Clinical Trial Readiness

Joel S Perlmutter
Elliot Stein Family Professor
Neurology, Radiology, Neuroscience,
Physical Therapy & Occupational Therapy
Washington University in St Louis
Financial Disclosures:

Salary & Grant Support: NIH (NINDS/NCATS), DMRF, Washington U., American Parkinson Disease Association (APDA), Greater St. Louis Chapter of the APDA, McDonnell Center for Higher Brain Function, Barnes-Jewish Hospital Foundation, Huntington Disease Society of America, CHDI, Fixel Foundation, Oertli Fund, MJ Fox Foundation, Murphy Fund, U Michigan, U Toronto, Paula C & Rodger Riney Parkinson Disease Fund

Honoraria: U Rochester; American Academy of Neurology, Emory U, St Louis U, CHDI, Stanford U, U Florida, Huntington Study Group, U Penn, Beth Israel (Harvard U), Huntington STUDY Group, Parkinson Study Group, U Illinois in Chicago (biscotti), Boston U

Speaker’s Bureau: none

Equity & Consulting Agreements: none
Clinical Trial Readiness

Diagnostic criteria - DC
Metrics of severity - DC
natural history
response to current therapies
Biomarkers - DC
Clinical Trial Endpoints - DC
Therapeutic interventions
Diagnostic Criteria

Homogenous cohorts
is it dystonia? - DC
dystonia subtypes? - DC

Generalizable results - DC
Diagnostic Criteria

Laryngeal dystonia – DC
Blepharospasm - DC
Cervical Dystonia – DC (subtypes)
Limb dystonia

Task-specific dystonia
musicians’ dystonia
Laryngeal Dystonia: Diagnosis-DC

Figure 2. Interrater Agreement After Viewing Speech Recording and Speech and Nasolaryngoscopy Recordings

Ludlow C, et al, JAMA Otolaryng 2018
Blepharospasm: DC

1° step
Self-administration of the blepharospasm screening questionnaire

377 subjects
(211 cases and 166 controls)

2° step
Answering YES to questions 3 and/or 5 and/or 6

250 subjects
(179 cases and 71 controls)

3° step
Neurologic examination by diagnostic algorithms

- Algorithm 123
  165 case-patients/ 15 control subjects identified as affected by Blepharospasm

- Algorithm 124
  164 case-patients/ 15 control subjects identified as affected by Blepharospasm

- Algorithm 1234
  170 case patients / 18 control subjects identified as affected by Blepharospasm

Sensitivity
78% (165/211) 78% (164/211) 81% (170/211)
Specificity
91% (151/166) 91% (151/166) 83% (138/166)
Metrics of Severity (severity vs spread)

General dystonia ratings

Specific rating scales
Cervical Dystonia
Blepharospasm
Laryngeal dystonia
Natural History: Spread - DC

Berman B et al, JNNP 2020
Factors related to progression-DC

Table 3. Influence of BoNT on HR-QoL within 1 yr

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Time</th>
<th>Group*Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Health (n=72)</td>
<td>p = .18</td>
<td>p = .73</td>
<td>p = .610</td>
</tr>
<tr>
<td>Physical Functioning (n=72)</td>
<td>p = .51</td>
<td>p = .27</td>
<td>p = .58</td>
</tr>
<tr>
<td>Physical Role Functioning (n=72)</td>
<td>p = .93</td>
<td>p = .01</td>
<td>p = .54</td>
</tr>
<tr>
<td>Pain (n=71)</td>
<td>p = .98</td>
<td>p = .56</td>
<td>p = .17</td>
</tr>
<tr>
<td>Energy/ Fatigue (n=72)</td>
<td>p = .60</td>
<td>p = .01</td>
<td>p = .46</td>
</tr>
<tr>
<td>Emotional Well-being (n=72)</td>
<td>p = .004</td>
<td>p = .02</td>
<td>p = .54</td>
</tr>
<tr>
<td>Emotional Role Functioning (n=71)</td>
<td>p = .30</td>
<td>p = .07</td>
<td>p = .79</td>
</tr>
<tr>
<td>Social Functioning (n=72)</td>
<td>p = .03</td>
<td>p = .02</td>
<td>p = .68</td>
</tr>
</tbody>
</table>

Junker J et al, submitted
Metrics of Severity: Effects of Interventions

Transient: Chemodenervation yo-yo
Long term: Surgical but still time dependent
A Biomarker

Objectively measured indication of normal biologic process, pathogenic process or drug response

Biomarkers

Diagnostic - DC
Metric of Severity - DC
Prediction of progression - DC
Endpoints of a clinical study surrogate endpoints
What is a Primary Endpoint of a clinical study?

Clinically important event:
-- death, stroke or MI
-- disability, quality of life

Categorical (e.g. need assistive walking device)

Continuous (e.g. time to walk a specified distance)

Power of a Clinical Trial Depends on:

- Clinically relevant effect of intervention on the Primary Clinical Endpoint
  - Sample size
  - Variance of measurement
  - Duration of Study
  - Effect Size
Surrogate Endpoint

A biomarker that can substitute for a clinically meaningful endpoint
Validation of a Biomarker as a Surrogate Endpoint

- Biomarker & clinical outcome:
  - Strong, consistent & independent
  - Biomarker response must be strong enough to predict

- Biomarker predicts efficacy & toxicity
Therapeutic Candidates

- Rationale
- Safety
- Efficacy
- Dose
- Target Engagement
- Phase 1, 2, 3 trials
Acknowledgments

The Dystonia Coalition: A Multicenter Network for Clinical and Translational Studies

Gamze Kilic-Berkmen, Laura J. Wright, Joel S. Perlmutter, Cynthia Comella, Mark Hallett, Jan Teller, Sarah Pirio Richardson, David A. Peterson, Carlos Cruchaga, Codrin Lungu and H. A. Jinnah

NIH (NINDS, NCATS), PAGS (DMRF, NSDA, etc)
The Important Issue of the Primary Endpoint

• The Primary Clinical Endpoint should be chosen for its clinical importance to patients, NOT to minimize the sample size or duration of the study.
Why use a surrogate endpoint?

- If treatment effect is greater or measurement variability is less then sample size or study duration decreases
Failures of Biomarkers as Surrogate Endpoints

The biomarker is not in the causal pathway of the disease process that affects outcome

Failure of a Biomarker as Surrogate Endpoint

Efficacy of encainide after myocardial infarction


<table>
<thead>
<tr>
<th></th>
<th>Encainide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPC Suppression</td>
<td>79%</td>
<td>37%</td>
</tr>
<tr>
<td>Mortality</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Failure of biomarkers as Surrogate Endpoints

The biomarker is not in the pathway of the intervention effect on the disease process

Failure of biomarkers as Surrogate Endpoints

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)

*JAMA* 2002;288:2998-3007

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Pravastatin 40 mg/day</th>
<th>Usual Care</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>177.6±33.8</td>
<td>195.5±37.3</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td>All Deaths</td>
<td>631</td>
<td>641</td>
<td>.88</td>
</tr>
</tbody>
</table>
Log odds ratios (ln OR) and 95% confidence intervals for active treatment vs control for 9 large statin trials are compared with regression lines (solid) from meta-analyses of 45 long-term trials using statins and other cholesterol-lowering interventions published before December 31, 2000.
A statistically significant change in the biomarker may not be of sufficient magnitude to produce a change in clinical outcome.
Optimal situation for a biomarker to be a valid surrogate endpoint

Changes in the biomarker mediate all of the effect of the intervention on clinical outcome

Aspirin v. aspirin + clopidogrel for prevention of stroke

(CARESS Circulation 2005; 1112233-2240; MATCH Lancet 2004; 364:7331-337)

<table>
<thead>
<tr>
<th></th>
<th>ASA</th>
<th>ASA + CPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCD Cerebral Emboli at 7 days</td>
<td>73%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>18 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Life threatening Bleeding</td>
<td>1%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Some reasons for failures of Biomarkers as Surrogate Endpoints

A biomarker that is a valid surrogate endpoint for one therapeutic mechanism/drug class may not be valid for a different therapeutic mechanism/drug class.
Clinical Trial Endpoints

Clinically meaningful

Surrogate endpoints
Primary Endpoint

• Primary Clinical Endpoints can be
  – Life Events (e.g. need assistive device to walk)
  – Quantitative Measurements (e.g. time to walk a specified distance)
Take Home Message

Biomarker of Efficacy:
reflect action of therapy
reflect relevant pathophysiology
Classification Scheme

Axis 1: clinical features
- age of onset
- body distribution
- temporal pattern
- associated features
  - isolated
  - combined

Albanese A, et al, Mov Disord 2013
Classification Scheme

Axis 2: etiology
CNS pathology
inherited or acquired
inherited
acquired
idiopathic

Albanese A, et al, Mov Disord 2013