National Institute of Neurological Disorders and Stroke

# Age as a Biological Variable - Trials with Children, Older Adults, Both?

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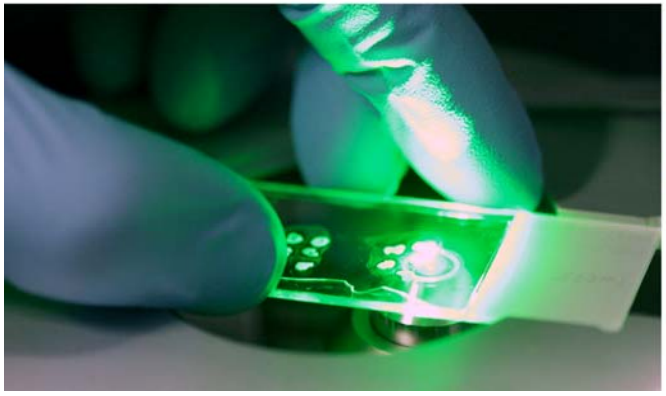
July 24, 2019

Clinical Trials Methodology Course



# Trevor’s lunch yesterday

# Objectives

1. List differences (relevant to clinical trials) between people at the extremes of age and those in the “middle”
2. Identify opportunities to be meaningfully inclusive in clinical trials

# Challenges and Opportunities

# Why Bother with the Spectrum of Age?

- Diseases occur in people of all ages
- Pharmacokinetics are different at the extremes of age
- Medication interactions are more common in older adults
- Children and older adults are understudied in clinical trials
  - Example: cancer diagnoses and deaths occur very frequently in people >65 yrs of age but they are under-represented in clinical trials
  - Example: virtually no seizure medicines have an FDA indication in neonates

# Changes Over Time: Renal Function

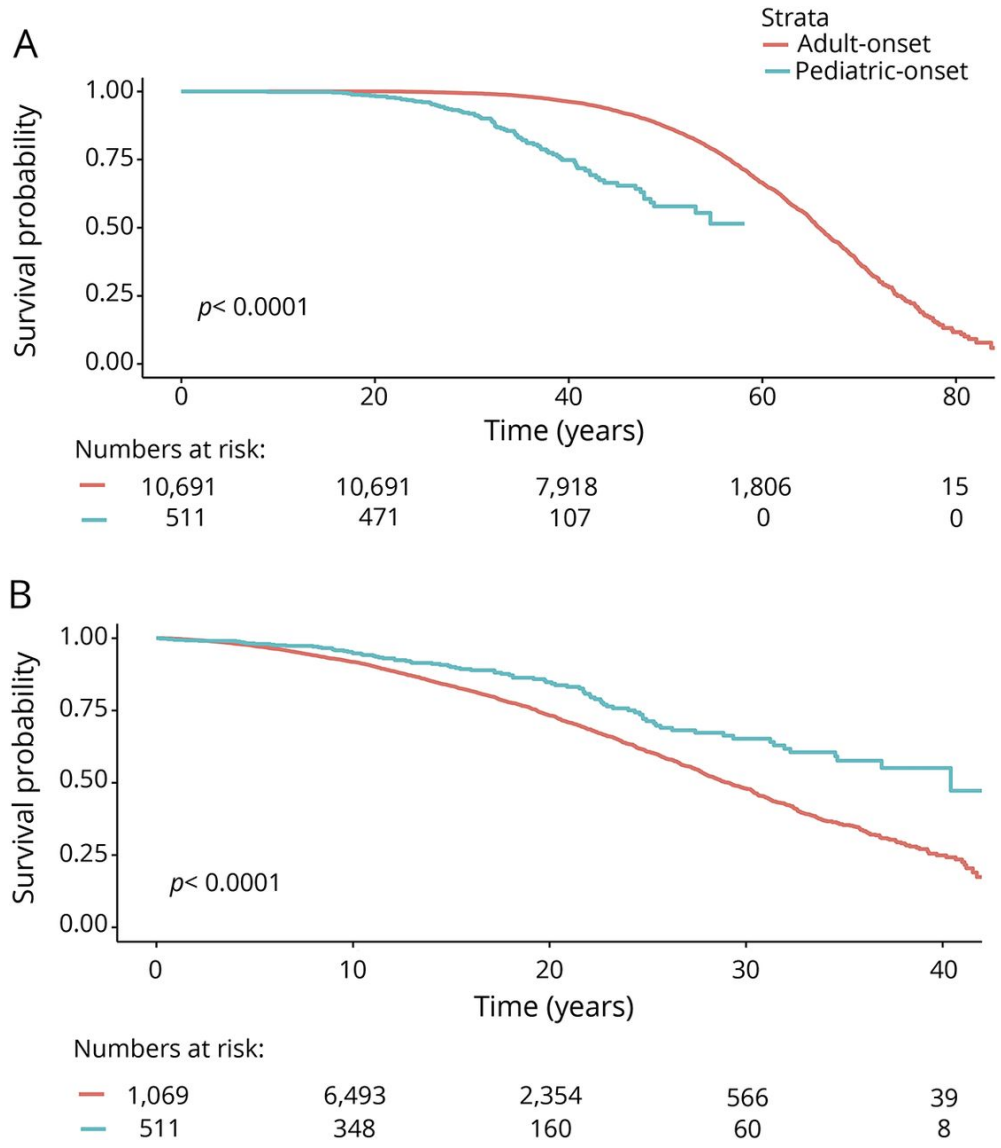
**TABLE 3.** Normal GFR in Children and Adolescents

| Age (Sex) | Mean GFR ± SD (mL/min/1.73 m²) |
|---|---|
| 1 wk (males and females) | 41 ± 15 |
| 2–8 wk (males and females) | 66 ± 25 |
| >8 wk (males and females) | 96 ± 22 |
| 2–12 y (males and females) | 133 ± 27 |
| 13–21 y (males) | 140 ± 30 |
| 13–21 y (females) | 126 ± 22 |

SD indicates standard deviation.

Hogg et al., Pediatrics 2003;111:1416

## Figure 4. Kaplan-Meier survival curve of time from birth and multiple sclerosis (MS) onset to Expanded Disability Status Scale (EDSS) 6 in pediatric-onset multiple sclerosis (POMS) vs adult-onset multiple sclerosis (AOMS)




POMS took longer to reach all 3 disability milestones from MS onset, but did so at a younger age than AOMS.



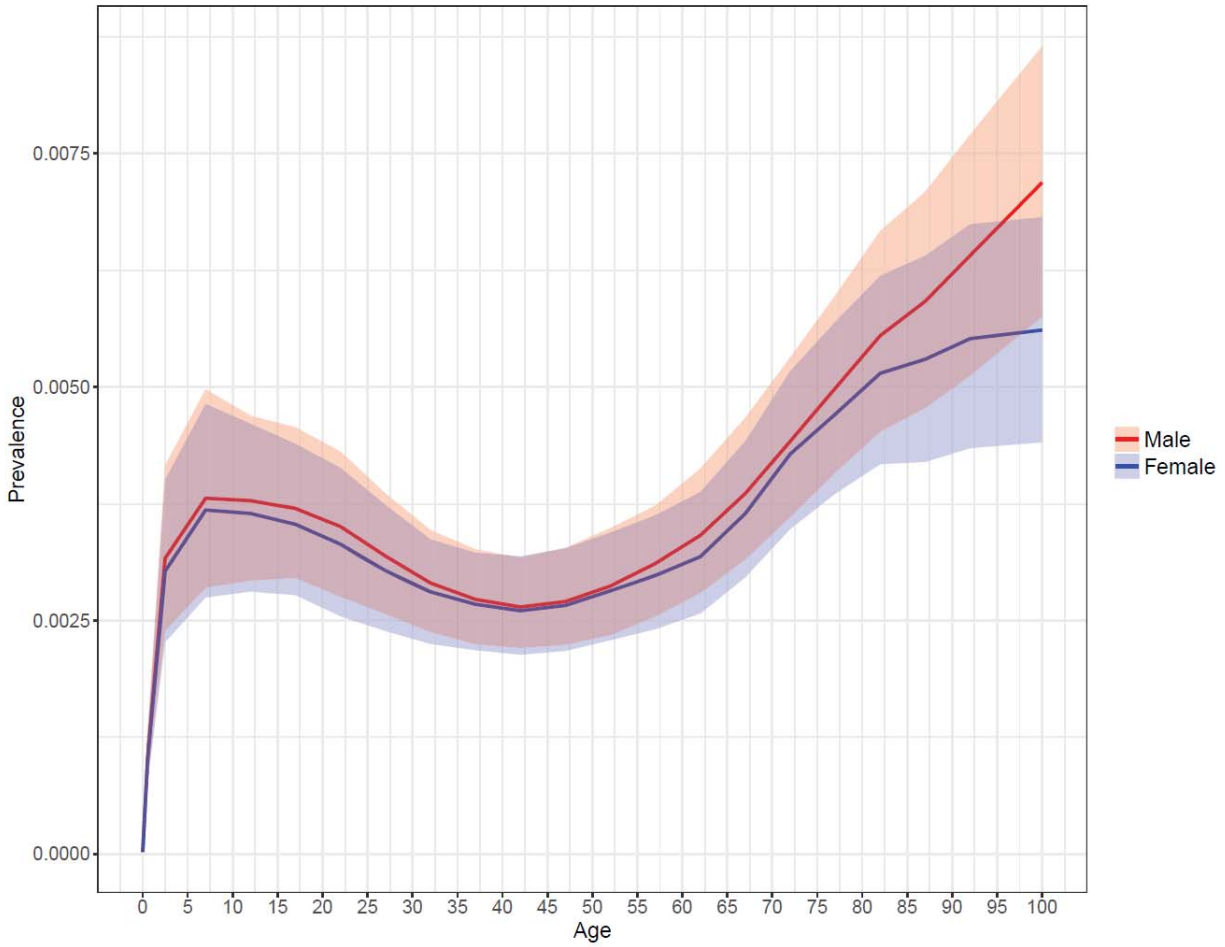
Kyla A. McKay et al. Neurology 2019;92:e2764-e2773

# Challenges at the Extremes of Age

- Limited number of patients
- Limited blood volume
- Perceived study risks – blood draws
- Variability in site enrollment and contracting
- Competing research priorities
- Low consent rates
- Lack of validated endpoints
- Limited research funding
- Lack of trained pediatric clinical investigators
- Lack of pediatric clinical pharmacology expertise

# Why bother with the spectrum of ages?

**Fig. 1.1** Global prevalence of idiopathic epilepsy by age and sex, 2016




Epilepsy: a public health imperative. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

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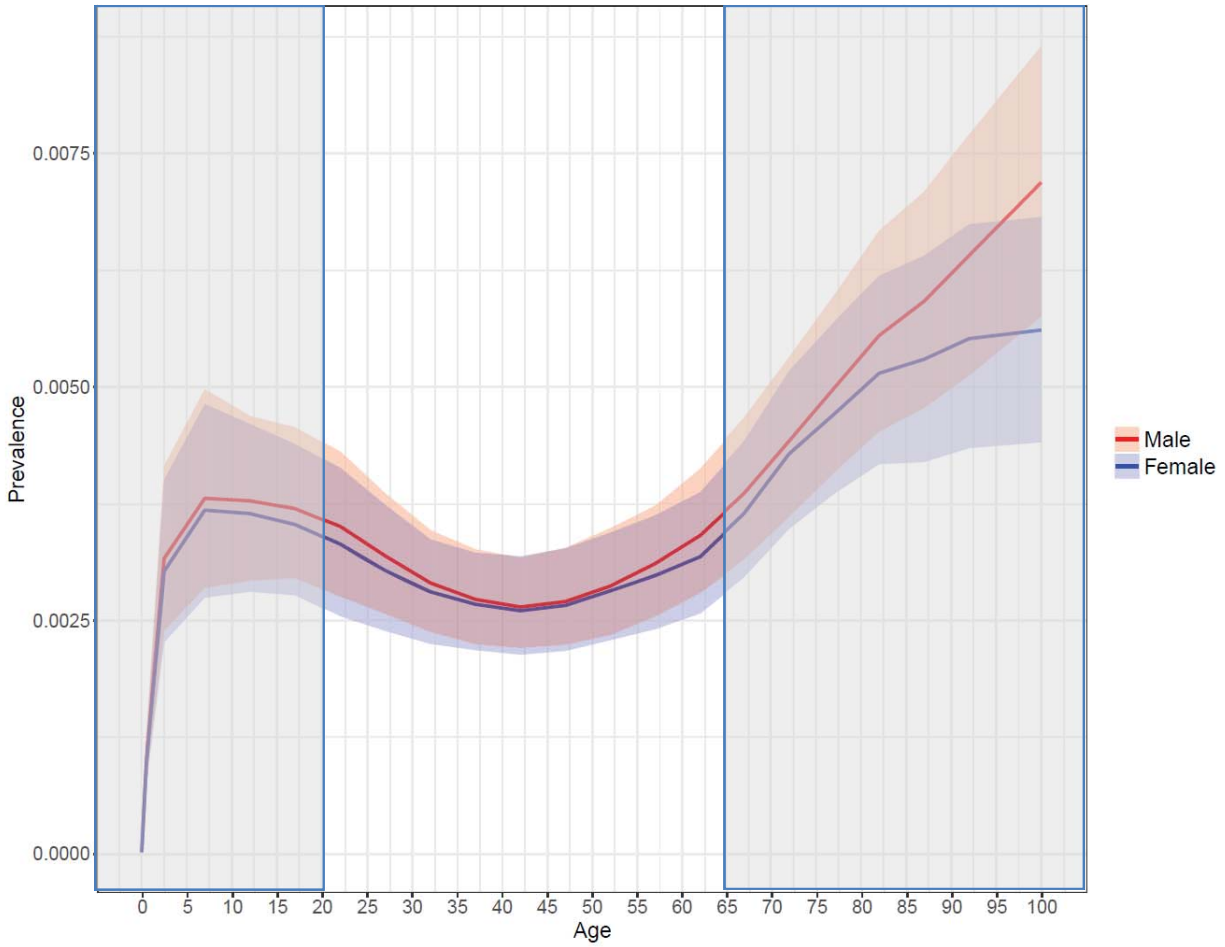
**Fig. 1.1** Global prevalence of idiopathic epilepsy by age and sex, 2016

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Epilepsy: a public health imperative. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

# Publication Problems

- ClinicalTrials.gov (2015): only **6%** of ~19000 trials in birth to 17 years
  - BUT this age group is **~25%** of the US population
- 85% of 66,896 PICU patients (39 hospitals) received medication off-label
- Of 559 randomized clinical trials, 19% discontinued early (8,369 children)
  - Difficulty with patient accrual most common
  - Less likely to be discontinued if funded by industry, compared with academic institutions
- 455 completed trials: 136 (30%) not published (69,165 children)
  - Industry-funded trials >2x as likely to not be published, had longer mean time to publication compared with academia trials

Bourgeois and Hwang, JAMA 2017;317:259
Czaja et al., J Pediatr Pharmacol Ther 2015;20:186
Pica & Bourgeois, Pediatr 2016;138:e20160223

# Table 3. Compounds or interventions investigated in registered pediatric phase 3 epilepsy clinical trials.

| Compound/Intervention | Published trials (N) | Unpublished trials (N) |
|---|---|---|
| Brivaracetam | 3 | 5* |
| Carbamazepine | 2 | 0 |
| Carisbamate | 3 | 3 |
| Clobazam | 2 | 0 |
| Diagnostic procedure (MEG vs. PET vs. MRI) | 0 | 1 |
| Diazepam | 2 | 0 |
| Eslicarbazepine | 0 | 2 |
| Fosphenytoin | 0 | 1 |
| Gabapentin | 2 | 0 |
| Lacosamide | 9 | 3** |
| Lamotrigine | 9 | 0 |
| Levetiracetam | 17 | 6* |
| Lorazepam | 4 | 0 |
| Melatonin | 0 | 1 |
| Midazolam | 1 | 0 |
| Modified Atkins diet | 2 | 0 |
| Natural progesterone | 1 | 0 |
| Oxcarbazepine | 2 | 2* |
| Paraldehyd | 1 | 0 |
| Perampanel | 3 | 0 |
| Phenytoin | 1 | 1 |
| Prednisolone | 1 | 0 |
| Pregabalin | 3 | 0 |
| Procedure (surgery) | 1 | 0 |
| Rufinamide | 3 | 1 |
| Topiramate | 7 | 5 |
| Valproate | 2 | 1 |
| Zonisamide | 4 | 1 |

Lampert A, Hoffmann GF, Ries M (2016) PLOS ONE 11(1): e0144973

# Ethics Considerations

- Prior perspective: is it ethical to include vulnerable populations in research?
  - Concerns re:limited ability to consent
  - Safety issues
  - "Protection from research"
- Current perspective: is it ethical to NOT include vulnerable populations?
  - "Protection through research"
- Safety and consent remain major concerns

# Solutions (?)

# NIH Inclusion Across the Lifespan Policy

- "…ensure individuals are included in clinical research in a manner appropriate to the scientific question under study so that the knowledge gained from NIH-funded research is applicable to all those affected by the researched diseases/conditions."

- applies to all grant applications submitted for **due dates on or after January 25, 2019**
- PHS Human Subjects and Clinical Trial Information Form
- Scientific Review Groups will assess each application/proposal as being "acceptable" or "unacceptable" with regard to the age-appropriate inclusion or exclusion of individuals in the research project.

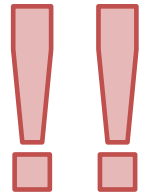
# BCPA & PREA

- 2002: Best Pharmaceuticals for Children Act (BCPA) grants an additional 6 months of market exclusivity in return for voluntarily performing FDA–requested studies in children
- 2003: Pediatric Research Equity Act (PREA) – mandatory program authorizes FDA to require study of new entities in children
  - Sponsors have to submit data on safety and efficacy in children OR
  - Justification for extrapolation
  - Waivers and deferrals granted in >85% of applications
  - Orphan drugs excluded: disproportionately affects children

# BCPA and PREA Results

- 772 products now labeled with pediatric-specific information
- 186 labels due to BPCA legislation
- 420 labels due to PREA requirements
- 49 are results of the Pediatric Rule (pre -PREA)
- 117 due to both
- More work to do…

(As of January 30, 2019)



Report of NICHD 2019 BPCA Stakeholders Meeting (March 22, 2019)

# Extrapolation: 2012

## Efficacy of antiepileptic drugs in adults predicts efficacy in children

### A systematic review

John M. Pellock, MD
Wendy J. Carman, MPH, PhD
Veena Thyagarajan, MPH
Tony Daniels, BS
Dexter L. Morris, PhD, MD
O'Neill D'Cruz, MD, MBA

Correspondence & reprint requests to Dr. Pellock: jpellock@mcvh-vcu.edu

**ABSTRACT**

**Objective:** Due to the challenges inherent in performing clinical trials in children, a systematic review of published clinical trials was performed to determine whether the efficacy of antiepileptic drugs (AEDs) in adults can be used to predict the efficacy of AEDs in the pediatric population.

**Methods:** Medline/PubMed, EMBASE, and Cochrane library searches (1970–January 2010) were conducted for clinical trials of partial-onset seizures (POS) and primary generalized tonic-clonic seizures (PGTCS) in adults and in children <2 and 2–18 years. Independent epidemiologists used standardized search and study evaluation criteria to select eligible trials. Forest plots were used to investigate the relative strength of placebo-subtracted effect measures.

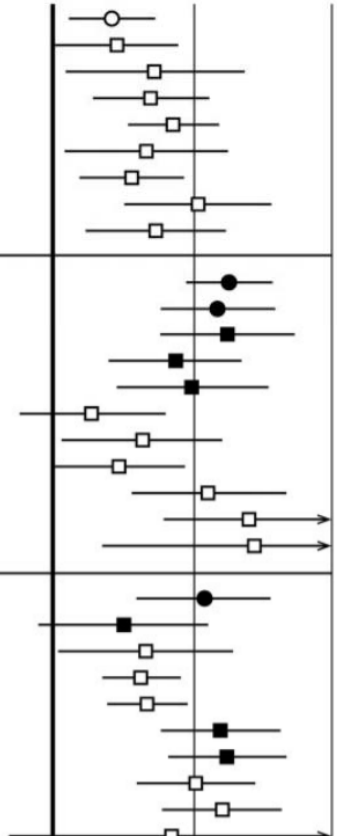
**Results:** Among 30 adjunctive therapy POS trials in adults and children (2–18 years) that met evaluation criteria, effect measures were consistent between adults and children for gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate. Placebo-subtracted median percent seizure reduction between baseline and treatment periods (ranging from 7.0% to 58.6% in adults and from 10.5% to 31.2% in children) was significant for 40/46 and 6/6 of the treatment groups studied. The ≥50% responder rate (ranging from 2.0% to 43.0% in adults and from 3.0% to 26.0% in children) was significant for 37/43 and 5/8 treatment groups. In children <2 years, an insufficient number of trials were eligible for analysis.

**Conclusions:** This systematic review supports the extrapolation of efficacy results in adults to predict a similar adjunctive treatment response in 2- to 18-year-old children with POS.
*Neurology*® 2012;79:1482–1489

# Extrapolation: 2012

**Figure 2** Efficacy comparison of differences in median % seizure reduction between baseline and treatment periods by drug for children and adults

| Drug | Reference | Study group within study | Mean Effect (SE) | 95% CI |
|---|---|---|---|---|
| Gabapentin | e-1 | mITT/T/23.2-35.3/Children (3-12yrs) | 0.105 (0.041) | 0.025, 0.185 |
| Gabapentin | e-2 | PP/T/1200/Adult | 0.115 (0.057) | 0.003, 0.227 |
| Gabapentin | e-2 | PP/T/1800/Adult | 0.182 (0.083) | 0.019, 0.345 |
| Gabapentin | e-3 | PP/T/1200/Adult | 0.215 (0.042) | 0.133, 0.297 |
| Gabapentin | e-3 | PP/T/1800/Adult | 0.175 (0.054) | 0.068, 0.282 |
| Gabapentin | e-4 | PP/T/600-1200/Adult | 0.167 (0.076) | 0.018, 0.316 |
| Gabapentin | e-4 | PP/T/1200/Adult | 0.141 (0.048) | 0.046, 0.236 |
| Gabapentin | e-5 | PP/T/1800/Adult | 0.260 (0.068) | 0.126, 0.394 |
| Gabapentin | e-5 | PP/T/600/Adult | 0.184 (0.066) | 0.055, 0.313 |
| Lamotrigine | e-6 | ITT/M/1-15mg/kg/Children (2-16yrs) | 0.312 (0.060) | 0.194, 0.430 |
| Lamotrigine | e-6 | ITT/T/1-15mg/kg/Children (2-16yrs) | 0.294 (0.055 | 0.187, 0.401 |
| Lamotrigine | e-7 | ITT/M/500/Adult | 0.313 (0.063) | 0.190, 0.436 |
| Lamotrigine | e-7 | ITT/T/500/Adult | 0.219 (0.061) | 0.100, 0.338 |
| Lamotrigine | e-8 | ITT/T/100-400/Adult | 0.250 (0.070) | 0.113, 0.387 |
| Lamotrigine | e-9 | PP/M/300/Adult | 0.070 (0.067) | -0.062, 0.202 |
| Lamotrigine | e-9 | PP/M/500/Adult | 0.160 (0.074) | 0.014, 0.306 |
| Lamotrigine | e-9 | PP/T/300/Adult | 0.120 (0.060) | 0.002, 0.238 |
| Lamotrigine | e-9 | PP/T/500/Adult | 0.280 (0.071) | 0.141, 0.419 |
| Lamotrigine | e-10 | PP/T/200-400/Adult | 0.352 (0.080) | 0.196, 0.509 |
| Lamotrigine | e-11 | PP/T/75-400/Adult | 0.361 (0.140) | 0.086, 0.636 |
| Levetiracetam | e-12 | ITT/T/20-60mg/kg/Children (4-16yrs) | 0.270 (0.062) | 0.149, 0.391 |
| Levetiracetam | e-14 | ITT/T/1000/Adult | 0.127 (0.079) | -0.028, 0.281 |
| Levetiracetam | e-14 | PP/T/1000/Adult | 0.167 (0.081) | 0.008, 0.327 |
| Levetiracetam | e-15 | inf ITT/T/1000/Adult | 0.159 (0.037) | 0.087, 0.231 |
| Levetiracetam | e-15 | inf ITT/T/2000/Adult | 0.169 (0.038) | 0.095, 0.243 |
| Levetiracetam | e-16 | ITT/T/1000/Adult | 0.300 (0.055) | 0.192,0.408 |
| Levetiracetam | e-16 | ITT/T/3000/Adult | 0.312 (0.055) | 0.204, 0.420 |
| Levetiracetam | e-16 | PP/M/1000/Adult | 0.256 (0.055) | 0.148, 0.364 |
| Levetiracetam | e-16 | PP/M/3000/Adult | 0.303 (0.055) | 0.194, 0.412 |

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Pellock et al., Neurology 2012;79:1482

# Extrapolation: 2017

**CRITICAL REVIEW AND INVITED COMMENTARY**

## Extrapolating evidence of antiepileptic drug efficacy in adults to children ≥2 years of age with focal seizures: The case for disease similarity

*[1]John M. Pellock, †‡Alexis Arzimanoglou, §O'Neill D'Cruz, ¶Gregory L. Holmes, #Douglas Nordli, and **Shlomo Shinnar for the Pediatric Epilepsy Academic Consortium for Extrapolation[2]

*Epilepsia*, 58(10):1686–1696, 2017
doi: 10.1111/epi.13859

**Dr. John M. "Jack" Pellock** (December 25, 1943–June 6, 2016) was a Professor

### Summary

**Expediting pediatric access to new antiseizure drugs is particularly compelling, because epileptic seizures are the most common serious neurological symptom in children. Analysis of antiepileptic drug (AED) efficacy outcomes of randomized controlled trials, conducted during the past 20 years in different populations and a broad range of study sites and countries, has shown considerable consistency for each drug between adult and pediatric populations. Historically, the majority of regulatory approvals for AEDs have been for seizure types and not for specific epilepsy syndromes. Available data, both anatomical and neurophysiological, support a similar pathophysiology of focal seizures in adults and young children, and suggest that by age 2 years the structural and physiological milieu upon which seizures develop is similar. Although the distribution of specific etiologies and epilepsy syndromes is different in children from in adults, this should not impact approvals of efficacy based on seizure type, because the pathophysiology of focal seizures and the drug responsiveness of these seizure types**

# Extrapolation: 2018

## Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older

## Guidance for Industry

***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Billy Dunn at 301-796-2250.

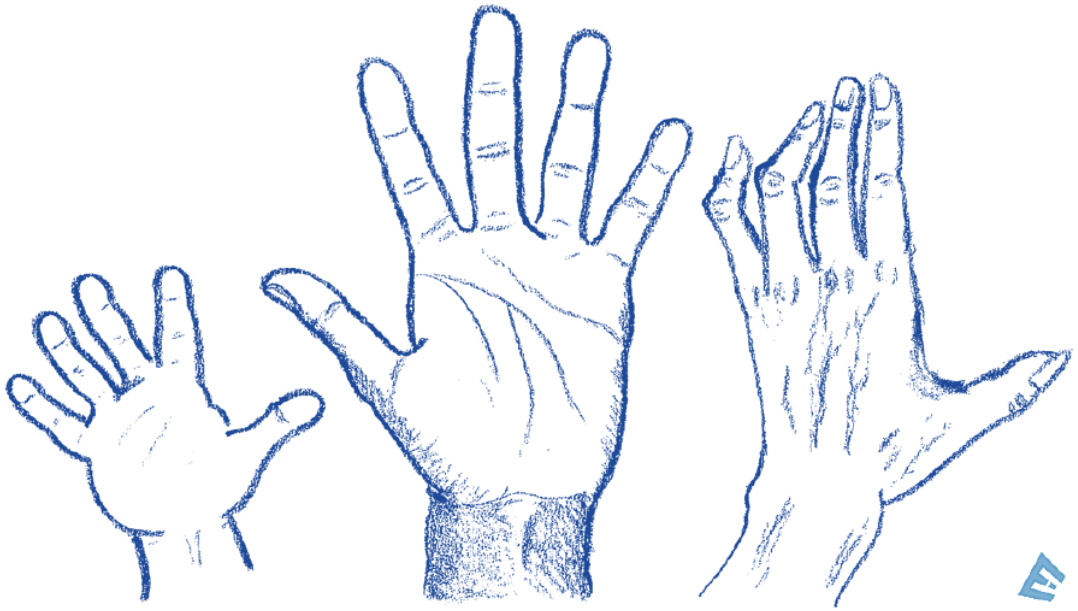
NIH National Institute of Neurological Disorders and Stroke

# Recent Legislation and Guidance

- 21st Century Cures Act: for clinical trials, NIH must collect data on inclusion by age
- Additional FDA guidance on pediatric trials
  - E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population Guidance for Industry (updates International Council for Harmonisation guidance)
  - Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials Guidance for Industry
  - And many others

National Institutes of Health
*Turning Discovery Into Health*

# Inclusion Across the Lifespan



## June 1–2, 2017 Workshop Summary

Revised July 2018

National Institute of Neurological Disorders and Stroke

# Participant Recruitment and Consent

- Involve stakeholders, including affected populations, in planning for study representativeness.
- Engage experts, community representatives, and clinicians to help identify, recruit, and retain populations needed for a study.
- Adapt studies to accommodate participants with impaired function.
- Define the unique abilities of adolescents to provide consent.
- Design studies for ease of participants.
- Use a universal assessment to assess a participant's capacity to provide consent.
- Develop a more robust assent process for individuals without the cognitive function needed to provide consent.
- Provide more detailed guidance for Institutional Review Boards (IRBs) related to assessing appropriateness of non-familial consent.

# Study Design

- Address challenges in balancing inclusion of a representative sample of population with need to minimize known risks & ethical considerations of participants.
- Recognize that study protocol or structure may make it difficult for certain populations to participate.
- Address the issue that complete information on the population prevalence of the disease or condition by age or other demographic variables is not always presented in the grant application.
- Ensure that inclusion of pediatric and older adult populations yields scientific value.
- Consider alternative study designs to allow for greater inclusion.

# Application and Review Process

- Consider inclusion in grant application structures.
- Integrate inclusion into existing Significance and Approach scored review criteria.
- Consider inclusion of peer reviewers with expertise in the proposed study populations in review panels, as this may inform assessment of proposed inclusion/exclusion criteria and study design, methods, and data analysis.

# Data Collection, Analysis, and Reporting

- Consider standardizing demographic data collection and reporting guidelines across the scientific community to enhance the availability of age information and facilitate analyses. [NIH Common Data Elements]
- Investigate requiring reporting by age and monitoring inclusion of children and older persons in clinical trials.
- Pursue standardization of age groupings for results reporting to allow more meaningful interpretation of results.
- Adjust age-range reporting in published reports of clinical trials to add clarity to clinical research data.
- Include age-related outcomes or comprehensive information about the age of study participants in clinical trial publications, as appropriate.
- Increase data availability and transparency to allow for secondary and meta-analyses.

# Training and Education

- Implement widespread changes to language used to define vulnerable and underrepresented groups to avoid alienation.
- Develop checklists, guidance, and training for investigators, reviewers, and IRB members to increase awareness and understanding of policies on inclusion and exclusion.
- Include appropriate expertise for the populations being studied to facilitate recruitment and retention of study participants.

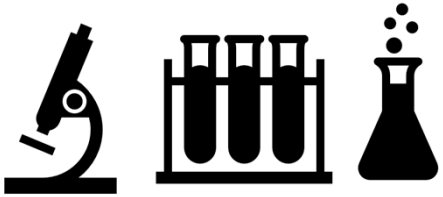
# Objectives

1. List differences (relevant to clinical trials) between people at the extremes of age and those in the “middle”
2. Identify opportunities to be meaningfully inclusive in clinical trials




# Thank you!!!!



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# Questions?