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Use the Chat Box to enter questions.

Instructions for how to obtain CMEs will be provided at the end of the webinar.
Rigor and Transparency: How to Use Preclinical Data to Inform Trials

Will Meurer and Laurie Gutmann
NINDS Clinical Trials Methodology Course

http://neurotrials.training
Disclosures

Laurie Gutmann
Research funding from Alexion Pharmaceuticals
NIH grants

Will Meurer
NIH grants
AHRQ grant
FDA/NIH review panels
Massey Foundation Grant
Sporadic Medico-Legal Consulting
No commercial relationships related to the content of this presentation
• General considerations
  ◦ What is rigor
  ◦ What items should be considered in design phase
  ◦ What are the STAIR criteria
  ◦ How does this relate to grant review
• Case Study 1: Progesterone in TBI
• Case Study 2: Vitamin C in CMT neuropathy
Some slides borrowed from presentation by Jill Jividen, PhD, Manager of Research Development at University of Michigan Medical School Office of Research OR Relevant referenced journal articles
General Considerations
Rigor and Transparency (How to Use Preclinical Research)
Background

Dr. Oswald Steward

_Sr. Assoc. Dean for Research, UC-Irvine_

_Director, Reeve-Irvine Research Center_

http://mediasite.health.uci.edu/Mediasite/Play/4de917befc7b4974b3889d2c270ae1d21d

2003: NINDS funded 3 contracts to replicate promising studies in spinal cord injury (UCI, Miami, Ohio State); over 10 years, 20 promising, high-profile studies were repeated (18 published to date)

**Outcome:** Only about 10% of the published findings could be replicated; methods sections incomplete or misleading

Background

2012: NINDS convened a workshop for stakeholders.

Outcome: Recommendations regarding minimal requirements to improve rigor involving pre-experiment sample size estimation, randomization, blinding, data handling (data inclusion/exclusion) stopping rules and thorough and transparent reporting.

A call for transparent reporting to optimize the predictive value of preclinical research


Back to Basics

Good experimental design (and reporting) underlies Rigor & Reproducibility of findings

5 requirements for “good” experimental design

• Be unbiased
• Have high precision
• Have a wide range of applicability
• Be simple
• Have the ability to calculate uncertainty

• See

<table>
<thead>
<tr>
<th>√ box</th>
<th>Criterion</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td><strong>General Considerations</strong></td>
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<tr>
<td>For preclinical studies, are the preclinical models (e.g. tg mouse, ipsc) relevant to the clinic? Are outcome measures and findings relevant to the clinic (includes effect size)?</td>
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<td>Are results reproducible? (e.g. variability when repeated in same lab)</td>
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<td>Are the findings robust? (e.g. independent replication in other laboratories, other animal models of disease under study or related diseases, other species)</td>
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<tr>
<td><strong>Criterion</strong></td>
<td><strong>Findings</strong></td>
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<tr>
<td>Was treatment allocation blinded?</td>
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<tr>
<td>Were outcome determinations/ratings blinded?</td>
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<tr>
<td>Were the experimental units randomized?</td>
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<tr>
<td>Was there appropriate justification for sample size?</td>
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<td>Were the statistical analytic methods for results appropriate?</td>
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<td>Is all data included (e.g. outliers not excluded, deaths not excluded)?</td>
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<td>Is missing data explained and appropriately handled in the statistical analysis?</td>
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<tr>
<td>Criterion</td>
<td>Findings</td>
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<tr>
<td>If site of action is in the CNS, is there data supporting adequate CNS penetration?</td>
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<td><strong>Is there adequate justification for the proposed dose?</strong> Typically requires dose response data from preclinical or prior clinical studies; data supported estimate of minimal effective dose.</td>
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<tr>
<td>Has target engagement been demonstrated (e.g., receptor occupancy, inhibition of enzyme target)?</td>
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<tr>
<td>Is there pharmacokinetic (PK) data? Is the relationship between PK and efficacy defined in the animal model?</td>
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<td>Were efficacy studies performed with the route of administration planned for clinic?</td>
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<td>Is there evidence that sufficient plasma/CSF levels can be achieved in humans using the planned route of administration?</td>
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<tr>
<td>Have pharmacodynamic (PD) markers been included (i.e. biomarker/measures of biological or physiological activity upstream from clinical outcome)? Is there data linking PK – PD – efficacy? Can the PD marker be used in the clinical trial?</td>
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</table>
# NIH Changes for 2016

<table>
<thead>
<tr>
<th>Key Area</th>
<th>Application Instructions</th>
<th>Review Instructions</th>
<th>Contribute to Overall Impact Score?</th>
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</thead>
<tbody>
<tr>
<td>Scientific Premise</td>
<td>Research Strategy: Significance</td>
<td>Scored Review Criterion: Significance</td>
<td>Yes</td>
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<tr>
<td>Consideration of Relevant Biological Variables, such as sex</td>
<td>Research Strategy: Approach</td>
<td>Scored Review Criterion: Approach</td>
<td>Yes</td>
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<tr>
<td>Authentication of Key Biological and/or Chemical Resources</td>
<td>Other Research Plan Attachment</td>
<td>Additional Review Consideration: Acceptable or unacceptable</td>
<td>No</td>
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Progesterone in TBI
Case Study 1
Animal research

Phase II trial (n=100): Annals EM: 2007;49:391-402
- 0.43 [0.18-0.99] rate ratio for mortality
- Loading dose/then infusion for 3 days
Preclinical Work

  - Progesterone in rats: 3 versus 5 days
  - 3 days
    - Reduced neuronal necrosis / edema
    - No change in functional / behavioral outcomes
  - 5 days
    - Reduced neuronal necrosis / edema
    - IMPROVED functional / behavioral outcome
• Exp Neurol 2006; 200:376-85
  ◦ 6 days of progesterone (rat TBI), 9 doses
    • Acute withdrawal
    • Tapered withdrawal
    • Finding: TW better behavioral outcomes
Original Article

Very Early Administration of Progesterone for Acute Traumatic Brain Injury

David W. Wright, M.D., Sharon D. Yeatts, Ph.D., Robert Silbergleit, M.D., Yuko Y. Palesch, Ph.D., Vicki S. Hertzberg, Ph.D., Michael Frankel, M.D., Felicia C. Goldstein, Ph.D., Angela F. Caveney, Ph.D., Harriet Howlett-Smith, R.N., Erin M. Bengelink, M.A., Geoffrey T. Manley, M.D., Ph.D., Lisa H. Merck, M.D., M.P.H., L. Scott Janis, Ph.D., William G. Barsan, M.D., for the NETT Investigators

N Engl J Med
Volume 371(26):2457-2466
December 25, 2014
Distribution of Extended Glasgow Outcome Scale (GOS-E) Scores, Stratified According to Initial Injury Severity.

Conclusions

- Phase III trial n=882/1140: NEJM: 2014;371:2457-2466
  - 0.95 [0.85-1.06] odds ratio for good outcome
  - Loading dose/then infusion for 3 days
- This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI.
• Dose and schedule is really important
• Be sure to consider relevant comparative pre-clinical data
• Listen to pre-clinical scientists
• Talk to pre-clinical scientists (so you can better work together)
Vitamin C in CMT 1A

Case Study 2
• CMT 1A – most common form of CMT
• Known PMP22 duplication on 17p11.2
• Causes diffuse demyelination of nerves – uniform slowing
• Slowly progressive disorder with impairment related to secondary axonal loss (can use CMAP amplitude as surrogate biomarker)
Several rodent models with PMP22 overexpression (mouse and rat models)
CMT1A-like symptoms expressed
Overexpression PMP22 protein observed in skin biopsies of CMT1A patients

Ascorbic acid treatment corrects the phenotype of a mouse model of Charcot-Marie-Tooth disease (Passage E et al Nat Med 2004)

Abstract
Charcot-Marie-Tooth disease (CMT) is the most common hereditary peripheral neuropathy, affecting 1 in 2,500 people. The only treatment currently available is rehabilitation or corrective surgery. The most frequent form of the disease, CMT-1A, involves abnormal myelination of the peripheral nerves. Here we used a mouse model of CMT-1A to test the ability of ascorbic acid, a known promoter of myelination, to correct the CMT-1A phenotype. Ascorbic acid treatment resulted in substantial amelioration of the CMT-1A phenotype, and reduced the expression of PMP22 to a level below what is necessary to induce the disease phenotype. As ascorbic acid has already been approved by the FDA for other clinical indications, it offers an immediate therapeutic possibility for patients with the disease.
• 11 female, 5 male mice treated
• 14 female, 12 male placebo
  ◦ Rotarod testing:
    • Males 46s vs 9 s (p 0.0007)
    • Females 48s vs 24s (p 0.002)
• Results: treated did much better than placebo
• Next: blinded examiner, all males, 2 sibships (homogeneity)
  ◦ 6 from each sibship treated, 6 untreated x 3mo
  ◦ 2 mo: treated 44 s, untreated <1s (p 0.0001)
• Next: same design – added 3 more measures
• Pathology: some thin myelin on treated
International Neuropathy Consortium developed CMT Neuropathy Score (Michael Shy, Mary Reilly, Davide Pareyson)

- Natural history control
- Showed it could be reproducible outcome measure – longitudinal change over 2 years
- 77 patients over 2 years
- 0.68 increase over 1 year, 1.3 increase over 2 years (significant)
- Score was key for outcome measure – trials started in US and Europe

Shy et al Neuropathy progression in Charcot-Marie-Tooth disease type 1A. Neurology 2008; 70:378-83
Shy M et al Reliability and validity of CMT neuropathy score as a measure of disability Neurology 2005 64:1209-14
High-dose Vitamin C in people with CMT1A

- 3 different trials
- No change CMTNS in treated group or placebo group
  - Placebo group didn’t match Natural History group

CONCLUSIONS AND RELEVANCE  Both treated patients and those receiving placebo performed better than natural history. It seems unlikely that our results support undertaking a larger trial of 4-g/d AA treatment in subjects with CMT1A.

TRIAL REGISTRATION  clinicaltrials.gov Identifier: NCT00484510
Figure 2. Changes in the Charcot-Marie-Tooth Neuropathy Score (CMTNS) Over the 2-Year Study

Adjusted mean changes in the CMTNS over 2 years are shown for the ascorbic acid group and placebo group. These are compared with the mean change at 2 years expected from published natural history and observed mean changes in the placebo groups in the French trial and the Italian/UK trial. Bars indicate 1 SEM. Larger (positive) changes indicate greater worsening.
What happened?
Dose conversion was good mouse to human
Mouse model (C22) used to study ascorbic acid treatment
  - dysmyelination rather than demyelination
  - Not as good a model for human disease
Male phenotype much more severe
Blinded investigator to treatment arm of mice after first study (bias)
Power lacking

Better mouse model – C3
Better rat model
Lessons

- Increased preclinical rigor
- CMTA partnered with company to do all preclinical trials – unbiased, rigorous study design

- Modification of CMTNS to enhance capturing change – CMTNSv2
Lithium and ALS
Case Study 3
ALS – devastating neuromuscular disorder with no treatment, no definitive cause

Lithium initially tried because of demonstrated effect of inducing autophagy

Pretreatment protected cultured brain neurons from glutamate-induced, NMDA receptor-mediated apoptosis

G93A mice (SOD1 mutation) had prolonged survival and recovery of cell pathology
Effects of lithium treatment on the lifespan and neurological symptoms of G93A mice.

Francesco Fornai et al. PNAS 2008;105:2052-2057
Neuroprotective effects of lithium on medium-size lamina VII neurons.

Francesco Fornai et al. PNAS 2008;105:2052-2057
Clinical trial in the same paper
  ◦ control group and similar baseline values between groups (total 44 – 16 riluzole and Li 28 riluzole alone)
  ◦ Daily dose of lithium for 15 months
Effects of lithium treatment on disease symptom progression and survival in patients with ALS. (a, b, d, and e) Symptoms progression (evaluated every 3 months) in controls (riluzole-treated) and treated patients (lithium plus riluzole-treated patients) expr...

Francesco Fornai et al. PNAS 2008;105:2052-2057
• None of the treated group died in 15 month f/u
• 30% of the controls died
• Push from patient community for open treatment
• Rapid movement for a time to event trial, randomized control
• Ended due to futility
• Mouse model – poor model for this disease
• Lithium levels done in clinical pilot study
• Single blind study
• Other preclinical studies suggesting limited range of efficacy for Li
• Concern for dose with potential toxicity of Li to motor neurons in other preclinical studies
• Didn’t eliminate small positive effect
Questions?