Rare Epilepsy Network (REN) Strategic Planning Workshop
Thursday, December 1, 2016
Hilton Americas-Houston

Meeting Summary

The goal of this workshop was to develop a REN research strategic plan, and implementation strategies for the next 1 and 5 years.

REN Co-Investigator Dale Hesdorffer welcomed participants to the meeting and asked for around-the-room introduction of attendees (participant list attached), who included representatives of rare epilepsy organizations, the REN professional advisory board, and researchers. REN Steering Committee member Ilene Penn Miller (Hope for HH) shared a perspective on why we are working together, and Dale shared the revised mission and values statement for REN:

Mission
The Rare Epilepsy Network is a consortium of partners committed to conducting research to improve outcomes of rare conditions associated with epilepsy and seizures.

Values Statement
We are committed to addressing the urgent health challenges of our rare epilepsy community by engaging patients and caregivers, making data available to researchers, and investigating causes and consequences in order to improve diagnosis, treatment, and find cures.

Dale Hesdorffer, PhD (Columbia University) provided a REN research update, describing some of the analyses that are underway using the REN dataset.

1) Comorbidities across 10 rare epilepsies.
Ten rare epilepsies were included in this analysis: Aicardi, CDKL5, Dravet, Dup15q, Hypothalamic hamartoma, Infantile spasms, Lennox-Gastaut, Phelan McDermid, and Tuberous Sclerosis. The comorbidity classes were: sleep, mental health, learning disability, vision, nervous system, brain abnormality, skin, pulmonary, mitochondrial, immune system, hearing, endocrine, digestion, dental, cardiac and bone.

a. We used a heat map, which graphically displayed the prevalence of each comorbidity class for each of the 10 rare epilepsy syndromes. This allowed us to see whether the prevalence of each comorbidity showed commonalities or differences across the 10 rare epilepsies.

There was a low prevalence of some comorbidities, ranging from 0% to 20%. These were: skin disorders (except for Tuberous Sclerosis, which had a prevalence of 100%); pulmonary disorders, mitochondrial disorders, and immune...
system disorders. Thus, excepting skin disorders in TS, the low prevalence of these comorbid conditions is similar across the 10 rare epilepsies.

There was a medium prevalence of some comorbidities, ranging from 20%-70%. These included: hearing, endocrine, digestion, dental, cardiac and bone conditions. There was some variability for each of these comorbidities across rare epilepsies. For example, dental conditions were most prevalent in CDKL5, Aicardi, Dravet, LGS, hypothalamic hamartoma, Phelan McDermid and Tuberous Sclerosis, whereas dental conditions were less prevalent in Dup15Q, PCDH19, and Infantile Spasms.

There was a variable prevalence of some comorbidities, across rare epilepsies, ranging from 20%-100%, although sleep, mental health disorders and learning disability had the highest prevalence.

1. Learning disability was highly prevalent in Aicardi, CDKL5, Dravet, Dup15Q, LGS, and Phelan McDermid. There was a medium prevalence for learning disability, ranging from 20%-50%, in hypothalamic hamartoma, PCDH19, Infantile spasms, and Tuberous Sclerosis.
2. Problems with sleep ranged from 50%-100%. A high prevalence was noted in Phelan McDermid, Dup15q, and a medium prevalence was noted in the remaining 8 syndromes.
3. The prevalence of mental health disorders ranged from 40%-100%. Dup16q and Phelan McDermid had the highest prevalence, 70% and 90% respectively. Those moderately affected were Tuberous Sclerosis, LGS, Pdch19, LGS, hypothalamic hamartoma, Dravet, CDKL5 and Aicardi.

**Next steps:** We will re-assess the factor analysis in response to the meeting discussions.

b. Antiepileptic drug (AED) prescriptions- lack of efficacy, lack of tolerability or both across eleven rare epilepsies.
   i. Ever use of levetiracetam was 100% across the 11 rare epilepsies. Ever use of carbamazepine, clonazepam, lamotrigine, oxcarbazepine, topiramate and valproate ranged from 20% to 100%.
   ii. Twenty-five out of 30 AEDs (83.3%) were dropped due to lack of efficacy, suggesting commonalities across the 11 rare epilepsies. The drugs most likely to be dropped included: ezogabine, felbamate, gabapentin, oxcarbazepine,
perampanel, phenobarbital, phenytoin, pregabalin, rufinamide, tiagabine, topiramate, valproate, and vigabatrin.

iii. Among the 11 rare epilepsies, 13 out of 30 AEDs (43%) were dropped to side effects. These were carbamazepine, clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, lorazepam, phenobarbital, prednisone, pregabalin, primidone, topiramate, and valproate. The three AEDs most likely to have side effects across the 11 rare epilepsies were from most to least likely: primadone, phenobarbital, and pregabalin.

**Next steps:** During the discussion, it was clear that we need to validate the use of the antiepileptic drugs. We are starting our first validation between TS in REN and in the Tuberous Sclerosis Alliance.

c. **Univariate polytomous logistic regression risk factors for pneumonia in the Rare Epilepsy Network.**

i. Statistically significant risk factors for aspiration or recurrent pneumonia and for both pneumonias were: topiramate, zonisimide, any immune disorder, hyperventilation, neuromuscular scoliosis, use of a breathing device during sleep, gross motor delay, ever used a G-tube and dysphagia. Hyperventilation had the greatest magnitude of risk--29-fold for aspiration or recurrent pneumonia and 47-fold for both pneumonias.

Next steps: We are finalizing the analysis and anticipate submitting a manuscript.

**Deborah Hirtz, MD (Pediatric Epilepsy Research Foundation)** moderated the open discussion on the short (1-2 year) and long-term (3-5 year) priorities of the group for REN’s work over the next several years. The discussion was introduced using the following questions:

*What are the research questions most urgently needed, including caregiver issues as well as other research questions?*

*What other research questions need to be answered to improve the health of the affected child?*

*Where are the gaps, and what data is needed to fill them?*

*Where are the areas of common interest?*
SHORT TERM PRIORITIES

- Validation of REN data
  - Individual record validation using medical record information (the TSC natural history database may be a good opportunity, others may exist (PMD, SCN8A?) Seizure Tracker data on med use, side effects, etc.)
  - Population level validation cross-syndrome consistency validation (Neuro involvement example; how representative of the syndrome is the REN population?)

- Analysis of caregiver priorities and perspective

- Improve the REN survey
  - Improve the user-friendliness of the survey language, and offer an “other” box
  - Reformat the survey into tiers of information (basic/entry level and advanced)
  - Return data to families in short form as incentive to participate (dashboard?)

- Incorporate seizure diary and wearables data into the REN database

- Increase participation in REN
  - Overall recruitment
  - Retention
  - Completion of modules

- Develop computable phenotypes to find additional people

- Conduct exploratory analyses as a starting point for more detailed studies

- Improve REN Resources
  - Make a template letter available to help families get insurance coverage of genetic testing (CURE has example, Ann Poduri may also)
  - Contact lists for families to engage in research studies (basic and clinical; global registry?)
  - Create a match-making process for physician referral

LONG TERM PRIORITIES

- Continue to build REN infrastructure as a clinical trials and studies network for pragmatic clinical trials and to feed into IND/IDE studies.

- Review and expand on list of explicit research questions for groups of syndromes (need to increase numbers first?); continue to refine the questions over time. Examples are:
  - Which therapy works best?
  - Which side effects are most common?
  - Get families connected to organizations and researchers (e.g., global genetic registry?)
  - Are there logical collections of syndromes that make sense for drug development?

- Create a priority list of treatment recommendations based on genetic signatures

- Compare environmental and other contributors to disease

- Apply for funding and/or collaborate to collect bio specimens and tissues.

GAPS/OPPORTUNITIES

- Increase REN’s reach to a broader parent population, reduce the barriers to participating and the burden of participating

- Maintain a process to hear family stories

- QOL issues – resources for families (support, educational, services)

- Differentiate how/whether family issues for rare epilepsies are unique from others with ID, epilepsy, autism
- Working closely with PERC (pediatric epilepsy research consortium)
- Are epilepsy-specific instruments validated across syndromes?
- Focus on parent priorities in REN (other registries have other focus – REN is unique)
- Establish a regular process for evaluating treatment recommendations for rare epilepsies
- Genetic testing for LGS population, especially adults
- Collaboration with companies to find geographic areas where prescribing trends fit the profile of patient populations like Dravet (they have prescriptions data)
- Partner with the genetic testing companies to include REN in their reports, if suspected epilepsy is the reason for test.
- Add REN to epilepsy.com pages that contain info on rare epilepsies
- Help find people who aren’t strong web users
- Utilize N=1 trials; use REN to help centralize randomization and pharmacy services
- Partner with companies to share info about REN via their sales teams?

**ACTION ITEM:** Please send corrections or refinements to the short and long-term priority items listed above to bfureman@efa.org. Please also mention if you are willing to serve on a working group for one or more items in particular.

**Zachary Grinspan, MD (Weill Cornell University)** gave a talk about “Your Role as REN Ambassador” which focused on;

1) How do we recruit patients and increase enrollment into the REN?
   a. Dr Grinspan described a project among New York City institutions to catalog synonyms of rare epilepsies in order to create a digital signature, or computable phenotype, for each of the rare epilepsies that can be used to search medical records to find new patients who match the signature and who could be evaluated for a rare epilepsy diagnosis. This project is underway through a CDC-funded grant to Dr. Grinspan and co-Investigator Dale Hesdorffer. The phenotypes are expected to be available by 2018. Disseminating those phenotypes to other health systems (through PCORI – PedsNET, and others, along with others outside of PCORI) and incorporating them into diagnostic coding systems and vocabularies (ICD 10/11, SNOWMED, OMIM, Orphanet, etc) should help a great deal.
   b. Lowering the barriers to participating in REN, both for families and for physicians, would help recruitment significantly. Things like shorter versions of the survey using simpler language, along with offering the survey in multiple forms (paper, by phone, and online) may help more families participate. For physicians, offering help with the IRB process, incentives or prizes for participation, or support for a research coordinator to help with enrollment may be useful.
   c. Increasing awareness of REN through seminars, publications, and outreach to pediatric neurologists (especially the Pediatric Epilepsy Research Consortium, PERC) and other physicians will help with awareness and recruiting.
   d. Work with clinical laboratories and genetic testing organizations (such as CURE’s EGI) to raise awareness about REN enrollment opportunity.
   e. Consider working with pharmaceutical companies to use their sales representatives to help promote REN.

2) How do we increase enrollment for greater demographic diversity in the REN?
   a. Making tools available in other languages, including Spanish, French, Chinese, Vietnamese, Tagalog, and Korean may help promote diversity of recruitment.
b. Increasing awareness of REN to physicians who treat underrepresented communities may help. This should include direct outreach and tools (in languages appropriate for the populations) to those physicians.

3) How do we increase requests from researchers who want to submit questions, obtain data, propose trials, etc.?
   a. Free the data! REN could create and disseminate an anonymized dataset, and/or make subset of data available online
   b. Target medical students / residents / fellows: REN could encourage/support mentorship from senior researchers, offer small grants for travel to AES or CNS, sponsor a “Best rare epilepsy abstract at AES / CNS / AAN”, or offer small grants to analyze REN data
   c. Link to Clinical Data – this may require a broader consent from patients
   d. Improve REN Website – by adding a “researchers” tab, a form for data request, a list of data elements, and high level summaries.

Gail Farfel, PhD (Zogenix) provided insight on “The Relevance of REN to Drug Companies” in a talk focusing on:

1) Do drug companies value the REN registry? If so, why and how would they use REN?
   a. Dr. Farfel emphasized that companies value REN because it helps them find participants who are qualified (meet the criteria) and willing to enroll in clinical trials. REN can be helpful in finding patients who don’t have a strong web capability, and can help companies identify endpoints or drug effects that are meaningful to patients and families.

2) What does a drug company consider when working with patient advocacy groups to evaluate the potential for outreach and RCTs?
   a. Companies consider the size of the market and return on investment for shareholders, also the feasibility of carrying out the trials required for approval of an indication. One opportunity for REN is initiation of studies (crowd-sourced, virtual) that provide essential data on quality of life and cost that drive big players to invest in epilepsy research.

Wrap-up
Concluding thoughts were that REN needs to identify new resources or initiatives to be able to address our research priorities. Opportunities may exist through partnerships with other PCORI-funded networks, like PEDSnet or other CDRNs, or with existing epilepsy consortia (PERC, Epilepsy Study Consortium, NINDS Centers Without Walls, etc). REN needs to develop and nurture a sustainable business model to continue over the long-term.

Action item: Develop REN’s business plan for Steering Committee discussion.