Authors:

Table 1: EPGP Collaborative Authors and Contributions

Author	Institution	Study PI	Clinical Site PI	Clinical Site Co-PI	Referral Center PI	Administrative Core	Phenotyping Core	Informatics Core	Neurophysiology Core	Imaging Core	Pharmacogenomics Core	Genomics and Data Analysis Core	Data Review Core	Publications Committee	Writing of manuscript
Abou-Khalil, Bassel, MD	Vanderbilt University Medical Center		X										X		
Alldredge, Brian, PharmD	University of California, San Francisco										X				
Bautista, Jocelyn, MD	Cleveland Clinic		X												
Berkovic, Sam, MD	The University of Melbourne		X												
Bluvstein, Judith, MD	New York University School of Medicine			X									X		
Boro, Alex, MD	Albert Einstein College of Medicine								X						
Cascino, Gregory, MD	Mayo Clinic College of Medicine Rochester, Minnesota		X							X					
Consalvo, Damian, MD, PhD	Hospital General de Agudos José Maria Ramos Mejía		X												

Author	Institution	Study PI	Clinical Site PI	Clinical Site Co-PI	Referral Center PI	Administrative Core	Phenotyping Core	Informatics Core	Neurophysiology Core	Imaging Core	Pharmacogenomics Core	Genomics and Data Analysis Core	Data Review Core	Publications Committee	Writing of manuscript
Cristofaro, Sabrina, RN, BSN, Phenotyping Director	New York University					X									X
Crumrine, Patricia, MD	Children's Hospital of Pittsburgh of UPMC		X												
Devinsky, Orrin, MD	New York University School of Medicine		X			X	X						X	X	
Dlugos, Dennis, MD, MCSE	The Children's Hospital of Philadelphia		X				X		X					X	
Epstein, Michael, PhD	Emory University School of Medicine											X			
Fahlstrom, Robyn, MPH, Data Monitor	University of California, San Francisco					X								X	X
Fiol, Miguel, MD	University of Minnesota Medical Center				X										
Fountain, Nathan, MD	University of Virginia Health System		X												
Fox, Kristen, RN,MS, Recruitment Director	University of California, San Francisco					X									X

Author	Institution	Study PI	Clinical Site PI	Clinical Site Co-PI	Referral Center PI	Administrative Core	Phenotyping Core	Informatics Core	Neurophysiology Core	Imaging Core	Pharmacogenomics Core	Genomics and Data Analysis Core	Data Review Core	Publications Committee	Writing of manuscript
French, Jacqueline, MD	New York University School of Medicine										X				
Freyer Karn, Catharine, Project Director	University of California, San Francisco					X								X	X
Friedman, Daniel, MD	New York University School of Medicine			X											
Geller, Eric, MD	St. Barnabas Health Care System		X												
Glauser, Tracy, MD	Cincinnati Children's Hospital Medical Center		X								X				
Glynn, Simon, MD	University of Michigan		X												
Haas, Kevin, MD	Vanderbilt University Medical Center		X												
Haut, Sheryl, MD, MS	Albert Einstein College of Medicine		X												
Hayward, Jean, MD	Kaiser Permanente: Oakland Medical Center				X										

Author	Institution	Study PI	Clinical Site PI	Clinical Site Co-PI	Referral Center PI	Administrative Core	Phenotyping Core	Informatics Core	Neurophysiology Core	Imaging Core	Pharmacogenomics Core	Genomics and Data Analysis Core	Data Review Core	Publications Committee	Writing of manuscript
Helmers, Sandra, MD	Emory University School of Medicine		X												
Joshi, Sucheta, MD	University of Michigan								X						
Kanner, Andres, MD	Rush University Medical Center										X				
Kirsch, Heidi, MD, MS	University of California, San Francisco		X											X	
Knowlton, Robert, MD	University of Alabama at Birmingham School of Medicine		X							X					
Kossoff, Eric, MD	The Johns Hopkins University School of Medicine			X											
Kuperman, Rachel, MD	Children's Hospital & Research Center Oakland				X										
Kuzniecky, Ruben, MD	New York University School of Medicine	X				X	X			X			X	X	
Lowenstein, Daniel, MD	University of California, San Francisco	X				X	X						X	X	X

Author	Institution	Study PI	Clinical Site PI	Clinical Site Co-PI	Referral Center PI	Administrative Core	Phenotyping Core	Informatics Core	Neurophysiology Core	Imaging Core	Pharmacogenomics Core	Genomics and Data Analysis Core	Data Review Core	Publications Committee	Writing of manuscript
McGuire, Shannon, MD	Louisiana State University Health Sciences Center		X												
Motika, Paul, MD	Rush University Medical Center			X											
Nesbitt, Gerard, MBA, Director of Informatics	University of California, San Francisco							X						X	X
Novotny, Edward, MD	Seattle Children's Hospital		X												
Ottman, Ruth, PhD	Columbia University						X					X		X	X
Paolicchi, Juliann, MD	Vanderbilt University Medical Center		X										X	X	
Parent, Jack, MD	University of Michigan			X											
Park, Kristen, MD	Children's Hospital Colorado		X												
Poduri, Annapurna, MD	Children's Hospital Boston		X										X	X	
Risch, Neil, PhD	University of California, San Francisco											X			

Author	Institution	Study PI	Clinical Site PI	Clinical Site Co-PI	Referral Center PI	Administrative Core	Phenotyping Core	Informatics Core	Neurophysiology Core	Imaging Core	Pharmacogenomics Core	Genomics and Data Analysis Core	Data Review Core	Publications Committee	Writing of manuscript
Sadleir, Lynette, MBChB, FRACP, MD	Wellington School of Medicine and Health Sciences, University of Otago		X												
Scheffer, Ingrid, MBBS, PhD	The University of Melbourne		X												
Shellhaas, Renee, MD	University of Michigan								X						
Sherr, Elliott, MD, PhD	University of California, San Francisco						X					X			
Shih, Jerry J., MD	Mayo Clinic College of Medicine Jacksonville, Florida		X										X	X	
Shinnar, Shlomo, MD, PhD	Albert Einstein College of Medicine						X								
Singh, Rani, MD	University of Michigan			X											
Sirven, Joseph, MD	Mayo Clinic College of Medicine Scottsdale, Arizona		X												
Smith, Michael, MD	Rush University Medical Center		X												
Sullivan, Joe, MD	University of California, San Francisco								X						

Author	Institution	Study PI	Clinical Site PI	Clinical Site Co-PI	Referral Center PI	Administrative Core	Phenotyping Core	Informatics Core	Neurophysiology Core	Imaging Core	Pharmacogenomics Core	Genomics and Data Analysis Core	Data Review Core	Publications Committee	Writing of manuscript
Thio, Liu Lin, MD, PhD	Washington University in St. Louis		X											X	
Venkat, Anu, MD	The Children's Hospital of Philadelphia			X											
Vining, Eileen, MD	The Johns Hopkins University School of Medicine		X											X	
Von Allmen, Gretchen, MD	University of Texas Health Science Center at Houston		X												
Weisenberg, Judith, MD	Washington University in St. Louis		X											X	
Widdess-Walsh, Peter, MB, FRCPI	St. Barnabas Health Care System		X										X		
Winawer, Melodie, MD, MS	Columbia University												X	X	

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Administrative Core Members:

- Kathleen McGovern, Recruitment Assistant
- Nora Stillman, Recruitment Assistant

Informatics Core Members:

- Kevin McKenna, Database Manager
- Vickie Mays, Data Coordinator
- Michael Williams, Informatics
- Alan Carpenter, Programmer Analyst
- Kevin Miller, Programmer Analyst

Study Coordinators:

- Prashant Agarwal; Study Coordinator; The Children's Hospital of Philadelphia
- Jennifer Ayala; Study Coordinator; Albert Einstein College of Medicine
- Cate Bakey; Study Coordinator; The Children's Hospital of Philadelphia
- Thomas Borkowski, PhD; Study Coordinator; Albert Einstein College of Medicine
- Riann Boyd, CCRP; Study Coordinator; Mayo Clinic College of Medicine Jacksonville, Florida
- Alicia Camuto, CCRP; Study Coordinator; The Children's Hospital Denver
- Cendy Carrasco; Study Coordinator; University of California, San Francisco
- Jennifer Cassarly; Study Coordinator; Cincinnati Children's Hospital Medical Center
- Yong Collins, RN; Study Coordinator; The Children's Hospital of Philadelphia
- Kevin Collon; Study Coordinator; University of Michigan
- Sean Collon; Study Coordinator; University of Michigan
- Heather Eckman; Study Coordinator; New York University School of Medicine
- Susan Fogarty, RN; Study Coordinator; University of Texas Health Science Center at Houston
- Dolores González Morón, MD; Study Coordinator; Hospital General de Agudos José Maria Ramos Mejía
- La June Grayson; Study Coordinator; Washington University in St. Louis
- Samantha Hagopian, RN; Study Coordinator; The Children's Hospital of Philadelphia
- Emily Hayden; Study Coordinator; University of Michigan
- Kristin Heggeli; Study Coordinator; Mayo Clinic College of Medicine Jacksonville, Florida
- Rachel Hennessy; Study Coordinator; New York University School of Medicine
- Jody Hessling, RN; Study Coordinator; Cincinnati Children's Hospital Medical Center
- Emily Hirschfield; Study Coordinator; Cincinnati Children's Hospital Medical Center
- Jennifer Howell, BA, BS; Study Coordinator; University of Alabama at Birmingham School of Medicine
- Sherry Klingerman; Study Coordinator; Mayo Clinic College of Medicine Rochester, Minnesota
- Maritza Lopez, RN; Study Coordinator; University of California, San Francisco
- Heather Marinelli; Study Coordinator; The Johns Hopkins University School of Medicine
- Brandy Maschhaupt; Study Coordinator; Mayo Clinic College of Medicine Scottsdale, Arizona
- Jennie Minnick; Study Coordinator; The Children's Hospital of Philadelphia
- Jade Misajon, RN; Study Coordinator; St. Barnabas Health Care System
- Jennifer Monahan, RN; Study Coordinator; Children's Hospital of Pittsburgh of UPMC
- Karen Oliver; Study Coordinator; The University of Melbourne
- Isha Parulkar; Study Coordinator; Children's Hospital Boston
- Laura Przepiorka, RN; Study Coordinator; Rush University Medical Center
- Paula Pyzik, BA, CRT; Study Coordinator; The Johns Hopkins University School of Medicine

- Brigid Regan; Study Coordinator; The University of Melbourne
- Catherine Shain; Study Coordinator; Children's Hospital Boston
- Lexie Slingerland; Study Coordinator; The University of Melbourne
- Caitlin Stanton, MPH; Study Coordinator; Seattle Children's Hospital
- Kelly Taylor, MS, CGC; Study Coordinator; Vanderbilt University Medical Center
- Stacy Thompson, RN, BSN, CCRC; Study Coordinator; University of Virginia Health System
- Jennifer Turczyk; Study Coordinator; Cleveland Clinic
- Alexander Vara; Study Coordinator; University of Texas Health Science Center at Houston
- Cindy Wesolowski, RN, NP; Study Coordinator; Cincinnati Children's Hospital Medical Center
- Andrew Yourich; Study Coordinator; University of Alabama at Birmingham School of Medicine

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Table 2: EPGP Inclusion and Exclusion Criteria

All Participants with Epilepsy
• Current age 4 weeks and older. No restriction on upper age limit • Two or more UNPROVOKED seizures. (Febrile seizures, acute symptomatic seizures, seizures from alcohol, metabolic seizures, or toxic seizures are allowed, in addition to unprovoked seizures) • One unprovoked seizure with epileptiform EEG with clear diagnosis of epilepsy type: **send for adjudication** • No identified antecedent cause of epilepsy (i.e., a structural or metabolic insult to the CNS prior to the first unprovoked seizure, such as stroke, brain tumor, severe head trauma, etc., or a progressive neurodegenerative disorder) • Head circumference <2.5 standard deviations from normal at the time of enrollment • Age at first unprovoked seizure <45 y.o. If age of onset is ≥45 y.o.: **send for adjudication** • No recognized genetic syndrome, chromosomal abnormality or pathogenic mutation in a previously identified epilepsy gene. If positive genetic result: **send for adjudication** • High quality clinical and laboratory data (medical records, MRI file or EEG file or report, or reference in the medical record of EEG and/or MRI results for the past 2 years, or from seizure onset if <2 years). If medical records are not available, site PI is to obtain details from the participant regarding eligibility, and history is sent for adjudication
Idiopathic Generalized Epilepsy (IGE)
• Clinical seizures consistent with IGE • Subject has affected full sibling, a biological parent, or a biological child with non-symptomatic epilepsy willing to enroll in EPGP • Sibling is not an identical twin of participant (fraternal twin is allowed) • Brain MRI optional: results of MRI normal, if done • EEG or video EEG required: shows generalized epileptiform activity and a normal posterior dominant rhythm for age • If normal EEG, clear and compelling clinical history required: **send for adjudication** • No history of premature birth before 32 weeks gestation • No evidence of moderate to severe developmental delay prior to the onset of seizures and medication (severe delay is characterized by 50% or more delay in any area: motor, social, language, cognition, or activities of living; or global delay). Cases with Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, Learning Disorders, etc. are not excluded. • No history of Autism or clear signs of autistic function (decreased eye contact, social interactiveness, moderate to severe language delay in a child who subsequently develops autism). Asperger's syndrome okay for inclusion
Localization-related Epilepsy (LRE)
• Clinical seizures consistent with LRE • Subject has affected full sibling, a biological parent, or a biological child with non-symptomatic epilepsy willing to enroll in EPGP • Sibling is not an identical twin of participant (fraternal twin is allowed) • Brain MRI required: results of MRI were normal, show focal cortical dysplasia, or show mesial temporal sclerosis • Brain MRI optional: results of EEG consistent with Benign Rolandic Epilepsy • If normal MRI, EEG or video EEG required: shows inter-ictal focal abnormality OR clinical or electrographic seizures on ictal EEG • If normal MRI, normal inter-ictal EEG, and no or normal ictal EEG, clear and compelling clinical history, required: **send for adjudication** • No history of premature birth before 32 weeks gestation • No evidence of moderate to severe developmental delay prior to the onset of seizures and medication (severe delay is characterized by 50% or more delay in any area: motor, social, language, cognition, or activities of living; or global delay). Cases with Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, Learning Disorders, etc are NOT excluded. • There is no Autism or clear signs of autistic function (decreased eye contact, social interactiveness, moderate to severe language delay in a child who subsequently develops autism). Asperger's syndrome ok for inclusion.
Infantile Spasms (IS)/Lennox-Gastaut Syndrome (LGS) – Cryptogenic
• Clinical seizures and EEG consistent with IS or LGS • No history of congenital TORCH infection, premature birth before 32 weeks gestation, neonatal hypoxic

ischemic encephalopathy with or without neonatal seizures, meningitis/encephalitis, stroke, intra-cranial hemorrhage, or significant head trauma
- No evidence of severe (50% or more delay in any area: motor, social, language, cognition, or activities of living; or global delay) developmental impairment prior to the onset of spasms
- Both biological parents available and willing to enroll in EPGP
- EEG required: results consistent with IS (hypsarrhythmia or hypsarrhythmia variant OR electrodecremental discharge) or LGS (slow or disorganized background, and slow spike and wave activity less than 2.7Hz or generalized paroxysmal fast activity-GPFA)
- Brain MRI required: normal, mild atrophy, or steroid-induced atrophy
- If present, Autism/signs of autism developed *after* the onset of seizures

Infantile Spasms (IS) / Lennox-Gastaut Syndrome (LGS) – Focal Cortical Dysplasia (FCD)

- Clinical seizures consistent with IS or LGS
- Both biological parents available and willing to enroll in EPGP
- EEG required: results are consistent with IS (hypsarrhythmia or hypsarrhythmia variant OR electrodecremental discharge) or LGS (slow or disorganized background, and slow spike and wave activity less than 2.7Hz or generalized paroxysmal fast activity-GPFA)
- Brain MRI required: shows focal cortical dysplasia
- If present, Autism/signs of autism developed *after* the onset of seizures

Polymicrogyria (PMG) / Bilateral Periventricular Nodular Heterotopia (PVNH)

- Clinical seizures consistent with GE, LRE, IS, LGS (mixed permitted)
- Both biological parents available and willing to enroll in EPGP
- No family history of X-linked PVNH, if known
- Filamin A sequence analysis for PVNH is negative
- Normal karyotype: no confirmed genetic syndrome or metabolic disease (Chromosome work up strongly suggested)
  a) If chromosomal analysis has been done and results show normal chromosomes, person can be enrolled
  b) If chromosomal analysis has been done and results show an abnormality, enrollment depends on the abnormality: **send for adjudication**
  c) If not yet done, chromosomal analysis is encouraged but not required prior to enrollment
- EEG not required for inclusion
- Brain MRI required: shows PMG (of any type) or bilateral PVNH (but NOT neural tube defects or schizencephaly or band heterotopia)
- Autism/signs of autism developed after the onset of seizures

Parent Controls

- No history of epilepsy (toxic/metabolic seizures and/or febrile seizures okay to include)

Figure 1: EPGP enrollment, phenotyping and data review process. EEG: electroencephalogram; MRI: magnetic resonance imaging; AED: antiepileptic drug

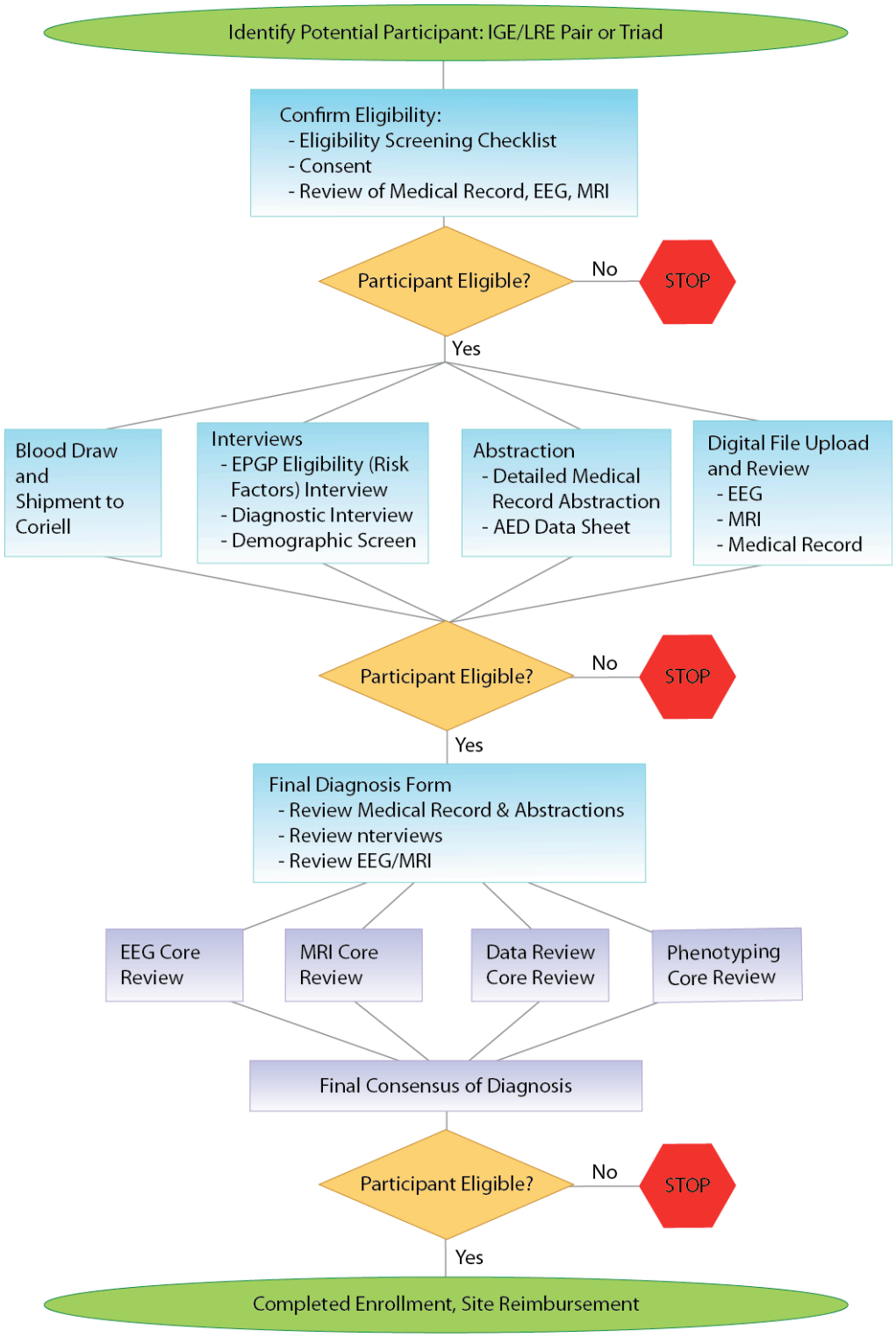


Table 3. Activities Included in Data Collection Protocol, by Participant Type

Activity Name	IGE Participant	LRE Participant	IS/LGS Proband	PMG/PVNH Proband	Parent Controls
Eligibility Checklist	Yes	Yes	Yes	Yes	Yes
Consent	Yes	Yes	Yes	Yes	Yes
Screening Interview	Yes	Yes	Yes	Yes	Yes
Specimen collection	Yes	Yes	Yes	Yes	Yes
Subject Demographics	Yes	Yes	Yes	Yes	Yes
Diagnostic Interview	Yes	Yes			
Medical Record Abstraction	Yes	Yes	Yes	Yes	
Pharmacogenomics Form	Yes	Yes			
AED Web Form	Yes	Yes			
EEG Review	Yes	Yes	Yes		
MRI Review	MRI optional	Yes	Yes	Yes	
Final diagnosis form	Yes	Yes	Yes	Yes	

Abbreviations: IGE – idiopathic generalized epilepsy; LRE – localization-related epilepsy; IS – infantile spasms; LGS – Lennox-Gastaut syndrome; PMG – polymicrogyria; PVNH – periventricular nodular heterotopia; AED – antiepileptic drug; EEG – electroencephalography; MRI – magnetic resonance imaging

Figure 2: The EPGP organizational structure. OSMB: Observational Study Monitoring Board

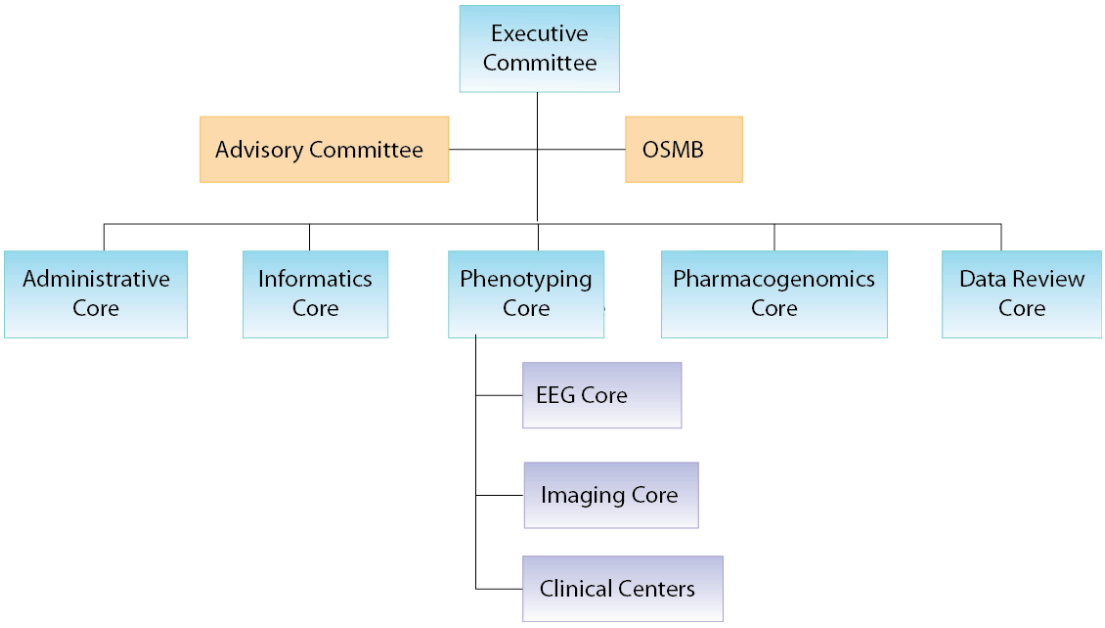
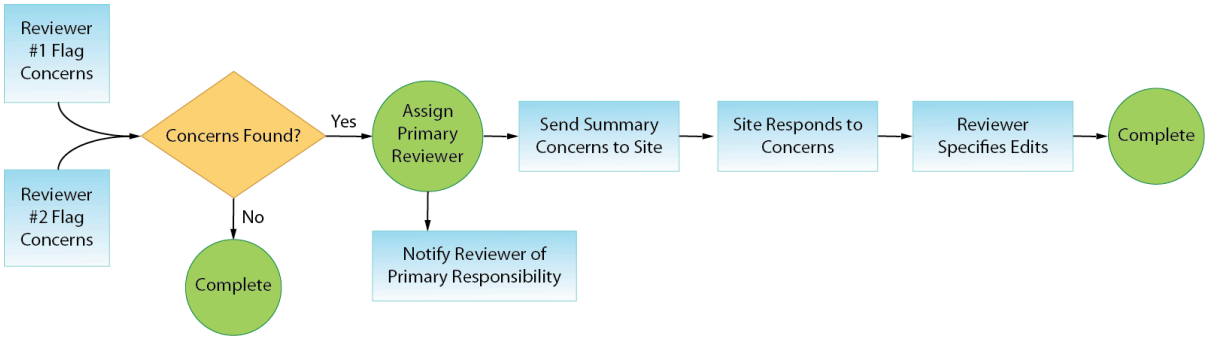


Figure 3: Workflow for the review of participant data by the EPGP Data Review Core



SUPPLEMENTARY (ON-LINE) MATERIAL

Figure 1: Example of the planning timeline used by the EPGP Administrative Core

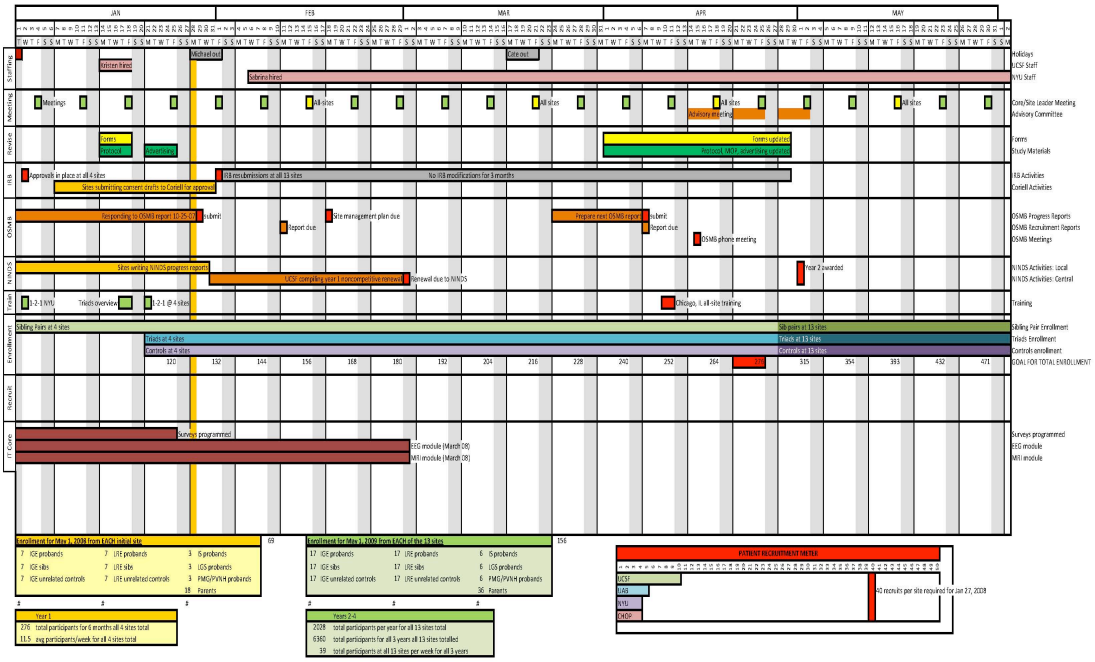


Figure 2: Example of the monthly EPGP newsletter (first two of three pages)

EPGP Newsletter: December 2011

UPCOMING DATES

Numbers are the same for all calls.
USA 877-594-8353
code 36746656#
Argentina 800-266-4969
Australia 1800-045-963
New Zealand 508-696-194

All meetings are Fridays from 2-3 PM eastern / 11-12 pacific

December meetings:
12/16: Publications
3rd Friday of month

Scientific Cores, and Data Review Core will check in via email. Happy holidays!

January meetings:
1/13: All-site
2nd Friday of month

1/20: Publications
3rd Friday of month

1/27: Scientific Cores, and Data Review Core

Overview

1. Ship blood by Thursday 12/22 and Thursday 12/29!
2. Meeting at AES
    1. Thank you!
    2. Unit completion doubled in the last 9 months!
    3. Phenotyping progress and work to be done
    4. Single-blood family option to help unit close-out
    5. Adjudications to keep participants in and skip activities
    6. Renew our recruitment efforts: we are trying to reach 4,000 by 4/30!
    7. Publications and data review
    8. Epi4K update
3. "Site future" poll
4. Recruitment and Phenotyping Tables

Blood Shipments over the Holidays

Christmas: blood shipments must be at FedEx by the afternoon of Thursday 12/22 with next business morning shipping and received at Coriell on Friday 12/23 in order to ensure that they'll be processed—Coriell is closed on Monday 12/26.

New Year: blood shipments must be at FedEx by the afternoon of Thursday 12/29 with next business morning shipping and received at Coriell on Friday 12/30 in order to ensure that they'll be processed—Coriell is closed on Monday 1/2.

Meeting at AES

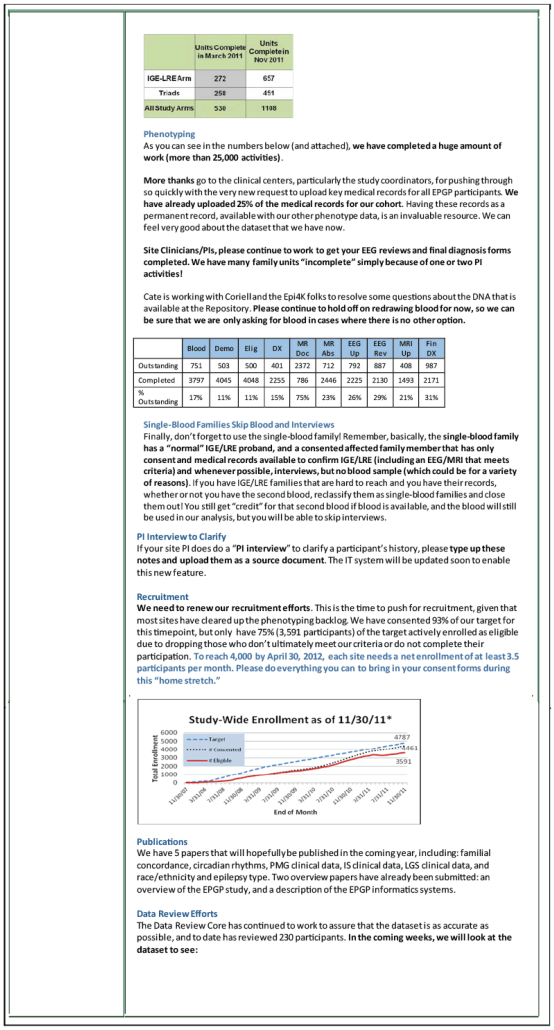
Representatives of most sites gathered on Sunday December 4, 2011 to review EPGP's current progress and challenges, and to come up with plans for the year 5-6 transition. A summary of the meeting is included in the newsletter, below, and the slides shown are attached.

We are filled with gratitude to the group for the dedication that is bringing EPGP to fruition. Although it's been said a hundred times, we are so **grateful for the work that everyone does every day**. Thank you!

As you may remember, our group has worked through and solved many challenges. We have fine tuned instruments and workflow, increased the size of the network, improved informatics systems, implemented central screening of referrals, established a data review core, and a number of other changes; through it all, what is most remarkable is this network's dedication and support of one another.

Thank you for being part of this historic effort.

Remarkably, we have gone from 40% unit completion in March 2011 to 80% unit completion today. This is an amazing accomplishment by our clinical center teams. Way to go!



	Units Complete in March 2011	Units Complete in Nov 2011
IGE-LRE Arm	272	657
Trads	258	451
All Study Arms	530	1198

Phenotyping

As you can see in the numbers below (and attached), **we have completed a huge amount of work (more than 25,000 activities)**.

More thanks go to the clinical centers, particularly the study coordinators, for pushing through so quickly with the very new request to upload key medical records for all EPGP participants. **We have already uploaded 25% of the medical records for our cohort**. Having these records as a permanent record, available with our other phenotype data, is an invaluable resource. We can feel very good about the dataset that we have now.

Site Clinicians/PIs, please continue to work to get your EEG reviews and final diagnosis forms completed. We have many family units "incomplete" simply because of one or two PI activities!

Cate is working with Coriell and the Epi4K folks to resolve some questions about the DNA that is available at the Repository. **Please continue to hold off on redrawing blood for now, so we can be sure that we are only asking for blood in cases where there is no other option.**

	Blood	Demo	Elig	DX	MR Doc	MR Abs	EEG Up	EEG Rev	MRI Up	Fin DX
Outstanding	751	503	500	401	2372	712	792	887	408	987
Completed	3797	4045	4048	2255	786	2446	2225	2130	1493	2171
% Outstanding	17%	11%	11%	15%	75%	23%	26%	29%	21%	31%

Single-Blood Families Skip Blood and Interviews

Finally, don't forget to use the single-blood family! Remember, basically, the **single-blood family has a "normal" IGE/LRE proband, and a consented affected family member that has only consent and medical records available to confirm IGE/LRE (including an EEG/MRI that meets criteria) and whenever possible, interviews, but no blood sample (which could be for a variety of reasons)**. If you have IGE/LRE families that are hard to reach and you have their records, whether or not you have the second blood, reclassify them as single-blood families and close them out! You still get "credit" for that second blood if blood is available, and the blood will still be used in our analysis, but you will be able to skip interviews.

PI Interview to Clarify

If your site PI does do a **"PI interview"** to clarify a participant's history, please **type up these notes and upload them as a source document**. The IT system will be updated soon to enable this new feature.

Recruitment

We need to renew our recruitment efforts. This is the time to push for recruitment, given that most sites have cleared up the phenotyping backlog. We have consented 93% of our target for this timepoint, but only have 75% (3,591 participants) of the target actively enrolled as eligible due to dropping those who don't ultimately meet our criteria or do not complete their participation. To reach 4,000 by April 30, 2012, each site needs a net enrollment of at least 3.5 participants per month. Please do everything you can to bring in your consent forms during this "home stretch."

Publications

We have 5 papers that will hopefully be published in the coming year, including: familial concordance, circadian rhythms, PMG clinical data, IS clinical data, LGS clinical data, and race/ethnicity and epilepsy type. Two overview papers have already been submitted: an overview of the EPGP study, and a description of the EPGP informatics systems.

Data Review Efforts

The Data Review Core has continued to work to assure that the dataset is as accurate as possible, and to date has reviewed 230 participants. **In the coming weeks, we will look at the dataset to see:**