Welcome

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Duke ALS Clinic, Durham NC
Why No Cure For ALS Yet?

- We don’t know what causes most cases
- We don’t understand disease progression
- It takes a long time to make a diagnosis
- Our measurement tools are noisy and slow to change
- It is a rare disease with limited resources available for study
- Enrollment in ALS research studies is surprisingly low
Outline

• Enrollment problems in ALS research studies
• Why did we create this program?
• Similar programs in other diseases
• What last year’s ALS Research Ambassadors have accomplished
• What you as participants can expect here
• What we hope to see from you when you leave
• Agenda
• Sponsor acknowledgement
• Questions
Enrollment Problems in ALS Research Studies
Case

- 60 year old university professor, newly diagnosed with clinically definite sporadic ALS. He currently has minimal bulbar weakness, moderate arm and leg weakness. No obvious cognitive or behavior problems. Following education about the disease itself, he is presented with stage-appropriate, evidence-based management options including riluzole, multi-disciplinary team care, and a research study.

- He opts for the first two, but **declines the research study** in favor of pursuing chelation at Hickey Center.
Why Patient’s Decision Surprised Me

- ALS is one of the most devastating diseases
- There is no markedly effective treatment for it
- Research offers the only path toward more effective future treatments
- Participation in research can provide positive feelings of hope, altruism
- Patients who participate in research studies may “do better” than patients who do not

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-Are randomized clinical trials good for us (in the short term)? Evidence for a “trial effect”
David A. Braunholtz, Sarah J.L. Edwards, Richard J. Lilford
Measuring Enrollment: “Percent Enrolled”

• First thought: number of participants enrolled/total number patients with ALS
  – Numerator issues
    • National versus single clinic
    • All studies combined or single study
    • Time period
  – Denominator issues
    • All versus just those eligible
    • If combining studies, entry criteria vary
    • Most ALS clinics lack sophisticated databases
    • For a given study, screening log unlikely to capture all eligible patients; some “pre-screening” always occurs
Measuring Enrollment: “Percent Enrolled”

- Next best: number of participants enrolled in all studies over some period of time/number seen in that clinic
  - Denominator still surprisingly difficult

- At Center 1
  - Between 1/01 and 12/08, 73 enrolled in at least 1 of 7 ALS studies
  - Approximately 739 unique patients seen
  - Enrollment 9.9%

- At Center 2
  - During a single trial in 2006, 6 enrolled
  - Approximately 268 patients being followed
  - Enrollment 2.2%
Measuring Enrollment: “Percent Enrolled”

- At other clinics across North America
  - 2007 ALSRG Online Survey
    - 18 questions, 10 minutes
    - Open on Survey Monkey 1/07-6/07
    - Repeated emails, face to face reminders
    - 40/177 members responded (23%)
Table I. Online survey of ALSRG members.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Where in North America do you practice?</td>
<td></td>
</tr>
<tr>
<td>2. How many patients with ALS do you follow?</td>
<td>132 Mean</td>
</tr>
<tr>
<td>3. How many new patients with ALS do you see each month?</td>
<td>10 Mean</td>
</tr>
<tr>
<td>4. How many specific ALS research studies were performed at your site in the past year?</td>
<td>3 Mean</td>
</tr>
<tr>
<td>5. What percentage of your patients participated in at least one of these studies?</td>
<td>25% Mean</td>
</tr>
<tr>
<td>6. What method did you use to answer the last question?</td>
<td>90% Estimated</td>
</tr>
</tbody>
</table>

Measuring Enrollment: “Trial Enrollment Rate”

- Number of participants enrolled in a published trial/number of centers enrolling/number of months enrollment was open
  - Even this measure has problems
- Literature review
  - Search terms “ALS” or “Amyotrophic” in title
  - Publication date 1990 to 2007
  - Type: clinical trials
  - 85 trials identified
  - 36 had info needed to calculate trial enrollment rate
• Mean ALS Trial Enrollment Rate: 2.2 participants/site/month
• Range: 0.1-7.5
Mean ALS Trial Enrollment Rate: 2.2 participants/site/month
Range: 0.1-7.5

Most of the clinics involved in these studies see 10 new and 40-50 return patients every month.

Does Poor Enrollment Matter?

• Huge problem! Poor enrollment means:
  – PALS are being deprived of the benefits of being in trials
  – Trials take longer, are more expensive, may be terminated without a definitive conclusion, results may not be generalizable
  – Unless this can be solved, it will take longer than it should to find a cure for ALS
Is Poor Enrollment Fixable?

There is tremendous variability in trial enrollment rate across previously published ALS studies (0.1-7.5 pts/site/mo); this suggests modifiable factors that might influence enrollment

• Bedlack et. al. Scrutinizing enrollment in ALS clinical trials: room for improvement? ALS 2008;5:257-265
Does Trial Design Influence Enrollment?

Table III. Unadjusted comparisons of ALS trial enrollment rate across trial factors.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Mean</th>
<th>SD</th>
<th>n (n=36)</th>
<th>p-value</th>
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<tr>
<td>1) Primary outcome</td>
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<td></td>
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<tr>
<td>Safety</td>
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<td>2.1</td>
<td>8</td>
<td>0.55</td>
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<tr>
<td>Efficacy</td>
<td>2.1</td>
<td>2.0</td>
<td>8</td>
<td>28</td>
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<td>2) Large (&gt;100pts) Phase III Trial</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.4</td>
<td>2.2</td>
<td>17</td>
<td>0.80</td>
</tr>
<tr>
<td>Yes</td>
<td>2.1</td>
<td>1.9</td>
<td>19</td>
<td>9</td>
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<tr>
<td>3) Placebo use in trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.4</td>
<td>2.1</td>
<td>6</td>
<td>0.78</td>
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<tr>
<td>Yes</td>
<td>2.2</td>
<td>2.0</td>
<td>30</td>
<td>0.19</td>
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<tr>
<td>4) Route of administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>3.3</td>
<td>2.9</td>
<td>5</td>
<td>0.19</td>
</tr>
<tr>
<td>Non-Invasive</td>
<td>2.0</td>
<td>1.8</td>
<td>31</td>
<td>9</td>
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<tr>
<td>5) Active drug to placebo ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 1</td>
<td>1.9</td>
<td>2.0</td>
<td>21</td>
<td>0.32</td>
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<tr>
<td>Greater Than 1 to 1</td>
<td>2.8</td>
<td>2.2</td>
<td>9</td>
<td>0.50</td>
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<tr>
<td>6) Drug available outside study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.6</td>
<td>1.3</td>
<td>10</td>
<td>0.50</td>
</tr>
<tr>
<td>Yes</td>
<td>2.1</td>
<td>2.2</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>7) Geographic sites</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Outside USA</td>
<td>2.4</td>
<td>2.2</td>
<td>12</td>
<td>0.61</td>
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<tr>
<td>USA</td>
<td>2.0</td>
<td>2.1</td>
<td>18</td>
<td>0.50</td>
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<tr>
<td>8) Number of sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>1.9</td>
<td>1.9</td>
<td>27</td>
<td>0.08</td>
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<tr>
<td>Single</td>
<td>3.2</td>
<td>2.0</td>
<td>9</td>
<td>0.50</td>
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<tr>
<td>9) FVC restriction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.8</td>
<td>2.4</td>
<td>10</td>
<td>0.33</td>
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<tr>
<td>Yes</td>
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<td>0.33</td>
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<td>10) Disease duration restriction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3.1</td>
<td>2.6</td>
<td>15</td>
<td>0.03</td>
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<tr>
<td>Yes</td>
<td>1.6</td>
<td>1.3</td>
<td>21</td>
<td>9</td>
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<tr>
<td>11) Medication restriction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.4</td>
<td>2.1</td>
<td>24</td>
<td>0.43</td>
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<tr>
<td>Yes</td>
<td>1.8</td>
<td>2.0</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>12) Strength restriction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.4</td>
<td>2.0</td>
<td>32</td>
<td>0.08</td>
</tr>
<tr>
<td>Yes</td>
<td>1.6</td>
<td>0.3</td>
<td>4</td>
<td>9</td>
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<tr>
<td>13) Pharm Company sponsorship</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2.0</td>
<td>1.8</td>
<td>19</td>
<td>0.55</td>
</tr>
<tr>
<td>Yes</td>
<td>2.4</td>
<td>2.3</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>
Power Issue or Reality?

- PMID16606934 Glatiramir trial (7.5 p/s/m) enrolled at single US site, tested invasive intervention available outside trial, primary safety outcome measure, 2:1 active to placebo

- PMID16401852 Pentoxyfilline trial (6.7 p/s/m) enrolled over multiple non-US sites, non-invasive intervention available outside trial, primary efficacy outcome measure, 1:1 active to placebo
Power Issue or Reality?

- PMID16753975 CWO trial (0.6 p/s/m) enrolled at single US site, tested non-invasive device available outside trial, primary efficacy outcome measure, 1:1 active to placebo

- PMID16753973 NIPPV trial (5.0 p/s/m) enrolled at single US site, tested non-invasive device available outside trial, primary efficacy outcome measure, 1:1 active to placebo
Clues: Other Fields

- ALS is not the only field to experience this problem

- Best studied in cancer
  - Harris Poll of 5,980 cancer patients, 425 physicians
  - ASCO Survey of 3,550 oncologists
  - NCI sponsored focus groups of primary care doctors

- Less than 5% of North American cancer patients enroll in a study

- “Patient factors” and “doctor factors” may play important roles in cancer study enrollment
  - Annals of Oncology 2000;11:939-945
Patient Factors:
Cancer Study Enrollment

- Lack of awareness (80%)
- Burden of travel
- Fear of unexpected costs
- Fear of “being a guinea pig”
- Perceived loss of control over decision making
- Possibility of not receiving “best possible care” especially with placebo designs
- Confusion about research process, specifics
- Choosing an alternative therapy
Doctor Factors: Cancer Study Enrollment

- Lack of awareness
- Concern for doctor-patient relationship
- Perceived loss of control
- Perceived increase in time and paperwork
- Doubts about protocols
Does any of this apply to ALS enrollment?
Evidence for Lack of Awareness

- Most ALS trials are run in specialized multidisciplinary ALS Clinics

- Evidence suggests that many PALS never make it to one of these clinics, and thus may never have awareness or option to participate
  - In Registry of 1359 Veterans with ALS, only 595 (43%) ever even once attended specialized clinic

Evidence for Patient and Doctor Factors: 2007 ALSRG Online Survey

7. What percentage of patients was offered at least one of these studies in the past year?  
   66% Mean  
   0-100% Range  

8. What are reasons you did not offer a study to a patient?  
   91% “Patient didn’t qualify based on entry criteria”.  
   25% “I didn’t believe patient could complete, even though they met entry criteria”.  
   13% “I didn’t believe patient’s family would accept protocol”.  

9. What percentage of patients that were offered a study refused?  
   40% Mean  
   0-80% Range  

10. What reasons did patients give for declining?  
    94% “Physical burden”  
    67% “Didn’t want chance of placebo”  
    49% “Seeking an alternative therapy”  
    24.2% “Didn’t believe in protocol”  
    12% “Afraid of unexpected expense”  

11. How often are you excited and enthusiastic about the ALS research studies you offer?  
    38% “Always”  
    28% “Sometimes”  
    25% “Often”  
    10% “Rarely”  

12. Do you advocate for patients entering a study or educate only?  
    85% Advocate  
    15% Educate only  

13. Do you discuss the preclinical science behind each study?  
    92% Yes  
    88% “Social good”  
    85% “Access to a new therapeutic option”  
    58% “Increased exposure to health care professionals”  

14. Which of these attributes of participation in research studies do you mention to patients?  
    73% proactive (before a specific question or use).  
    48% reactive (in response to specific patient question or use).  

15. When addressing ‘alternative therapies’ for ALS, check all that apply to your approach  

Bedlack et. al. Scrutinizing enrollment in ALS clinical trials: room for improvement? ALS  
2008;5:257-265
Evidence for Patient and Doctor Factors: 2009 PALS Online Survey

- 17 questions, 10 minutes
- Open on Survey Monkey 1/09-6/09
- Advertised in ALSRG clinics, support groups, ALSA and MDA literature
- 90 “PALS” answered at least 1 question
  - 57 years old, men = women, 100% white, 69% at least some college or greater education, ALS for 4 years, 80% attended specialized ALS clinics

Evidence for Patient and Doctor Factors: 2009 PALS Online Survey

3. Have you ever been invited to participate in any ALS research study within a specialized ALS clinic?  
   \[ n = 89 \]  
   Yes 53%  
   No 47%  

4. If you were invited, did you ever turn down an invitation to participate?  
   \[ n = 55 \]  
   No 76%  
   Yes 24%  

5. If you did turn down an invitation like this, what were the reasons (check all that apply)?  
   Study appeared too physically demanding 44%  
   I didn't think the study would help me 39%  
   My doctor didn't think the study would help me 17%  
   Family and friends advised against it 11%  
   I was afraid of being harmed by the study 11%  
   I was worried about costs 6%  
   \[ n = 18 \]  

6. For those of you that have participated in a study within an ALS clinic, what were the reasons you decided to participate (check all that apply)?  
   I thought the study would help others 90%  
   I thought the study might help me 77%  
   My doctor thought it was a good idea 46%  
   My family thought it was a good idea 26%  
   I heard that patients who participate in research studies generally fare better than those who don't 10%  
   \[ n = 39 \]  

9. For those that have participated in an ALS research study within a clinic, were you ever contacted to participate in another study?  
   \[ n = 40 \]  
   No 70%  
   Yes 30%  

Evidence for Patient and Doctor Factors: PLM Survey

- Created and hosted by Patients Like Me
- Advertisement for NEALS Biomarker Study emailed to 3000 registered PALS 7/09-9/09
- 628 unique PALS opened email; these were emailed 6 question survey designed to understand responses to the advertisement

Evidence for Patient and Doctor Factors: 2009 Patients Like Me Survey

Figure 1. Flow diagram of Study 2.

Evidence for Patient and Doctor Factors: 2009 Patients Like Me Survey

- Of the 35 survey responders who chose not to visit biomarker study website, reasons given:
  - Lack of time (43%)
  - Lack of interest (31%)
  - Fear of out of pocket expenses (26%)
  - Felt study would not help them (26%)
  - Already enrolled in this study (23%)
  - Advice against it from family/friend (14%)
  - Advice against it from doctor (14%)
  - Burden of travel (9%)

Evidence for Patient and Doctor Factors: 2009 Patients Like Me Online Survey

– Of the 13 survey responders who visited biomarker study website, but did not enroll reasons given:
  • Fear of out of pocket expenses (3)
  • Burden of travel (3)
  • Burden of study protocol itself (3)
  • Felt study would not help them (1)

– Open text responses clearly show confusion about this study and research process in general

Burden of ALS Trial Participation

- Cost analysis of existing literature
  - 33 published trials, conducted in America between 1992-2006
  - Time burden: number of study visits, 6h per visit (grooming, assembling assistive devices, loading car, driving to and from site, outcome measures)
  - Dollar burden: gas mileage of average vehicle and cost of gas mid-point of studies (1999), round trip of 100 miles

• 1992-2006, 33 American ALS trials
  – 1,093,655 study visits @ 6h per visit means PALS contributed 6.6 million hours
  – 24.5 MPG
    (www.nhtsa.dot.gov/cars/rules/cafe/FuelEconUpdates/1999/Index.html), $1.21 gallon
    (www.eia.doe.gov/emeu/steo/pub/special/summogas.html), 100 mile round trip means PALS contributed $5,401,317 just for gas alone

Summary

• Enrollment in ALS studies is difficult to measure
• Measurements we have suggest that enrollment is low and highly variable
• Enrollment variability is not explained by ALS “trial factors”
• Patient factors that appear to play a role include:
  – Lack of awareness, fear of burdens (cost, time, physical), confusion
• Doctor factors that appear to play a role include:
  – Failure to ask, failure to advocate, lack of enthusiasm, failure to educate proactively about alternative options
• Data we have is from small, biased samples
Why We Created This Program

- Enrollment barriers can likely be lessened by education and advocacy

- Education and advocacy will be most effective when undertaken by large, diverse groups
  – Examples: PALS, CALS, ALS clinician-scientists

- PALS, CALS have the most at stake in clinical research yet opportunities for voice may appear limited

- We want to help you maximize your potential as research educators and advocates, and have you help us design better studies and awareness campaigns, in hopes that all this will improve enrollment in ALS studies and speed our progress toward a cure
The Advocate Report

There are now more than 180 trained PDF Research Advocates working around the United States to advance Parkinson’s research and speed new treatments. Browse their inspiring stories.

The Advocate Report: Tom and Becky Help Choose PDF Grantees

In 2011, Tom Shifman and Becky Houde, participated in PDF’s annual grant review, helping to decide which researchers received funding for Parkinson’s research. Watch this video to hear their perspectives on their role in the process...
ALS Research Ambassadors

- ALSC RLI first held 2011
- 20 graduates
- “Contacts” this far include:
  - PatientsLike Me posts
  - Facebook posts
  - Participating in National ALS Registry Planning Meetings
  - Helping NEALS develop new Trial Search tool
  - Attendance at 2012 National ALS Advocacy Days
  - NEALS research blog posts
Clinical Research Blog

PALS Highlight
Posted by: ALS Trial Expert August 14, 2012

Since learning in December 2009 that she had ALS, Laura has been a prominent clinical trial advocate and strong voice in the PALS community. Shortly after her diagnosis, her decision to enroll in ALS clinical trials was an easy one. “When I was first diagnosed with ALS, the very first thing I did was start researching clinical trials because, as an RN and former hospice nurse, I knew what the progression was going to be.” She has been proudly enrolled in five ALS clinical trials. “My philosophy is I would rather do something than nothing. Nothing to me just means sitting back and letting the disease drive my life.”

Laura’s experiences as a participant in clinical trials have been highly positive. With each trial she has felt appreciated and
• Expectations from faculty in this program are to:
  
  – Teach you about the research process, how to critique a scientific publication, the ALS pipeline, barriers to success, and opportunities for overcoming these barriers via education and advocacy;
  
  – Be available from now forward to you for questions, suggestions and mentoring.
Expectations

- Expectations from attendees in this program are to:
  - Engage in discussion throughout this program and afterward
  - Work in your small group on site to critique a paper and be prepared to weigh when groups get back together
  - Complete your evaluation form afterward to help us improve the program
  - Become “Research Ambassadors”; In this role, to educate and advocate to/for other PALS, CALS, decision makers and help us design better trials and awareness campaigns
  - Maintain your individual section of ALSRG/NEALS Web Pages with “contacts” you make
<table>
<thead>
<tr>
<th>Outreach Efforts by NEALS Research Ambassadors</th>
<th>Number of Each</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speaking at a Fundraiser</td>
<td>0</td>
</tr>
<tr>
<td>Speaking at a Support Group</td>
<td>0</td>
</tr>
<tr>
<td>Speaking to a Congressman</td>
<td>0</td>
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<tr>
<td>Interview</td>
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<tr>
<td>Writing in a Newspaper</td>
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<tr>
<td>Writing in a Blog</td>
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<tr>
<td>Writing in a Website</td>
<td>0</td>
</tr>
<tr>
<td>Writing to a Congressman</td>
<td>0</td>
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</tbody>
</table>

This table shows the types of outreach efforts being undertaken by our NEALS Research Ambassadors. Through these, they are educating and advocating about ALS research to patients, clinicians, press and policymakers. We are very proud of them! If you would like to be a NEALS Research Ambassador please apply for the 2013 ALS Clinical Research Learning Institute [here](#).
Agenda and Facilities Overview
Questions