ENPR-EMA Workshop

Case Study: Novel Pediatric Trial Design

A Study to Evaluate the Efficacy, Safety, and Tolerability of Brivaracetam as Monotherapy in Patients 2 to 25 Years of Age With Childhood Absence Epilepsy or Juvenile Absence Epilepsy (EXPAND)

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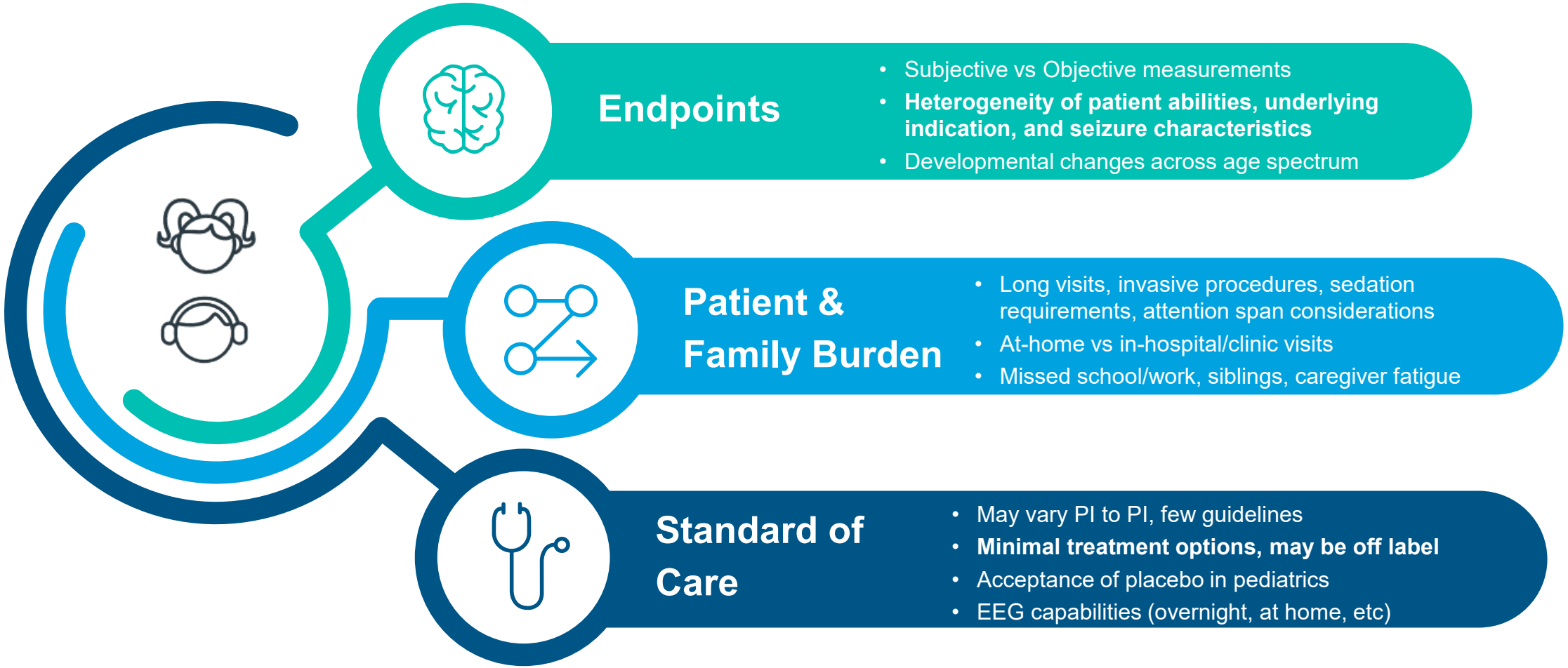
Case Study Presentation Summary

- Challenges: Pediatric Epilepsy, Absence Seizures
- Historical designs
- Design Summary & Breakdown
- Considerations

Abbreviations & Terminology

CRA	Clinical Research Associate (aka monitor)
DEE	Developmental Encephalopathy Epilepsy
EDV	Early Discontinuation Visits
EEG	Electroencephalography
IDMC	Interim Data Monitoring Committee
LTFU	Long-term Follow Up
PI	Primary Investigator
PK/PD	Pharmacokinetics / Pharmacodynamics
PRO	Patient Reported Outcomes
QOL	Quality of Life
RDW	Randomized Dose Withdrawal

Overview of Challenges: Pediatric Epilepsy, Absence Seizures



Endpoints and Progression of Clinical Trials, Pediatric Epilepsy

Historical Precedence

- ✓ **Primary Endpoints**
  - Seizure frequency reduction (% change from baseline, frequency over 28 days) via diary/logs
  - Seizure Freedom – complete absence over defined period
  - EEG-Based Measures (DEEs and Absence Seizures particularly benefit from more objective measurements)
- ✓ **Secondary Endpoints**
  - Responder rates / reduction of seizure frequency by %
  - Time to first seizure
- ✓ **Exploratory** – QOL, Neurodev/behavioral assessments, Sleep, cognitive function, PROs (caregiver and/or patient), Digital biomarkers, biochemical markers

Phase of trial – standard progression	Enrollment Range # patients	Average
I (safety, PK/PD)	10 – 30	20
II (dose-finding, efficacy)	40 – 120	80
III (confirmatory evidence)	150 - 400	250

Examples: FDA-Approved Drugs for Pediatric Epilepsy

Historical precedence and data needs for labeling/approval

Drug	Indication	Age Approved	Primary Efficacy Endpoint	Data Basis
Ethosuximide (Zarontin)	Absence (petit mal) epilepsy	≥3 years	Reduction in absence seizures (EEG + seizure diary)	**Pediatric trials demonstrating seizure control** [cureepilepsy.org]
Valproic Acid / Divalproex (Depakote, Depakene)	Absence, generalized seizures	≥2 years	Seizure frequency reduction	**Controlled pediatric studies + historical data** [webmd.com]
Clobazam (Onfi)	Adjunctive for Lennox-Gastaut Syndrome	≥2 years	Percent reduction in drop seizures	**Randomized controlled pediatric trials** [cureepilepsy.org]
Cannabidiol (Epidiolex)	LGS, Dravet, TSC	≥1 year	Change in convulsive seizure frequency	**Phase 3 pediatric trials (placebo-controlled)** [cureepilepsy.org]
Fenfluramine (Fintepla)	Dravet Syndrome	≥2 years	Reduction in convulsive seizure frequency	**Pediatric Phase 3 trials** [webmd.com]
Brivaracetam (Briviact)	Focal onset seizures	≥1 month	Seizure frequency reduction	**Extrapolation from adult data + pediatric PK and safety** [cureepilepsy.org]
Eslicarbazepine (Aptiom)	Focal onset seizures	≥4 years	Seizure frequency reduction	**Extrapolated efficacy + pediatric safety studies** [cureepilepsy.org]
ACTH (Acthar Gel)	Infantile spasms	<2 years	Resolution of spasms and EEG hypsarrhythmia	**Historical controlled studies** [cureepilepsy.org]

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Novel, Adaptive Approach for Pediatric Epilepsy

Case Study Overview

A Randomized, Dose-Finding and Confirmatory, Double-Blind, Placebo-Controlled, Parallel-Group Multicenter Study With a 2 Stage Adaptive Design and Randomized Withdrawal to Evaluate the Efficacy, Safety, and Tolerability of Brivaracetam as Monotherapy in Patients 2 to 25 Years of Age With Childhood Absence Epilepsy or Juvenile Absence Epilepsy

- **Combined Phase II/III design** to minimize # of patients needed for dose finding, safety, tolerability, and efficacy
  - Phase 2 (Stage1, up to 23 wks) dose selection and futility assessment

    Interim Analysis then open to

    Safety assessed by IDMC ~25% completing Stage 1
  - Phase 3 (Stage 2, up to 23 wks) optimal-dose, confirmatory

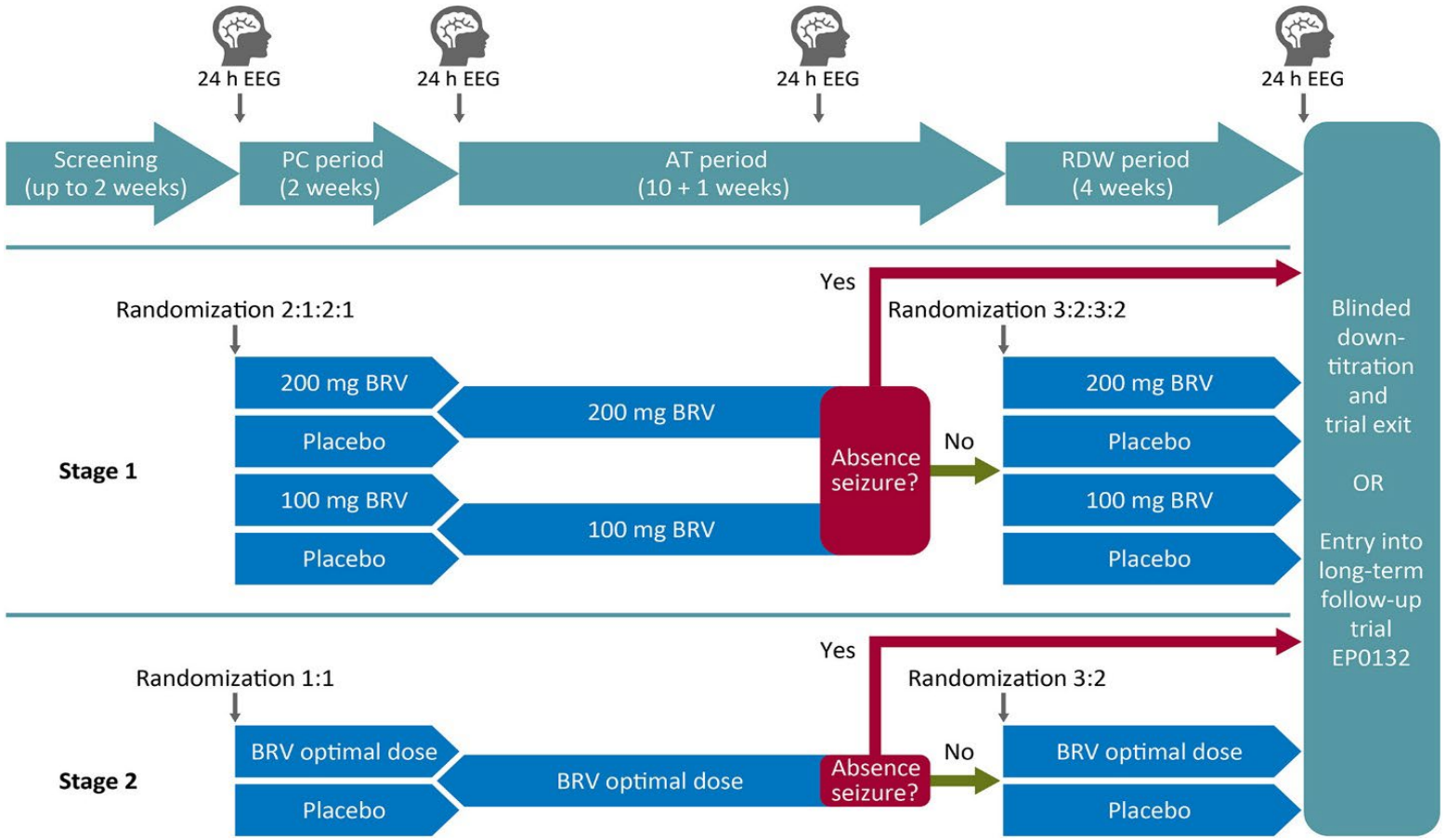
Only participate in Stage 1 or Stage 2, NOT both

- **Adaptive Design**
  - Multiple randomization timepoints with potential placebo : therapy, ending with open label LTFU
  - Clear, objective evaluations to guide decisions and progression or movement to RDW and LTFU
- **Randomized withdrawal**
  - Measures treatment effect over time, minimizes placebo use, participants act as their own control
- **Primary endpoint**: 24 hr EEG @ Day 14 seizure free, secondary efficacy measures include diary

N = 160 (Stage 1 approximately 84) – nearly half patients required c/t standard Ph II then III approach

Bast T, Schulz AL, Floricel F, Morita D, Cleveland JM, Elshoff JP. Efficacy and tolerability of brivaracetam monotherapy in childhood and juvenile absence epilepsy: An innovative adaptive trial design. Epilepsia Open. 2022 Dec;7(4):588-597. doi: 10.1002/epi4.12628. Epub 2022 Aug 4. PMID: 35844134; PMCID: PMC9712476.

Stage 1 (Phase II) vs Stage 2 (Phase III) Schematic



PC – Placebo control
AT – Active Therapy
BRV - Brivaracetam

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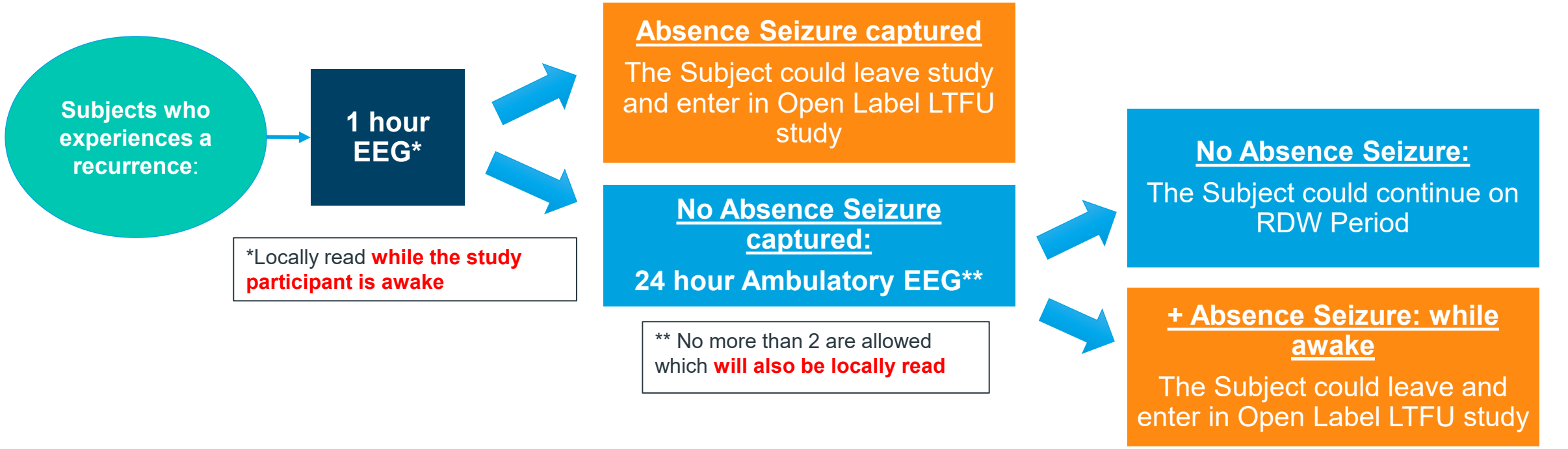
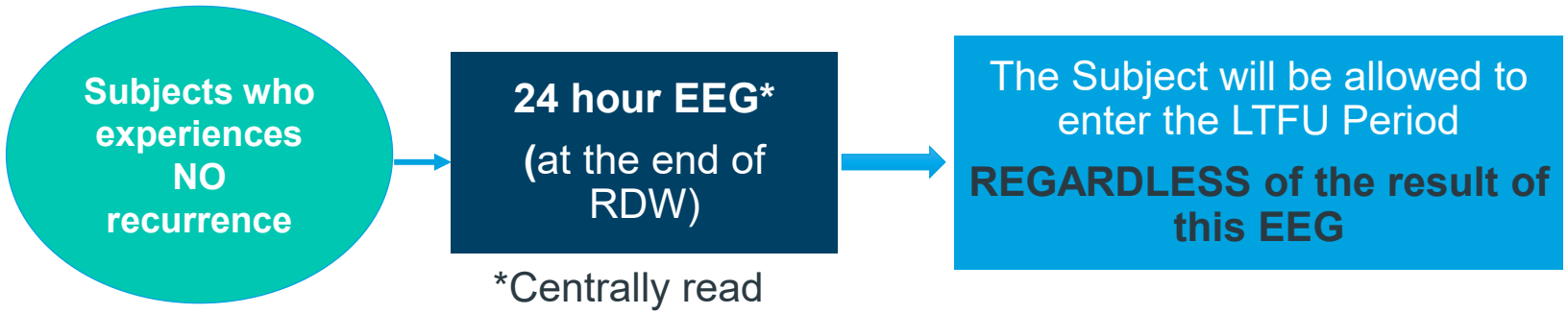
Study Design Schema Randomized Withdrawal





All study **participants will complete an EDV**, unless they completed Visit 7, or they completed Visit 6 and their Week 12 24-hour EEG showed confirmation of a seizure.

If **study discontinuation** occurred at any scheduled visit, then **EDV assessments** will be conducted instead of the scheduled visit assessments.

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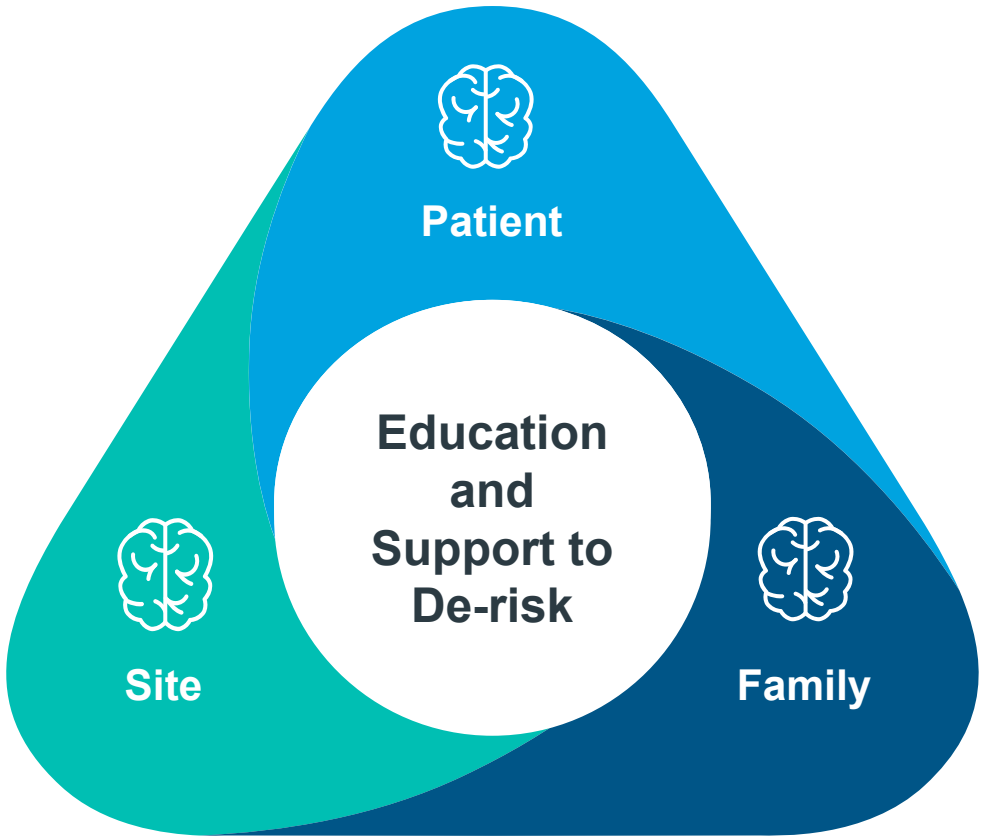
Delivery Considerations to Build Trust and Quality



Patient

- Assent support, mapping study assessments, visits, responsibilities
- **Diverse, age appropriate**

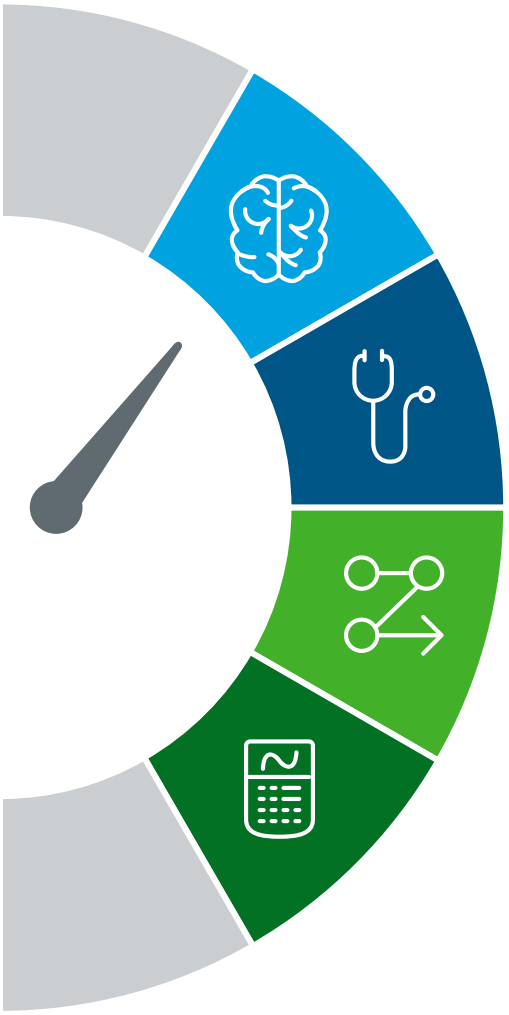
Family

- Empathetic consent process, shareable education materials
- Communication pathways, dosing, concomitant therapies
- Visit mapping, reminders, proactive scheduling, **home diary / seizure tracking, EEG** (at home and hospital)

Sites & Study Team

- CRA as support, experts on protocol/design, robust initiation training
- Communication pathways and expectations, central portal
- Permitted/prohibited therapies, seizure capture, RDW, discontinuation/withdrawal

Key Considerations Supporting Acceptance of Novel Approach



Historical Safety Data

- Asset approval age 4 years and above, adjunctive therapy
- Prior adult and pediatric data to support dose selection for monotherapy

High Unmet Need

- Few therapies available
- No new data for indication in nearly a decade

Conservative Decisions Balanced Risks

- Patient eligibility strict and rigourous to mitigate undue risk with placebo use
- Short placebo window
- Clear criteria for RDW and efficient actions if seizures reported

Patient and Family Centric Approach

- Less patients required to be enrolled and exposed to placebo or sub-optimal dosing
- Streamlined timelines creating more efficient development program
- Smart use of technology to ease burden (home EEG)

Thank you

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