

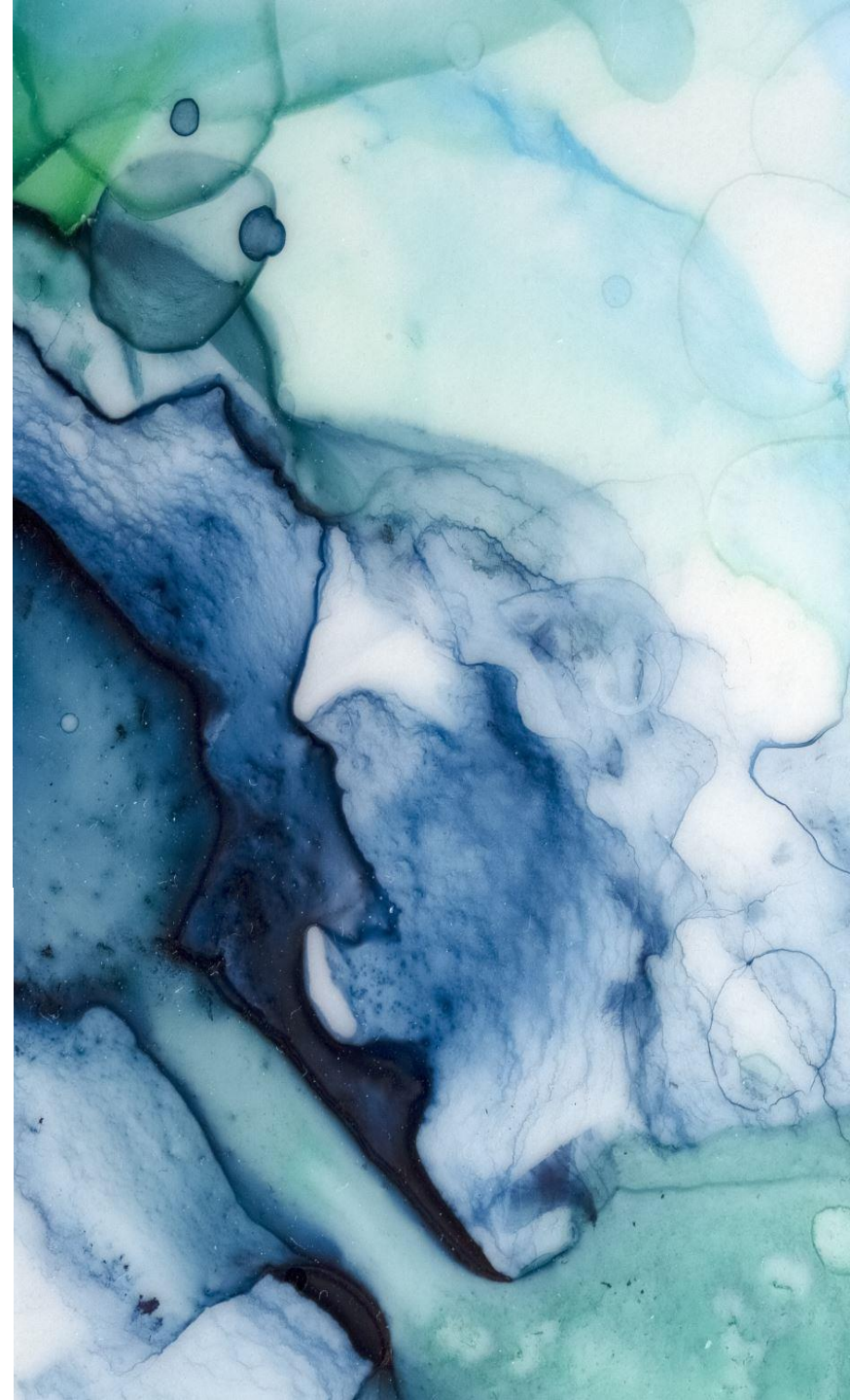
# OVERCOMING CHALLENGES IN EPILEPSY CLINICAL TRIALS:

## THE ROLE OF EUROPEAN CONSORTIUM FOR EPILEPSY TRIALS (ECET)

*Sébile Tchaicha & Alexis Arzimanoglou*

*ERICA GA*

*December 12, 2024*



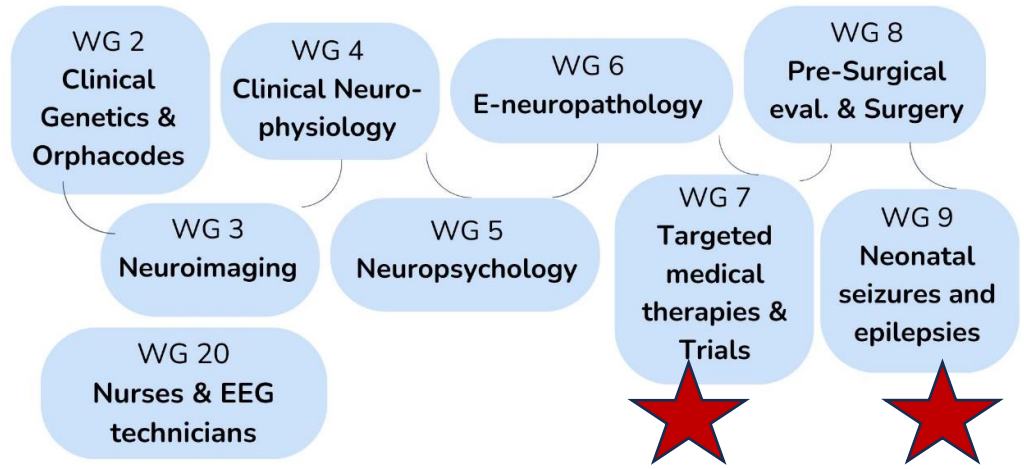
# The History of ECET



**European Reference Network**  
for rare or low prevalence complex diseases

- Network**  
Epilepsies (ERN EpiCARE)
- Coordinator**  
Hospital Sant Joan de Déu — Spain

## ERN EpiCARE Working Groups



Use the QR code to find out more about EpiCARE structure, missions, actions



Coordinators: R. Surges, F. Jansen, V. De Giorgis, E. Perucca



## Special Interest Groups

N of-1 trials for precision treatment of predefined genetic epilepsies

Ketogenic Diet

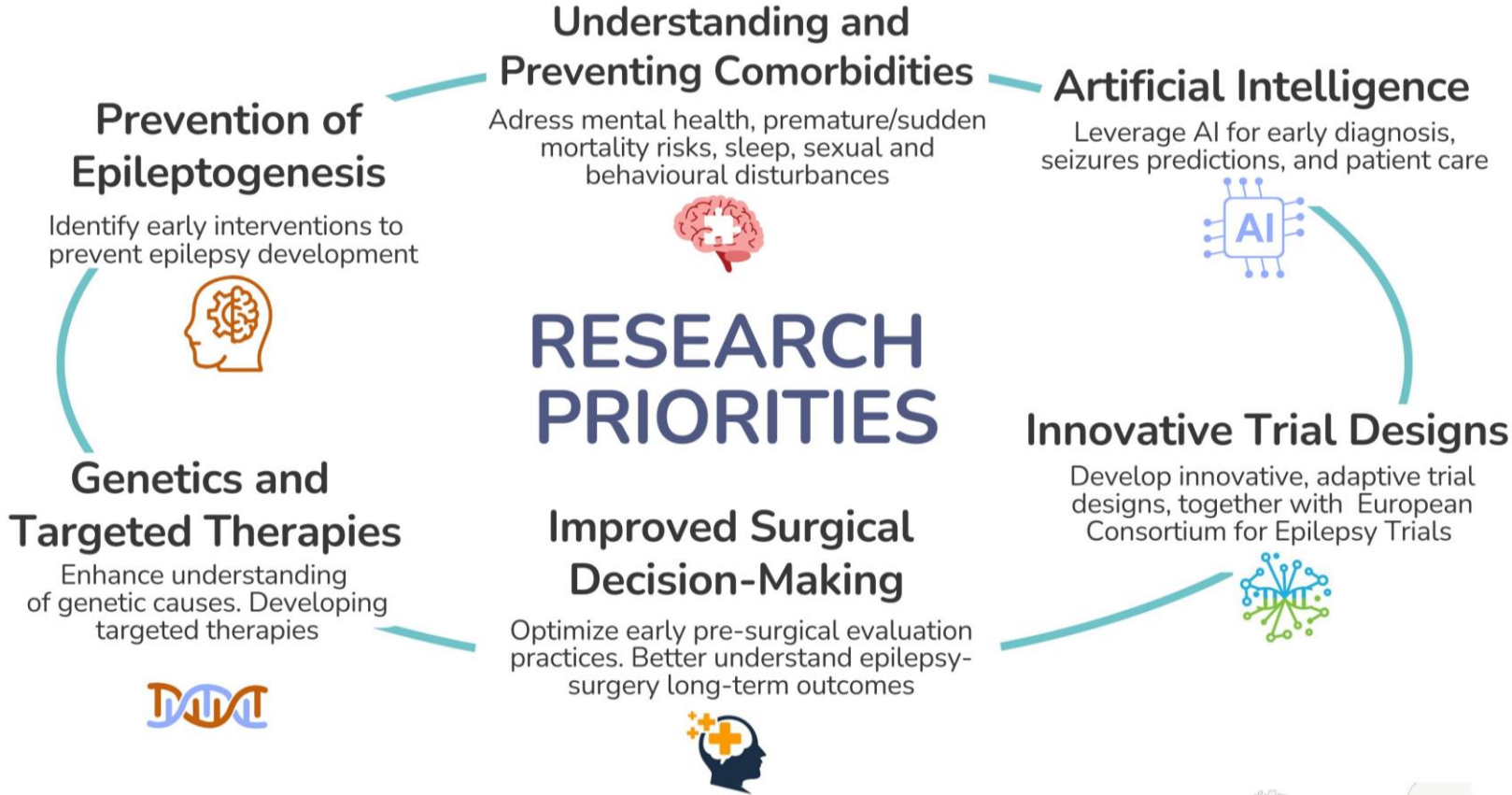
Autoimmune diseases with seizures and epilepsy as a core manifestation

Patient Centred Outcome Measures (PCOMs)

Design for, and analysis of trials for small sample size

- To promote and facilitate the development of better treatments or interventions, possibly in the context of clinical trials for people with epilepsy.
- To support and make newly undertaken academic treatment and intervention trials, designed by EpiCARE centers.
- To facilitate implementation of high-quality evidence from clinical trials in daily clinical care by creation of clinical recommendations for targeted treatments.

# Innovative Trial Designs: one of the ERN EpiCARE Priorities in Research



## SHAPING THE FUTURE OF EPILEPSY RESEARCH IN EUROPE: THE ERN EpiCARE PRIORITIES

Alexis Arzimanoglou / Sébile Tchaicha / Helen Cross / Kees Braun /  
The ERN EpiCARE Research Council and Executive Committee



# The challenge of epilepsies in Europe

- The annual number of new epilepsy patients in Europe is estimated to be
  - 30,000 children and adolescents; 96,000 in adults 20–64yrs; 85,000 in the elderly.
- More than 30% develop a rare or complex form, often drug-resistant.
- Nearly 150 rare diseases have epileptic seizures as their main symptom.

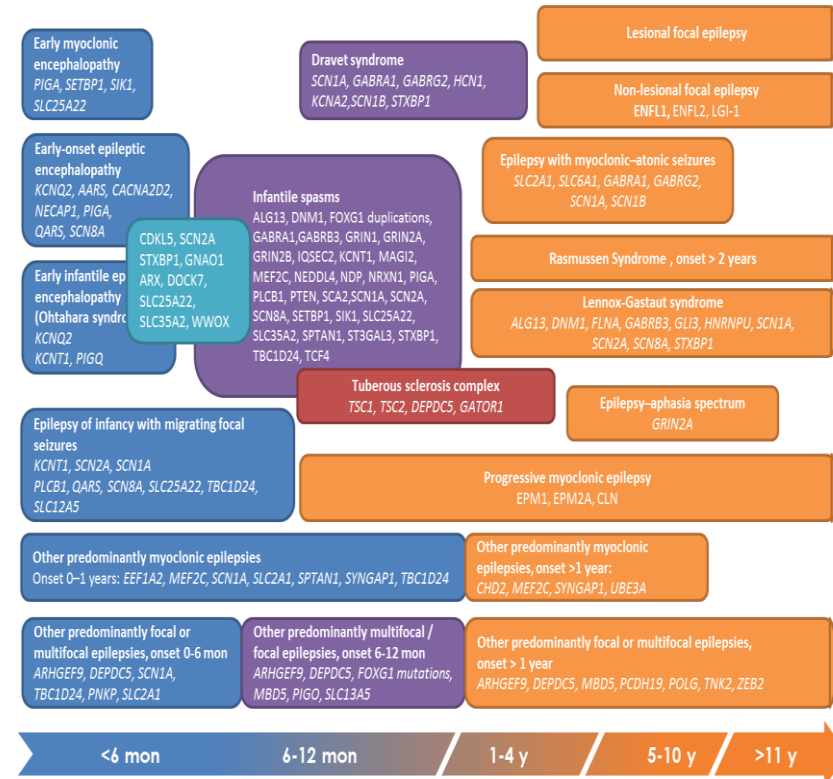
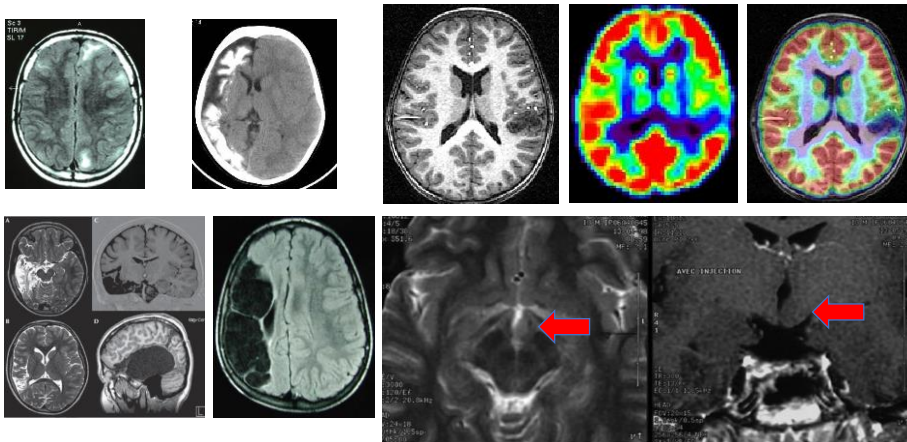
## ■ Seminar of Epileptology

Epileptic Disord 2021; 23 (1): 1-16

Epileptic  
Disorders

## The aetiologies of epilepsy

Simona Balestrini <sup>1,2</sup>, Alexis Arzimanoglou <sup>3,4</sup>, Ingmar Blümcke <sup>5</sup>, Ingrid E. Scheffer <sup>6</sup>, Samuel Wiebe <sup>7</sup>, Johan Zelano <sup>8,9</sup>, Matthew C. Walker <sup>1</sup>



# Why a European Consortium for Epilepsy Trials (ECET) ?

**The need to adapt clinical trials design to a rapidly expanding knowledge in the field**

- Epileptic Seizures are the key symptom **but only among others**
- Persisting confusion (both by Regulatory Agencies and often Pharma) between: “ASMs” and ”Disease modifiers”; Seizures/Syndrome/Aetiologies; etc.

**Ion Channels**

**Neurotransmitters**

**Stem cell-derived GABAergic interneurons**

**SV2A**

**NMDA subtype of glutamate receptors**

**Glutamate**

**Serotonin**

**Genetic treatments**

- **FOCAL EPILEPSIES, the presence or not of brain lesions; those with a genetic component; etc.**
- **Avoid oversimplification of patient selection when it comes to lobar epilepsies.**

# Why a European Consortium for Epilepsy Trials (ECET) ?

## IMPACT ON DESIGN OF CLINICAL TRIALS (examples)

- Trials in children with a well-advanced epilepsy introduce an important selection bias.
- Specificities of the epilepsies: genotype-phenotype correlations (ex. SCN8A)
- Biomarkers, when known, do not have the same significance (ex. VEEG monitoring)
- Seizure-counting may also need to be adapted to the type of epilepsy (countable seizures; days with/without seizures)

# Some facts on current trial designs & methodologies

- Often a rather **random selection of types of epilepsies** to perform trials, particularly in children.
- A design not always adapted to the rarity of these disorders.
  - **Result:** a rather impressive (and costly) number of sites opened *per trial*, leading to **significant heterogeneity of the patients included**.
  - Forced titration, short observation period....
- Barriers due to the nature of the epilepsies: randomness of seizures, inability of patients to recognize with certainty certain seizure patterns or to report them correctly, small effect sizes in newly diagnosed and refractory patients.
- Training of caregivers and/or patients required in the trial not adaptable to real life.
- The content of the feasibility studies often ignores the specificities of the type of epilepsy



# European Consortium for Epilepsy Trials (ECET)

## How can an entity like ECET help ?

Involvement of established epilepsy experts (multidisciplinary) and patient advocates is needed **from the very first steps of trial design**:

- ✓ Identify priorities; Regular contact with regulatory agencies; Inclusion/Exclusion criteria;
- ✓ Definition of primary and secondary endpoints; Content of the eCRFs;
- ✓ Content of feasibility questionnaires (**NOT** a technical or N° of patients' issue);
- ✓ Selection of competent centres; Validation of individual inclusions etc.
- ✓ Rigorous modalities of seizure tracking;
- ✓ Extrapolation based on scientifically sound approaches

# European Consortium for Epilepsy Trials (ECET Ltd.)



## Which is the most appropriate structure ?

- An independent entity providing services to academia and industry for improving and accelerating the design and conduct of clinical research.
  - **Endorsed** by Epilepsy Alliance Europe, the ERN EpiCARE, the International League Against Epilepsy (ILAE) and the corresponding patient advocate groups.
- A collaborative group of European investigators with shared interest and established expertise in the design and conduction of epilepsy trials.
- Individual Confidentiality Agreements signed.
- Respect of National/EU legislations (GDPR)
- Information about **site competencies and facilities** collected.



# ECET Ltd. Structure



## Scientific Advisory Committee:

- Stéphane AUVIN (France)
- Andreas BRUNKLAUS (UK)
- Valentina DE GIORGIS (Italy)
- Norman DELANTY (Ireland)
- Nicolas GASPARD (Belgium)
- Floor JANSEN (The Netherlands)
- Reetta KALVIAINEN (Finland)
- Lieven LAGAE (Belgium)
- Rima NABBOUT (France)
- Ronit PRESSLER (UK)
- Philippe RYVLIN (Switzerland)
- Rohit SHANKAR (UK)
- Nicola SPECCHIO (Italy)
- Bernhard STEINHOFF (Germany)
- Pasquale STRIANO (Italy)
- Adam STRZELCZYK (Germany)
- Rainer SURGES (Germany)
- Vicente VILLANUEVA (Spain)

## Ex Officio members

- Pr. Helen CROSS (ILAE President)
- Pr. Jacqueline FRENCH (Epilepsy Study Consortium)
- Pr. Emilio PERUCCA (Founding member and Honorary Consultant)



Eugen Trinka  
Director



Alexis Arzimanoglou  
Director




Sebile Tchaicha  
Executive Director



# Where are ECET experts?

 **IRELAND** Irish Centre For Fetalpediat and Neonatal Translational Research, Cork University Maternity Hospital / Beaumont Hospital & FutureNeuro hosted by the Royal College of Surgeons in Ireland

 **THE NETHERLANDS** University Medical Center Utrecht (UMCU)


 **BELGIUM** University Hospitals, Leuven / Hôpital Universitaire des Enfants Reine Fabiola (HUDERF) / Hôpital ERASME


 **GERMANY** Universitätsklinikum Erlangen / University Medical Center Freiburg / University Hospital Bonn / University Berlin Charite / Universitätsklinikum Tübingen / Centre for Paediatrics and Adolescent Medicine, University Hospital Heidelberg / Epilepsieambulanz für Erwachsene Epilepsiezentrum Kork Landstrasse / Goethe-University Frankfurt, Epilepsy Center Frankfurt Rhine-Main / University Medical Center Frankfurt / LMU Munich Epilepsy Center, Children`s Hospital / Philipps-University Marburg


 **SWITZERLAND** CHU Vaudois – Lausanne

 **FRANCE** CHU Lille / Hospices Civils de Lyon - Hôpital Femme Mère Enfant / Necker Enfants Malades Hospital / Hospices Civils de Lyon - Hôpital neurologique Lyon / Paris-Robert Debré / Pitié Salpêtrière Paris, France / University Hospitals of Marseille, AP-HM, France

 **SPAIN** Hospital Sant Joan de Déu and Hospital Clínic, Barcelona / Hospital Universitario La Fe Valencia / Vithas Madrid University Hospitals

 **PORTUGAL** Centro de Referência para Epilepsias Refratárias. Hospital de Santa Maria – CHU Lisboa Norte / CHU do Porto / CHU de Coimbra

 **DENMARK** Rigshospitalet, Copenhagen / Danish Epilepsy Center Filadelfia, Dianalund / Aarhus Universitets Hospital


 **SCOTLAND** Queen Elizabeth University Hospital, Glasgow / Royal Hospital for Children, Glasgow / Royal Hospital for Children and Young People & Department of Clinical Neurosciences Edinburgh

 **UK** Great Ormond Street Hospital / John Radcliffe Hospital/University of Oxford / University College London Hospitals NHS Foundation Trust / Cornwall Partnership Foundation NHS Trust / Peninsula Medical School University of Plymouth




 **MALTA** Mater Dei Hospital

 **ITALY** IRCCS Istituto delle Scienze Neurologiche, Azienda USL di Bologna, Ospedale Bellaria / Fondazione Mondino / ASST Santi Paolo Carlo-San Paolo Hospital; University of Milan / "Claudio Munari" Epilepsy Surgery Centre, Milan / Fondazione IRCCS Istituto Neurologico Besta, Milan / Azienda Ospedaliero-Universitaria Meyer, Firenze / Department of Neuroscience at Bambino Gesù Children's Hospital, Rome / Agostino Gemelli University Policlinic, Rome / AOUI di Verona, Unità Operativa Complessa (UO) di Neuropsichiatria Infantile / IRCCS Istituto Giannina Gaslini, Genova

 **FINLAND** Epilepsy Center, Kuopio University Hospital / Oulu University Hospital, Pediatric Neurology Unit / Helsinki University Hospital (Helsinki -Oulu ERNEpi Consortium)


 **NORWAY** National Centre for epilepsy

 **SWEDEN** University of Gothenburg, Sahlgrenska

 **ESTONIA** Children's Clinic of Tartu University Hospital

 **LATVIA** Children's clinical university hospital, Latvia


 **LITHUANIA** Vilnius University hospital Santaros Clinics / Hospital of Lithuanian University of Health Sciences, Kaunas

 **POLAND** The Children's Memorial Health Institute, Warsaw / Medical University of Gdańsk / Instytut Centrum Zdrowia Matki Polki, Centrum Medyczne Plejady

 **CZECH REPUBLIC** Brno Epilepsy Center (St Anne university for adult part and University Hospital Brno for pediatric part) / Motol University Hospital, Prague


 **AUSTRIA** Allgemeines Krankenhaus Wien / Medizinische Universität Wien, Vienna / Christian Doppler Medical Centre, Paracelsus Medical University and Centre for Cognitive Neuroscience, Salzburg

 **HUNGARY** SE Neurosurgery and Neurointervention Clinic

 **SLOVENIA** Ljubljana University Medical Centre, Dpts. of Child, Adolescent and Developmental Neurology & Department of Neurology

 **CROATIA** UHC Sestre Milosrdnice, Zagreb / University Hospital Centre Zagreb and School of Medicine, University of Zagreb

 **SERBIA** Institute of Mental Health / Institute for Mother and Child Healthcare of Serbia / Institute for Children and Youth Health Care of Vojvodina

 **CYPRUS** The Cyprus Institute of Neurology and Genetics, Nicosia

 **GEORGIA** Epilepsy Centre at the University Clinic in Tbilisi

 **TÜRKIYE** Karadeniz Technical University Medical Faculty, Neurology Department

# ECET *Ltd.* Structure



- **Respect and reflect the multidisciplinary of the epilepsies**
- 10 Task Forces composed of experts available for the needs of specific trials :

Trial Design	Clinical Pharmacology
Genetics	Neuroimaging
Neonatal seizures	Epilepsy Surgery
Paediatric Epilepsies	Neurophysiology
Adult Epilepsies	Neuropsychology

- **Experts validating inclusions in a trial (ex. EEG reading)**



# What can ECET offer to Academia & Industry

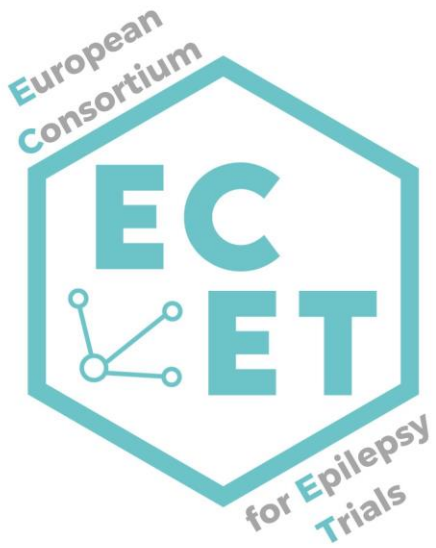
## Ensure consistency

- Lead and support **natural history studies**.
- **Promote precision medicine** via potentially disease modifying approaches.
- **Advise on clinical drug development** in liaison with scientific societies and EpiCARE.
- Advice on **clinical trials design**.
- **Feasibility questionnaires** reflecting disease specificities.

## Reproducibility

- **Selection of trial sites in Europe**, based on expertise in given types of epilepsy.
- **Review panels**, to be consulted during the trials.
- **Centralized/standardized adjudication processes** to reduce variability in multicentre trials.
- Collaboration with **CROs**.
- Collaboration with **patient associations**.
- **Educational activities**.

## Reliability



For more information, please contact Mrs. Sébile Tchaicha:

[s.tchaicha@ecetepilepsy.org](mailto:s.tchaicha@ecetepilepsy.org)

### Acknowledgments:

- ERN EpiCARE members & Staff
- International League Against Epilepsy

