

1 Introduction

1.1 Background and Scientific Rationale

Epilepsy is a recurrent tendency to spontaneous, intermittent, abnormal electrical activity in the brain, manifesting as seizures. It is a common neurological disorder, affecting approximately 1 % of the population (Longmore M et al., 2014). Epileptiform discharges initially involve either a localized area of the brain resulting in a focal seizure or both cerebral hemispheres, resulting in a generalized seizure. In adults, the most common type is focal epilepsy (Panebianco M et al., 2015).

About two thirds of patients have a good prognosis to achieve satisfactory seizure control by treatment with anti-seizure medications (ASMs). Seizure control means reduction of seizure frequency and/or severity to the point that the patient can live a normal life without epilepsy-related limitations and with minimal or no drug toxicity (Greenberg MS, 2016). There are currently over 20 drugs for symptomatic treatment of epileptic seizures available.

In 30 % of patients with focal epilepsy, seizures are not effectively controlled by a single ASM and often require treatment with a combination of different ASMs (Shan et al., 2021; Stern et al., 2020). A failure of monotherapy indicates an 80 % risk that seizures will not be controllable pharmacologically. In contrast, increased drug load, due to polytherapy in patients non-responsive to antiepileptic treatment in monotherapy, often leads to an increased rate of medication-related adverse effects, such as cognitive impairment or mood disturbance (Eddy et al., 2011). In addition, patients with pharmaco-resistant epilepsy have an increased risk of premature death, injuries, drowning, psychosocial dysfunction and reduced quality of life (Löscher et al. 2020).

Therefore, non-pharmacological treatments are becoming increasingly attractive for patients with pharmaco-resistant epilepsy. Epilepsy surgery is one option with high success rates. However, the procedure can be performed only in a limited number of patients and carries risks for functional domain-specific deficits, depending on the regions of the brain which have been resected or disconnected (Loring DW et al., 2015). For those patients who are not surgical candidates, or refuse resective surgery, or continue to have seizures after surgery, neurostimulation may offer an alternative treatment option (Sprengers M et al., 2014, Salanova V et al., 2015; Stefan H et al., 2012).

Over the last 25 years, the clinical efficacy of electrical stimulation of the vagus nerve and deep brain structures for the treatment of several neurologic and psychiatric conditions, including epilepsy, depression, and Parkinson disease, has been extensively investigated (Schulze-Bonhage, Seizure 2017). Both extracranial stimulation, (including vagus nerve and transcranial direct current stimulation) as well as intracranial stimulation (deep brain and cortical stimulation) have been applied as adjunctive treatment options for medically refractory epilepsy. These devices have successfully completed pivotal efficacy and safety trials and are commercially available in Europe or the USA (Wong, Neurotherapeutics, 2019). Despite their potential clinical benefit, the mechanisms by which deep brain stimulation and other forms of neurostimulation modulate neuronal activity remain unknown (Sohal VS et al., 2011). Direct interaction with oncoming seizures may be a potential mechanism. About 15 % of patients are able to feel the seizure onset and are therefore able deliver additional stimulation at this time for example via the vagus nerve stimulation activation magnet (Fisher, Acta Neurol Scand, 2015).

A novel implantable extra-cranial and subgaleal neurostimulation therapy has been developed recently. The EASEE® system (Precisis AG, Heidelberg, Germany) is being used in two ongoing multicentre clinical studies: EASEE II and PIMIDES I (both single arm studies). The two studies are identical in terms of eligibility criteria, study device and study procedures, except for inclusion of patients who are aware of early seizure symptoms and can initiate an additional bolus stimulation in PIMIDES I. Both studies have completed enrolment and the follow-up required for primary safety endpoint analysis.

The goal of this meta-analysis is to evaluate initial efficacy, safety and performance of this novel therapy based on all clinical data available in patients with medically refractory focal epilepsy.

In epilepsy studies that evaluate drugs or medical devices, a ≥50 % reduction in seizure frequency is often used as the outcome measure to assess treatment efficacy and defines the responder rate (Wong, Neurotherapeutics, 2019). Other efficacy endpoints reported by medical device studies include the reduction in seizure frequency over time, neuropsychiatric, mood and memory effects and shall be evaluated in this meta-analysis along with the safety and performance data.

1.2 Device Description

The EASEE® System (**E**picranial **A**pplication of **S**timulation **E**lectrodes for **E**pilepsy) is an implantable neuromodulation device, which is intended for the treatment of medically refractory focal epilepsy in adults.

The EASEE® System consists of:

- The implantable components: EASEE® Power (the implantable pulse generator) and EASEE® Lead (electrode array and connecting link). EASEE® Lead has a specific design which allows it to be placed subgaleally on the skull surface and to transmit electrical stimulation through the skull bone to the grey matter of the neocortex. EASEE® Lead consists of five single disc electrodes arranged in a silicone matrix and linked to a five-polar cable.
- The surgical tools: EASEE® Template (tool for determining implant location), a torque wrench and a screw/screwdriver set (tool used to fix the array onto the skull) and a tunneling tool (for the subcutaneous routing of the connecting link from the electrode implant location on the skull to the implantable pulse generator location in the subclavian region).
- The external control elements: EASEE® Set (physician programmer), EASEE® Connect (telemetry wand for physician), EASEE® Access (patient remote control for device status check and/or request of bolus stimulation) and an Activation Magnet (for activation of the device by the physician).

The EASEE® System provides a stimulation scheme that combines AC (alternating current) and ULFA (ultra-low frequency asymmetric) stimulation. AC stimulation is applied continuously throughout the day (0.5 seconds every two minutes) with the exception of the time required for the ULFA burst and consists of a short burst of bipolar rectangular current controlled pulses with a pulse width of 160 µs and a frequency of 100 Hz. ULFA stimulation is delivered once a day for 20 min and consists of an asymmetric 20 ms rectangular active pulse, followed by a 100 ms charge equalization pulse at $1/5^{th}$ of the current amplitude used for the active pulse, corresponding to pulse frequency of 8Hz. All pulses are supplied with constant, programmable current.

Furthermore, when allowed in the study, patients can directly request additional “bolus stimulation” bursts via the EASEE® Access remote control (“patient controlled neurostimulation”). These bursts have the same parameter as the AC bursts with the exception of the burst duration, which can be programmed between 10 s and 60 s. The patient can request additional stimulation bolus once every 2 minutes, and for a maximum total duration of 6 min per day.

EASEE Power logs several data points, including all stimulation parameter settings, the daily applied stimulation bursts, time and date of each received bolus stimulation request, as well as the electrode’s impedances.

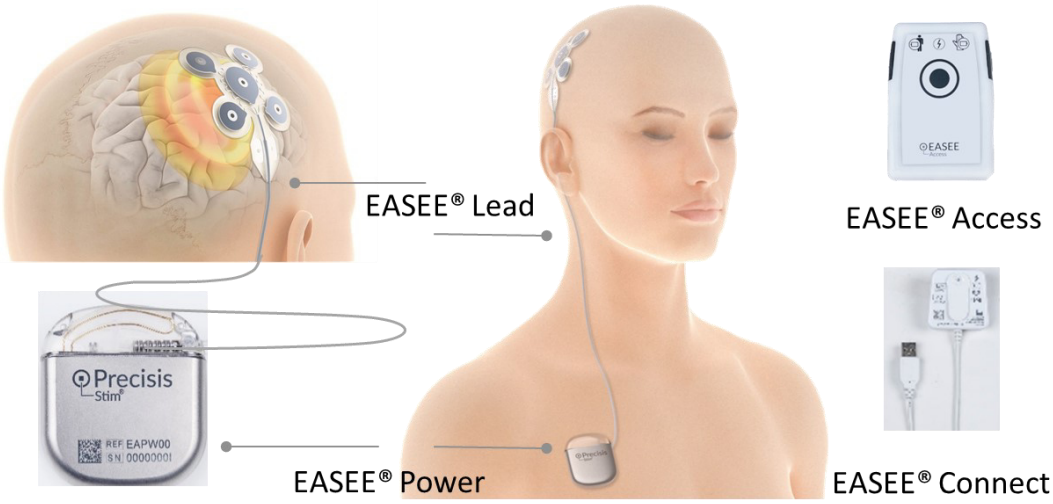

Figure 1 EASEE System elements

The fixation screws, the screwdriver set, the tunneling tool and the Activation Magnet are CE-marked accessories. All other elements of the EASEE® System were used for the first time within clinical investigations in Europe as of 2019 and do not have market approval.

1.3 Clinical Studies Eligible for Meta-Analysis

Two clinical studies investigating the safety and performance of the EASEE® System for the treatment of medically refractory focal epilepsy were identified: the EASEE II and the PIMIDES I clinical investigations. The study designs and current status are summarized below.

The EASEE II Study

- EASEE II is a first-in-human, prospective, interventional, unblinded, multicenter study conducted in Germany and Belgium.
- The study collects data on 15 subjects implanted with the EASEE® System and followed for 36 months post-implant. The study design and statistical analysis plan are described in the protocol.
- The primary endpoint is the safety defined as the number of SAEs of the EASEE® System evaluated at 4 months post-implant.
- The secondary endpoints are:
    - Seizure frequency, responder rate[1] and seizure severity at baseline compared to respective values at 4-, 8-, 16-, 24-, and 36 months post-implant.
    - Quality of life, mood and neurocognition at baseline compared to respective values at 8-, 16-, 24-, and 36 months post-implant.
    - Epileptiform activity (scalp EEG) at baseline compared to data collected at 1-, 8-, 16-, 24-, and 36 months post-implant.
- The EASEE II clinical investigation plan and related study documentation were initially approved by the German Competent Authority (CA, BfArM) in August 2018 and by the ethics committee (EC) in September 2018. The Patient Informed Consent of the study allows the sponsor and manufacturer of the device, Precisis AG, to undertake further research and to use the data for CE marking file. The trial is registered in the German Clinical Trials Register (DRKS) under the number 00015918 (https://www.drks.de/drks_web/setLocale_EN.do).

[1] responder rate: defined as at least 50 % reduction in seizure rate from baseline

- The enrollment of 15 subjects was completed in January 2020; the long-term follow-up of patients is ongoing.

The PIMIDES I Study

- PIMIDES I is a prospective, interventional, unblinded, multicenter international study in Germany and Belgium.
- The study collects data on 18 subjects implanted with the EASEE® System and followed for 36 months post-implant. The study design and statistical analysis plan are described in the protocol.
- The primary endpoint is the safety defined as the number of device/procedure related SAEs of the EASEE® System evaluated at 4 months post-implant.
- The secondary endpoints will assess the same parameters as the EASEE-II study.

The PIMIDES I design is identical to the EASEE II design, with the exception of the following aspects:

- EASEE® System includes patient-controlled bolus stimulation.
- One additional inclusion criterion, which requires that patients are able to apply bolus stimulation during their seizures (intact consciousness at least during part of a habitual seizure type, as well as motor ability to operate the device to trigger stimulation in this phase).
- An optional extension of the neuropsychological test battery which includes *Intelligence (MWT-B/A), Executive functions (RWT semantic, 5-points test), Memory (VLMT, DCS-R, Subtest Digit spans and Block spans), Language (BNT, speech comprehension), Visuospatial function (block design, VSWin), Motor functions (Perdue Pegboard), CES-D*

The common clinical study timepoints in EASEE II and PIMIDES I are presented in the Figure 2 below.

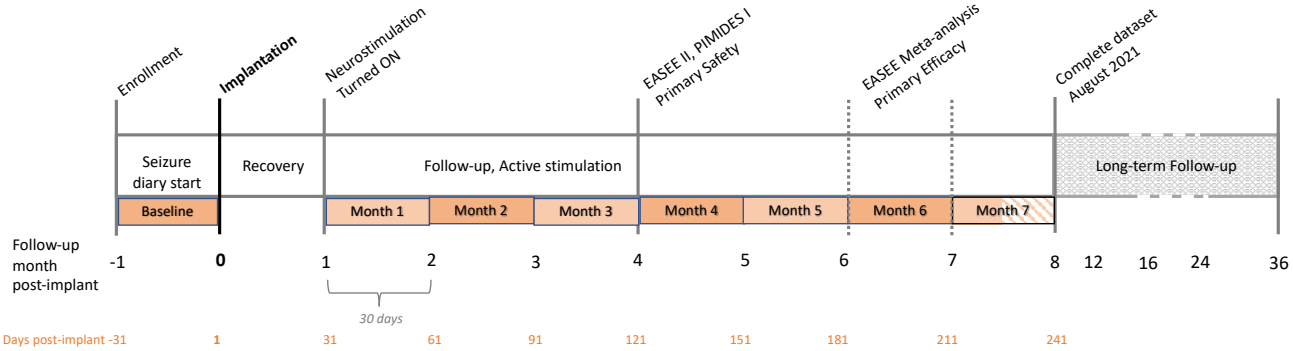

Figure 2 Timepoints in EASEE II and PIMIDES I clinical studies

The aim of this meta-analysis is to evaluate the efficacy, safety and performance of neurostimulation with the EASEE® System to treat patients with medically refractory focal epilepsy.

Seizure burden is the critical aspect that impacts the lives of patients with focal epilepsy, therefore the clinical performance evaluated according to different seizure burden measures will be the main focus of the meta-analysis. Additionally, any common endpoints from the original studies will be analyzed.

2 Methods

2.1 Study Design – Eligibility Criteria and Selection Process

Studies will be selected according to the following procedure: all studies using the EASEE System® will be included. Two studies are either started or are planned but were not analysed yet. Both are prospective, single arm studies investigating the safety and performance of the EASEE® System (see 1.3).

The same inclusion and exclusion criteria, research hypotheses and endpoints ensure comparability of the data collected from the two studies. In addition, identical stimulation devices were used with an additional trigger mode enabled in the PIMIDES I trial, the mechanisms of action of the stimulation are therefore identical in the two studies. That is, first, Ultra-Low Frequency Asymmetric stimulation enables seizure frequency reduction in patients with medically refractory focal epilepsy. Second, Alternative Current stimulation influences seizure severity independent of its mode of application via the stimulation device (continuously, on demand). All further technical details of the stimulation devices are identical as is the case for the expected safety of the devices of the EASEE® system.

2.2 Information Sources

No systematic literature search will be performed. All ongoing studies are run by Precisis AG. Information on trial design (trial protocol, informed consent, etc.) will be provided by the company.

2.3 Search strategy

Not applicable.

2.4 Study records

Information about trial patients will be kept confidential and managed under the applicable laws and regulations. The data collection system for both studies which are included in this meta-analysis use built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential patient information. Access to the system will be controlled by individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

The analysis of both individual studies will be performed according to respective Statistical Analysis Plans on all available data. Data will then be merged on an individual patient level. All patients included in the individual studies will be kept for the meta-analysis.

At the point of writing the protocol of this meta-analysis no data and results were available to the authors of this protocol.

3 Data-Items: Subject Population and Selection Criteria

Data on all design aspects of the clinical trial will be collected and compared (inclusion / exclusion criteria, research question, funding source, pre-planned assumptions).

4 Outcomes and Prioritization

The primary aim of this meta-analysis is to analyse the seizure burden reduction as defined by the responder rate (≥50 % of seizure reduction respective to baseline) in patients receiving treatment with the EASEE® System for medically refractory focal epilepsy.

Details of all objectives and related endpoints can be found in the table below.

	Objective	**Endpoint**
Primary	Assess changes in seizure burden	Responder rate, defined as at least 50 % reduction of seizure frequency between month 6* and baseline month
Secondary	Assess changes in seizure burden	Seizure frequency: • median percent seizure reduction at month 6 of active therapy compared to baseline month

	Objective	Endpoint
		• mean percent seizure reduction at month 6 of active therapy compared to baseline month
	Assess changes in seizure severity	Seizure severity (SSQ): seizure severity at 4-, 8-, 16-, 24- and 36-months post-implant compared to baseline seizure severity
	Assess modulation of focal epileptic activity	Epileptiform activity (scalp EEG): baseline measurements of epileptiform activity compared to data collected at 1 month and 8 months post-implant.
	Assess changes in quality of life	QOLIE-31-P: baseline subject rated quality of life compared to 8 months post-implant.
	Assess changes in mood	Mood (NDDI-E): baseline subject rated mood compared to 8-, 16-, 24- and 36 months post-implant.
	Assess changes in cognitive functioning	Neurocognition: baseline neurocognition compared to 8 months post- implant.
Safety	Assess device safety and performance	- device or procedure related SAEs, all SAEs, AEs at 1 month, 4-, 8-, 12-, 16-, 24- and 36-months post-implant
Performance	Assess device performance	- number of devices per patient and procedure - implant procedure duration - device deficiency - device duration

* Month 6 of active therapy: neurostimulation starts after 30 days, hence month 6 corresponds to day 181–211 post-implant, data being collected at 8-month follow-up (+/- 2 weeks), for details see Figure 2 above.

5 Risk of bias in individual studies

Patients enrolled in the selected studies for the meta-analysis are all medication-refractory for focal epilepsy. Nevertheless, their medication regime and medical characteristics might differ.

6 Data Synthesis and Statistical Analyses

Before the start of the final analysis a detailed statistical analysis plan (SAP) will be prepared. If the SAP contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given. All statistical programming for analysis will be performed with the Statistical Analysis System (SAS).
The statistical population to be investigated is defined according to the intended use of the investigational device as well as the inclusion and exclusion criteria of the study. The full analysis set (FAS) includes all patients who had an implantation of the EASEE® System regardless of what happened after the surgery.

6.1 Primary Endpoint

The analysis of the primary endpoint (responder rate) will be per individual. As only single arm studies will be included, no further aspects for combining different types of studies have to be considered. An individual participant data meta-analysis for the responder rate at 7 months post-implant (6 months of active stimulation) using a restricted maximum likelihood (REML)-based mixed model for repeated measures will be performed, including the trial as fixed effect and a random subject effect.

6.2 Safety and performance

Safety analyses will be performed in the safety set including all patients for whom the surgery was performed. Adverse events will be coded with MedDRA and summarized by body system. The incidence of device/procedure

related serious adverse event (SAE) for the surgical implant procedure and the following 4 to 36 months will be summarized with corresponding exact one-sided 95 % confidence intervals based on a binominal distribution. Incidence of AEs and SAEs will be analyzed in a similar way. Descriptive analyses of the number of devices per patient and procedure, the implant procedure duration, device duration and device deficiency will be performed.

6.3 Secondary Endpoints

Seizure frequency (mean and median changes in seizure frequency compared to baseline (-30 to day -1)) at 4 months, 7 months (181 to 211 days post-implant), 8 months, 12 months, 16 months, 24 months and 36 months post-implant will be analysed via the monthly (defined as 30 days) count of seizures for each subject, calculated from the seizure diary. A mixed-effects Poisson regression model will be used to analyse the monthly count data. Additionally, frequencies will be displayed descriptively in summary tables at baseline, 4 months, 7 months, 8 months, 12 months, 16 months, 24 months, 36 months and for changes to baseline.

Seizure severity at baseline, 4-, 8-, 16-, 24- and 36-months post-implant. Seizure severity questionnaire (SSQ) will be displayed descriptively compared to baseline for each patient.

Epileptiform activity: scalp EEG data will be analyzed descriptively.

Quality of Life in Epilepsy Inventory (QOLIE-31-P) at baseline, 8-, 16-, 24- and 36-months post-implant. The post-implant scores will be compared to baseline for each patient.

Mood: subjects complete the Neurological Disorder Depression Inventory for Epilepsy (NDDI-E) survey at baseline, 8-, 16-, 24- and 36-months post-implant. The post-implant scores will be compared descriptively to baseline for each patient.

Neurocognition: subjects complete a battery of cognitive tests (for example EpiTrack®) at baseline, 8-, 16-, 24- and 36-months post-implant. The post-implant scores will be compared to baseline for each patient.

SSQ, QOLIE-31-P, Mood and Neurocognition will be analysed using a linear mixed model for repeated measures, including a fixed trial and centre effect and a random patient effect in a similar fashion as the analysis of the seizure frequency.

It should be emphasised that as little patients as possible should discontinue treatment and that all patients should be followed up and also documented after discontinuation of the treatment in order to record data required. The clinical heterogeneity will be tested by considering the variability in participant factors in the studies (age, sex, etc.).

7 Meta-Bias(es)

The fact that patients from the PIMIDES I trial can decide to enable therapy with a limited amount of additional neurostimulation per day may lead to better study results or alternatively to increased side effects.

The population characteristics of both initial studies shall be reported and analyzed for heterogeneity.

8 Confidence in Cumulative Evidence

Results of the EASEE II and PIMIDES I study will be assessed concerning the risk of bias in individual studies (see chapter 6), the consistency of results between studies, and the precision of trial results.

9 Ethical and Legal Principles

9.1 Subject Informed Consent

The EASEE II and PIMIDES I individual trial data will be collected based on a broad consent procedure in which patients are informed that their data can be reused anonymously for scientific purposes.

9.2 Ethical and Regulatory Requirements

In Germany, there is no obligation to obtain regulatory approval for a meta-analysis on clinical data.

9.3 Data Protection and Confidentiality

The pertinent provisions on data protection must be fully complied with.

Patients of the EASEE II and PIMIDES I studies were informed of the purpose and extent of the data collection, the (re-)use of personal data, particularly medical data, and their individual rights according to EU data protection regulation.

For the protection of these data, organizational measures have been taken to prevent disclosure to unauthorized third parties. For example, the subject data is captured in pseudonymized form (subject ID No. for the study, year of birth) throughout the documentation and evaluation phase.

Data will be analyzed anonymously for this meta-analysis.

10 Registry

The Sponsor will ensure that the key design elements of this protocol are posted in a publicly accessible registry, such as PROSPERO. Reporting guidelines will be taken into account (see www.equator-network.org), e.g. the PRISMA statement should be adhered to in the preparation of papers on the results of transparent reporting of systematic reviews and meta-analyses.

11 Administrative Agreements

11.1 Financing of the Project

The prospective meta-analysis will be financed by Precisis AG. The funders do not control the final decision regarding any of aspects of the meta-analysis: design, conduct, data analysis and interpretation of results.

11.2 Study Report – Final Meta-Analysis

After completion of the analysis by the responsible biostatistician, Prof. Dr. Schulze-Bonhage (medical writer) will prepare and sign the final integrated medical and statistical report jointly with the biostatistician.

Except when required by law, the Sponsor will not disclose the results of the study to third parties unless all parties involved have first agreed on the results of the analysis and their interpretation.

All results of this meta-analysis will remain sole property of the Sponsor and may be used only by the Sponsor, including their use in publications, communications or in submissions to any regulatory authorities or other governmental agencies. Data may be published (in writing) by the Sponsor in collaboration with the investigators and Clinical Trials Unit, after consideration of comments from all relevant parties.

The Sponsor supports the exercise and academic freedom and recognizes the investigators interest in making publications and presentations relating to this meta-analysis.

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