Registries & Natural History Studies

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Despite major advancements in research, 95% of all rare disorders still don't have an FDA-approved therapy[1]

- With novel therapeutic approaches, including gene and cell therapies, there is increasing investment in drug development for rare disorders

- However, FDA requires inclusion of observational data (like natural history) to evaluate therapies for these conditions

1.Global Genes Rare Disease Facts. Accessed May 23, 2022. https://globalgenes.org/rare-disease-facts/

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In order to understand the disease, we need to **generate and access data** about the disease

What’s what?

Four key terms that are important to understand and distinguish:

Clinical Study

Observational Study

Patient Registry

Natural History Study

Observational vs. Clinical Studies

Observational studies observe people in normal settings. Researchers gather information, group volunteers according to broad characteristics, and compare changes over time.

- **No experimental therapy or intervention**
- (Incorrectly) perceived as a “lower in the hierarchy” of evidence hierarchy
- Challenging to engage patients with lots of drop of

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Clinical trials are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people.

- **Focus on safety/efficacy of intervention**
- Critical step to approving a therapy
- Generally take place *after* disease is understood

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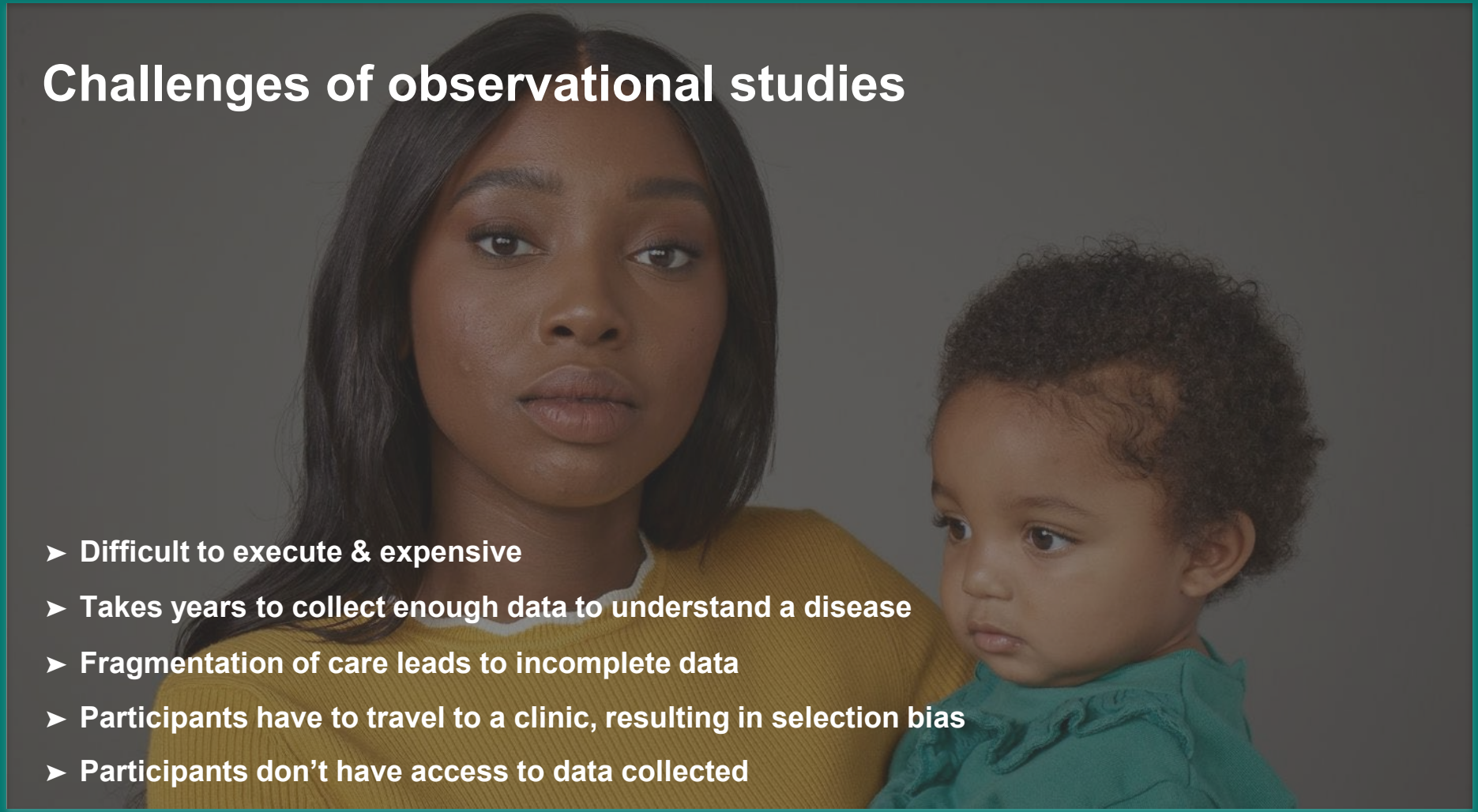
Observational data supports trial success

Pre-Clinical	Phase 1/2/3	Postmarket
➤ Support phenotype characterization across the lifespan ➤ Define study inclusion/exclusion criteria ➤ Support endpoint selection and characterization ➤ Inform clinical trial design	➤ Serve as external control arm ➤ Support or confirm evidence of efficacy ➤ Enable effective recruitment and site planning strategies	➤ Support or confirm evidence of efficacy ➤ Monitor for long-term outcomes and/or adverse effects ➤ Evaluate real world prescribing, use, and/or reimbursement

Challenges of observational studies



- Difficult to execute & expensive
- Takes years to collect enough data to understand a disease
- Fragmentation of care leads to incomplete data
- Participants have to travel to a clinic, resulting in selection bias
- Participants don’t have access to data collected

Registries and Natural History Studies

- “A registry is an organized system that collects clinical and other data in a standardized format for a population defined by a particular disease, condition, or exposure” - FDA
  - Clinician-reported outcomes
  - **Patient- and observer-reported outcomes**
  - Medical claims data
  - Pharmacy records
  - Electronic medical records
- A natural history study collects information about the natural history of a disease in the absence of an intervention, from the disease's onset until either its resolution or the individual's death.
  - **Clinician-reported outcomes**
  - Patient- and observer-reported outcomes
  - Medical claims data
  - Pharmacy records
  - Electronic medical records

Rare disease registries are powerful but present limitations for natural history data

- Registries have powerful applications:
  - Identify participants for a clinical trial
  - Clinical endpoint selection and characterization
  - Serve as an external (historical) control
- And importantly, create an opportunity to **incorporate the patient perspective**

Challenge

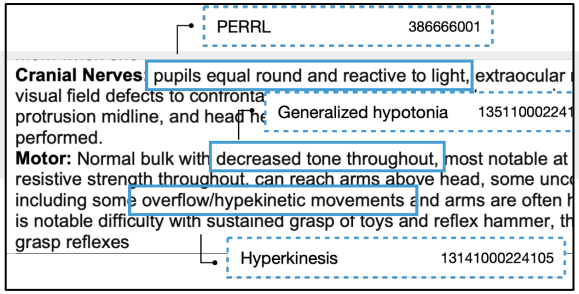
Since in-person observational studies to conduct natural history are expensive and burdensome, we often rely on patient-reported data as a “proxy” to collect clinical information. Often times, the use of this data in research or for regulatory purposes is limited due to data quality challenges as the data isn’t confirmed by a doctor or clinician.

Ciitizen: a novel approach to accelerating research

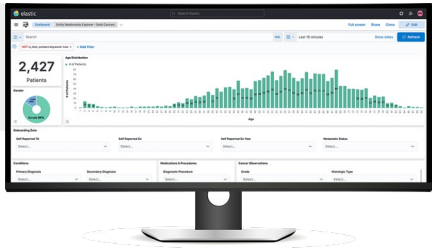
Ciitizen: a patient-centric RWD platform enables natural history studies at scale

Ciitizen **follows the patient** and leverages HIPAA right of access to obtain medical records from *all* providers patient sees (average 6+ providers)

Medical records & images scanned and uploaded to patient's account



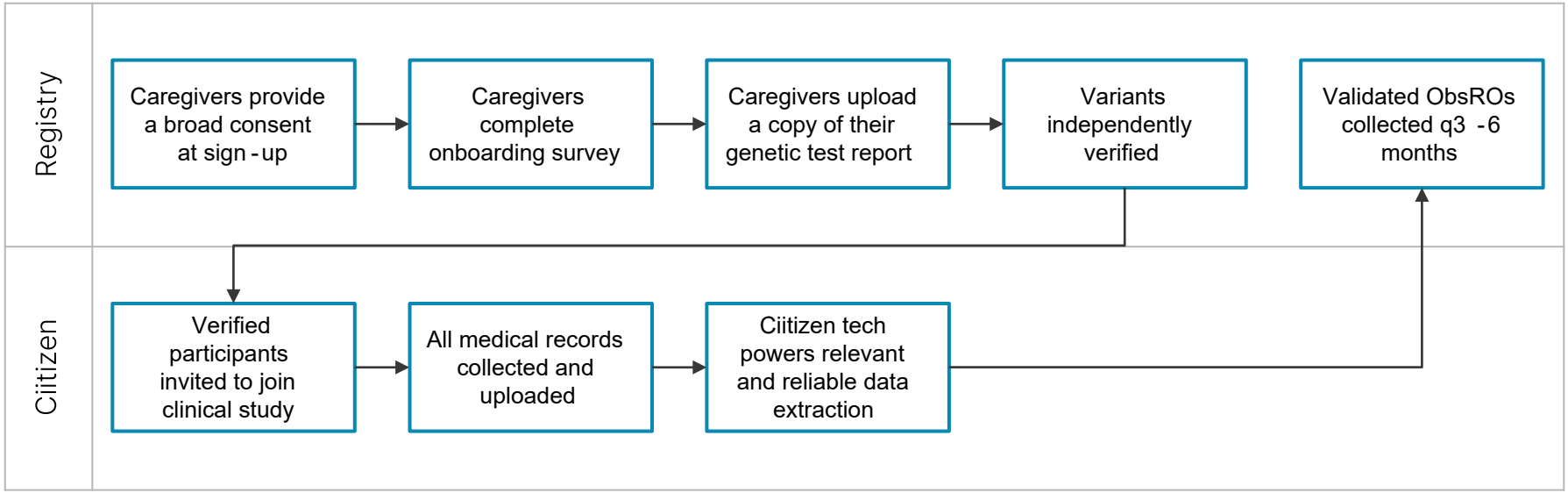
Raw records processed by machine-learning engine + human QA to extract, normalize and codify defined data elements



De-identified data output is structured and ready to share for research

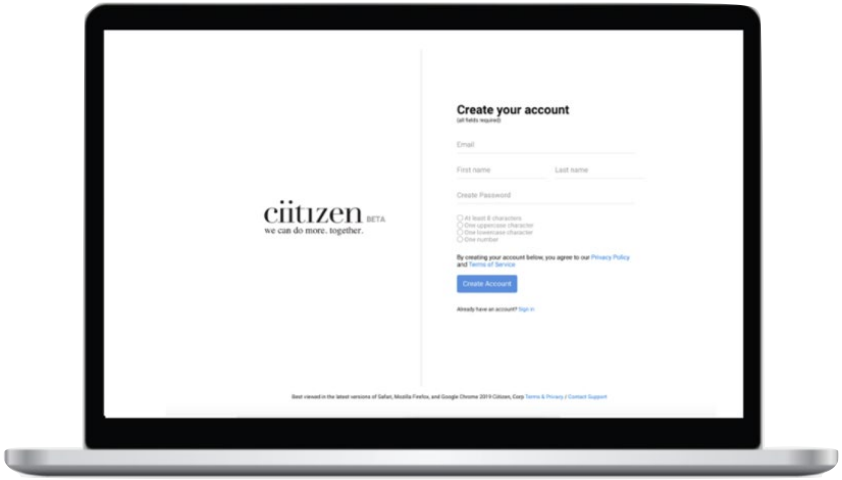
Registry aims and architecture

- How can a patient advocacy organization accelerate collection of relevant clinical outcome assessments to de-risk pharma investment in rare disease?



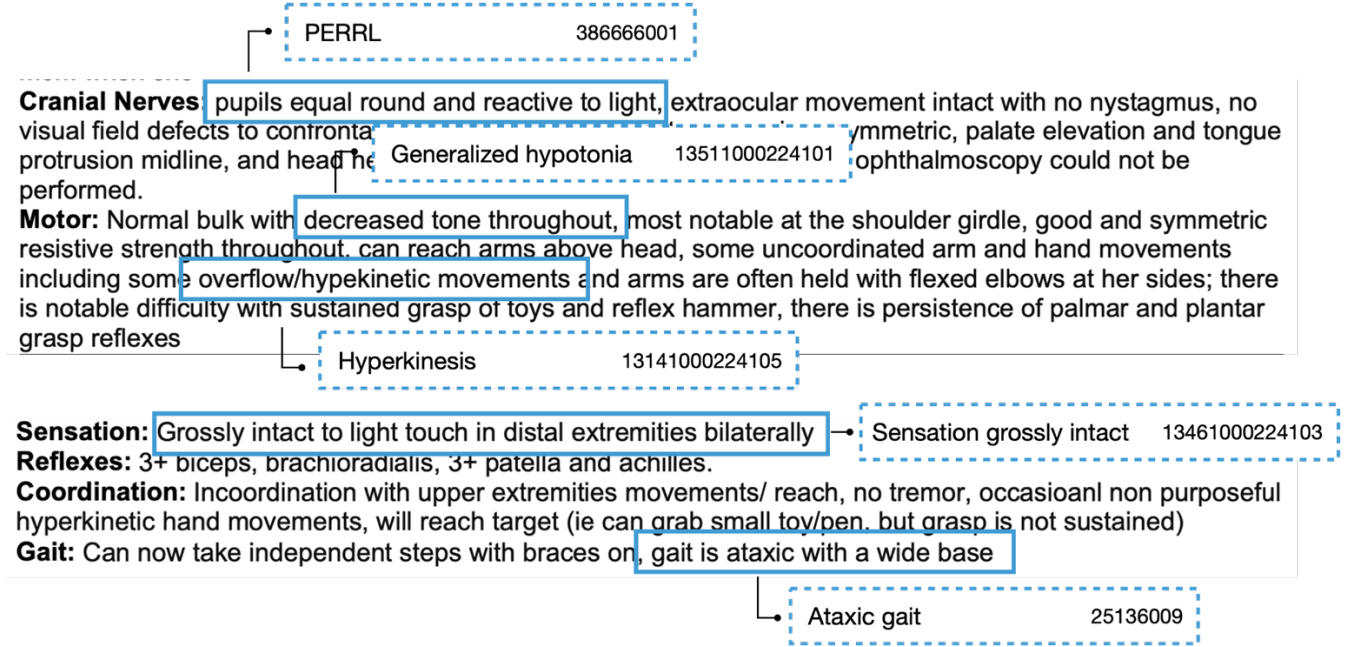
Data is collected for and owned by the patient

- Completely digital - no clinic visit required
- Collects participant's medical records from all the institutions visited
- Data from medical records is organized and summarized at no cost to the patient
- Extracts large amount of critical data in weeks (not years)
- Participants get full access to their medical records and can choose to share with researchers



It only takes 10 minutes for patients or caregivers to register - we do the heavy lifting!

Research-ready data is created from unstructured records



- Machine learning/NLP-assisted extraction engine that normalizes data
- Human assistance and review of pipeline generated data for QA/QC
- Terminologies such as SNOMED, RXNORM and LOINC used for normalization

Comprehensive entity extraction focused on defining history of disease and endpoints that can be measured

Demographic Year of birth, Date and Age of Diagnosis, Ethnicity	**Seizure History** Classification, Frequency, >5 min, Meds	**Clinical Diagnosis** (includes comorbidities) Diagnosis, Date, Status
Genetic Diagnosis Gene and Variant	**Diagnostic Imaging** Modality, Date, Abnormal/Normal findings	**Hospital Admissions** Admission/Discharge Date, Diagnosis, Significant Event
Growth Height, weight	**Diagnostic Procedures** Procedure, Date, Abnormal/Normal findings	**Procedures** Surgical Procedure, EEG, NCV, Polysomnogram
Physical Exam Findings Date, Cranial Nerves, Muscle Bulk/Tone & Strength, Gait, Sensation, Coordination, Reflexes	**Development** Milestone, Age, Attainment, Standardized Assessments, Regression, Use of Devices	**Medication** Name, Indication, Start/Stop Date, Dose, Frequency, Route of Admin, Treatment & Adverse Effect

Considerations for registry design

- Thoughtful registry design broadens utility:

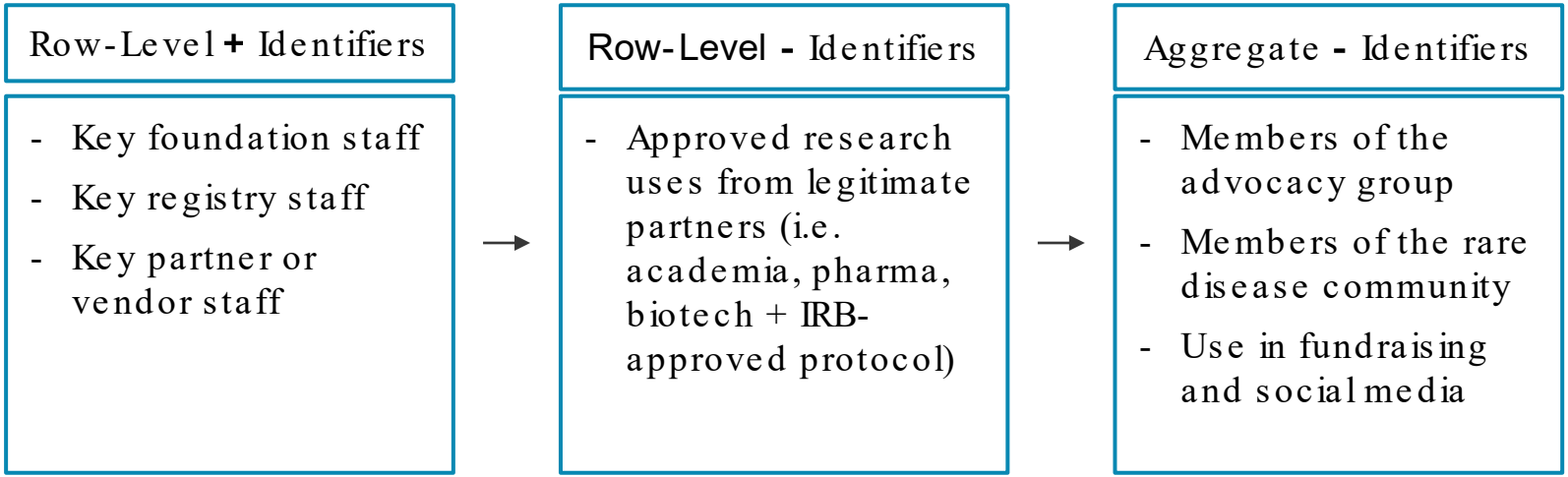
Relevance	Reliability	Curation
Ensure capture of key data elements across a representative patient population	Input processes to maximize data accuracy and comprehensiveness	Harmonize source data through use of terminologies

Considerations for registry design

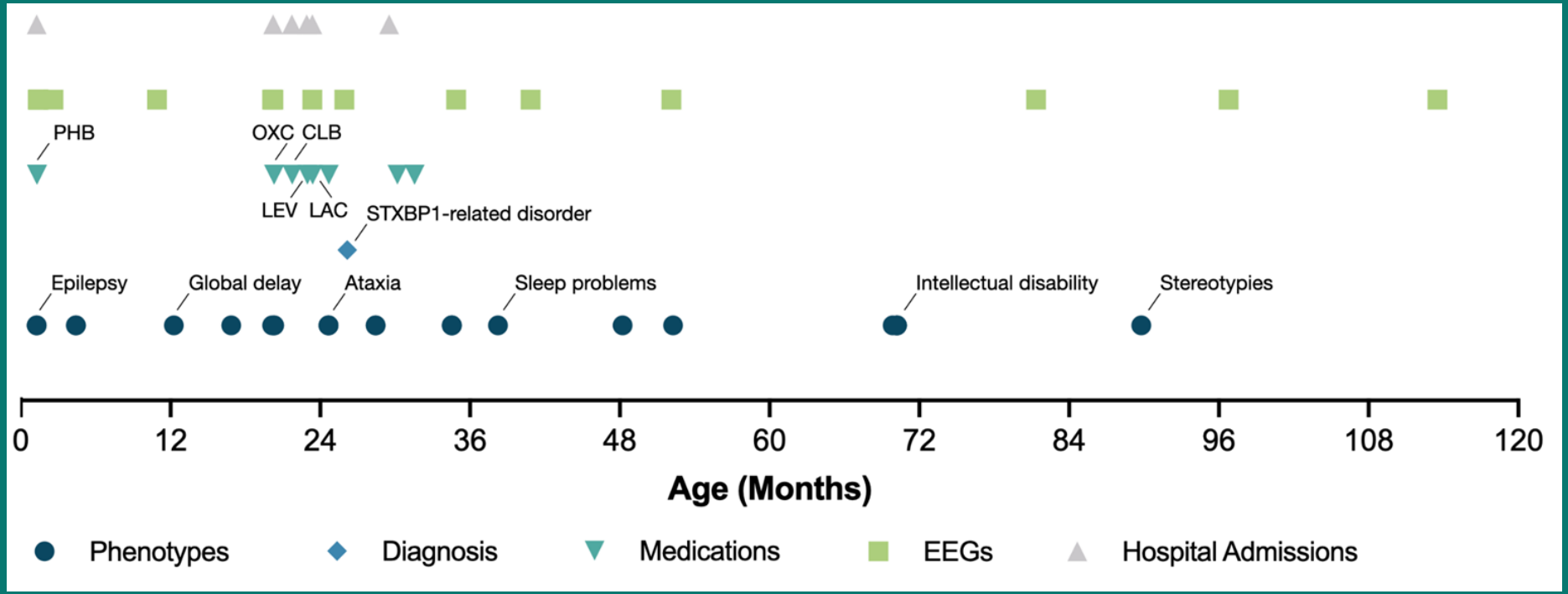
- Patient privacy and security are paramount:

Privacy	Data Access	Terms of Use
Remove common identifiers, assign unique identifiers, store data securely	Control who has (and who is given) access to patient - level data	Specify conditions and restrictions for users of the data to protect patient privacy

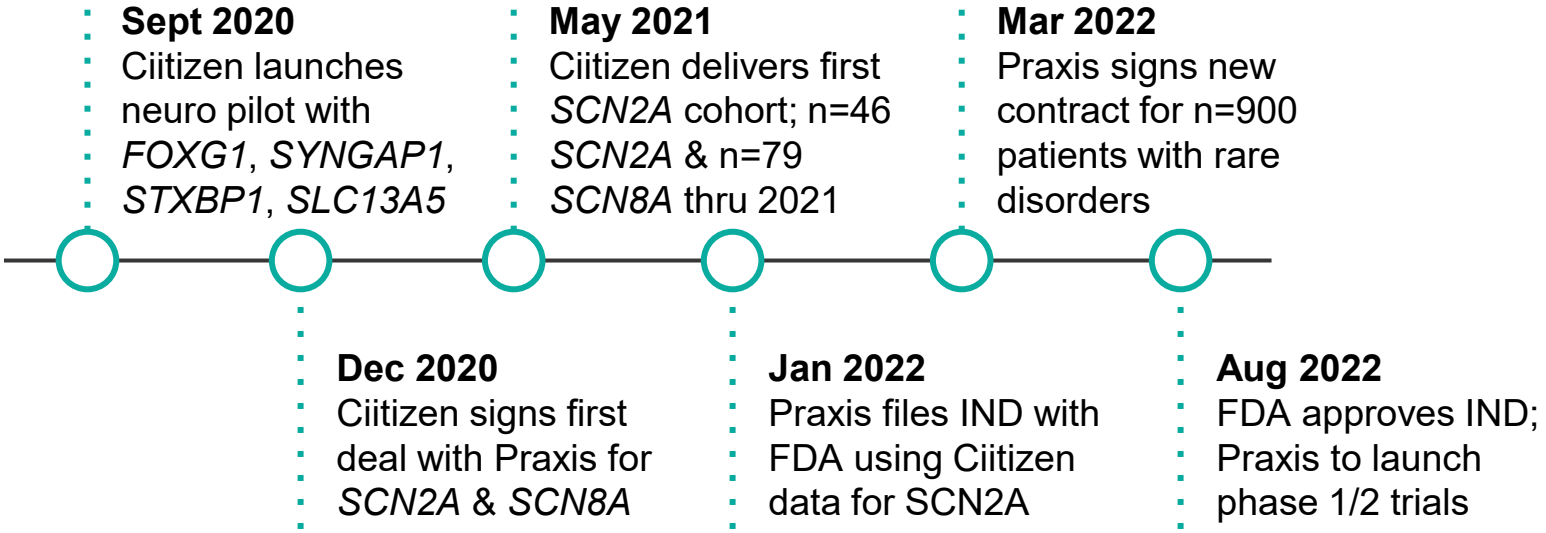
Data access and control



Create detailed patient journeys



Ciitizen and Praxis, a proof-of-concept



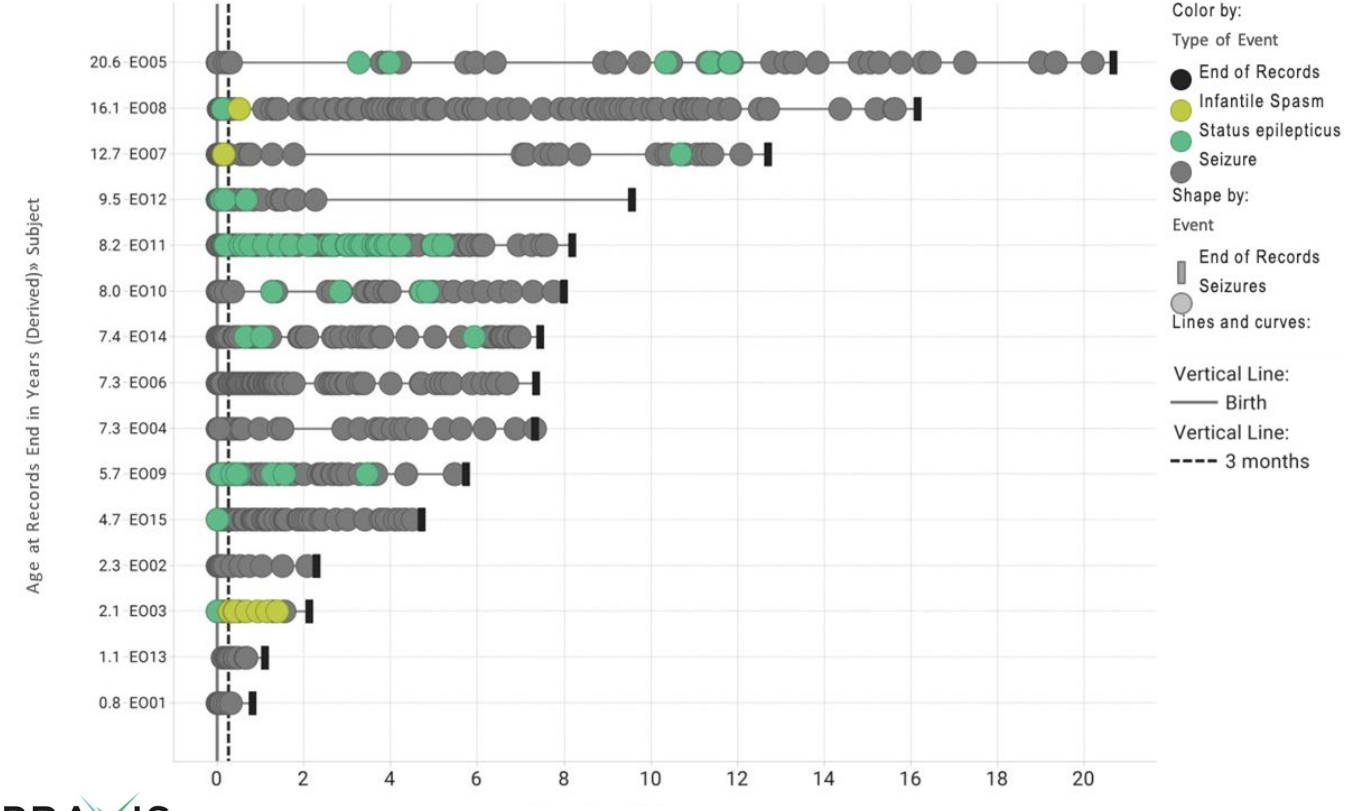
Through exclusive use of Ciitizen for clinical data, Praxis to launch trials ***years earlier.***

Praxis obtained investigational new drug (IND) clearance from FDA for PRAX-222[1]

- PRAX-222 - ASO therapy for SCN2A-DEE
- Invitae's Ciitizen RWD used to synthesize lived experience of SCN2A-DEE patients
- Invitae's Ciitizen data was the only natural history data used in FDA submission package
- Using Ciitizen data led to ~5 years in time savings

1.Praxis Precision Medicines Press Release. Issued September 7, 2022. **https://investors.praxismedicines.com/news-releases/news-release-details/praxis-precision-medicines-provides-updates-clinical-stage**

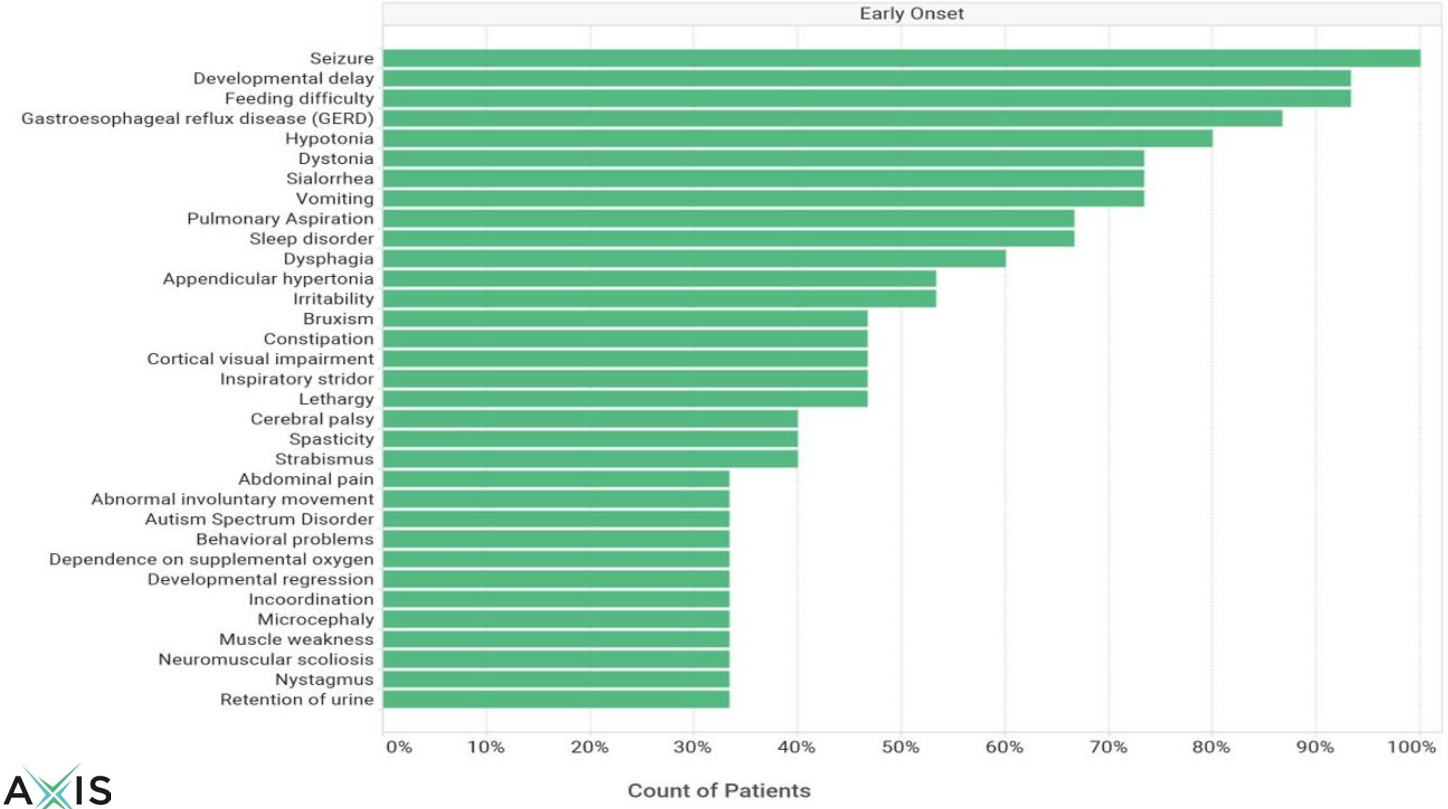
Praxis use of Ciitizen data: Seizure frequency as primary endpoint for SCN2A-DEE *throughout life*



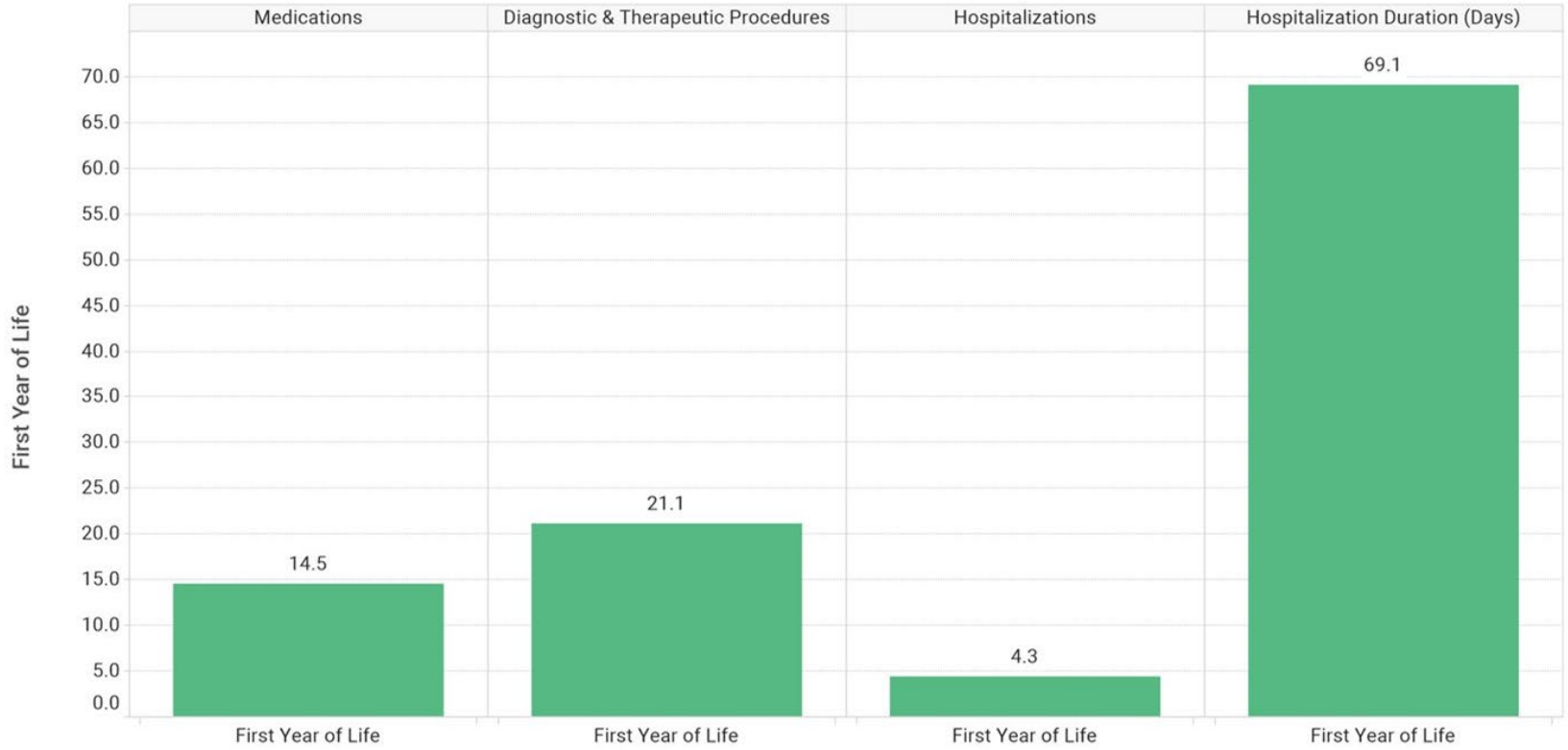
- Literature suggests early onset seizures remit
- Ciitizen data found seizure frequency persists through life
- Data helped confirm primary endpoint and age criteria

PRAXIS

Praxis use of Ciitizen data: Exploratory endpoints and clinical design



Praxis use of Ciitizen data: Burden of Disease



PRAXIS

Success Factors

- Ensure the data being generated in a registry OR traditional natural history study is **accessible and can be democratized** based on patient consent
- Data must be **available to the individual patient** so it can help in their course of care
- **Focus on quality** even if it is at smaller scale to identify the right signal for researchers
- Make data accessible to KOLs, academics and pharma to generate further interest

We are just getting started!

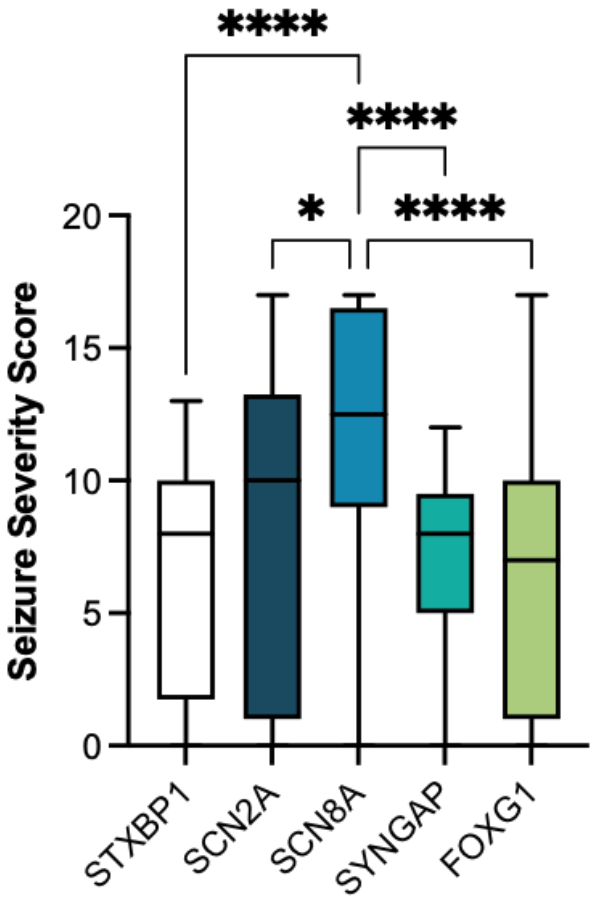
- We go **beyond the medical records** to all different modalities such as wearables
- Generate this level of data seamlessly *at all times* so we understand cross-indication implications, long-term outcomes and have a continuous feedback loop
- Leverage data as a placebo arm to ensure interventions are available to more patients and **accelerate path to treatment**
- …change the course of drug development for rare disease to shorten the cycle by at least half

Thank you

Develop novel seizure severity scores for endpoint measurement

We developed a seizure severity metric score that encompasses

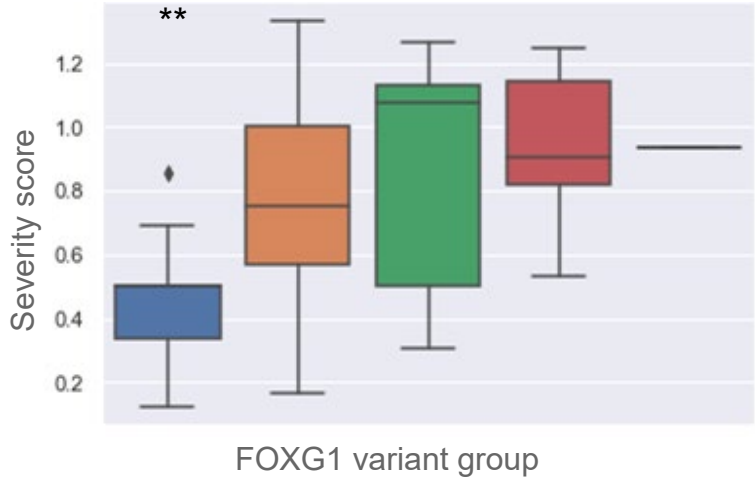
- Seizure frequency
- Concomitant anti-seizure medication use
- Number of hospital admissions for increased seizure frequency or status
- Presence of prolonged seizures

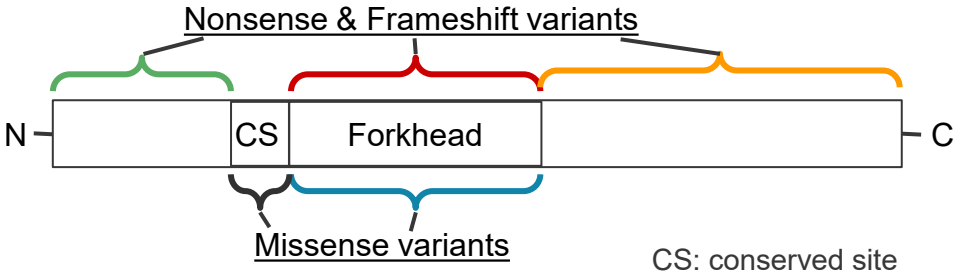


Conduct in-depth genotype/phenotype analysis

- Using Ciitizen data to analyze a monogenic neurodevelopmental cohort, we found that missense variants in the forkhead domain are associated with a less severe phenotype.
- Severity is defined along several phenotype axes including somatic growth, MRI, behavior, neurological features, and motor and speech development

Design mutation specific medicines and understand which patients will respond to treatment around more accurate endpoints





How real-world data can be used throughout drug development

Category	Example Impact
Clinical phenotype	Use seizure frequency as primary endpoint confirmed
Biophysical characterization	Rely on clinical phenotype independent of complex biophysical determination
Trial endpoints	Optimize and prioritize endpoints with full clinical picture
Recruitment	Develop optimal plan for patient recruitment
Modeling	Key parameters used to inform drug exposure modeling
Biomarker	Refine EEG biomarkers
Regulatory documents	Leverage findings in key regulatory interactions