U.S. Food and Drug Administration
Protecting and Promoting Public Health

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Drug Development for CFS and ME: Public Workshop

April 26, 2013

Bethesda Marriott

5151 Pooks Hill Road,

Bethesda, MD 20814

Welcome

RADM Sandra Kweder, MD
Deputy Director, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

FDA Workshop: Drug Development for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis

Drug Development Scientific Workshop
April 26, 2013

RADM Sandra Kweder, MD
Deputy Director, Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

Objectives

Listen and learn

Day 1

- To engage patients and patient representatives
- Most significant symptoms and negative impacts of disease
- Range of therapies

Day 2

- Examine common issues in drug development
- Consider tools – scientific and regulatory

Move forward!

Chronic Fatigue Syndrome

- Serious, complex, and debilitating disease
- Unknown etiology
- Characterized by profound fatigue >6 months duration; worsened by physical or mental activity
- Multiple body systems affected
- No diagnostic tests
- No approved therapies
- Lack of consensus on nomenclature and disease definition

Nomenclature

- Chronic Fatigue Syndrome and Myalgic Encephalomyelitis (CFS and ME)
  - Disease definition
- Drug development

CDER's Mission

….promote and protect the public health by assuring that *safe* and *effective* drugs are *available* to Americans

…Careful judgment applied to scientific assessment of risk and benefit balance.

Marketed drugs: Balance of Safe & Effective

- Safe
  - Risks are managed
  - Quality is assured
  - Advertising is appropriate
  - Information is available
- Effective
  - Studied with proper endpoints & standards
  - Drugs of today – not a century ago
  - Quality is maintained

Code of Federal Regulations
Safe and effective for their Intended use in the intended population

Who does the work and who makes the decisions?

- FDA regulations began as interstate commerce
  - Companies who intend to market drugs usually fund their development
  - Engage academic and community researchers to conduct the studies
- FDA oversees drug development
  - Assures safety and that appropriate regulations are being followed to protect patients
  - Work with “sponsors”
    - Review their strategies, protocols for study, etc.
- Review all findings when submitted to FDA for review
  - NDA (New Drug Application) or BLA (Biologic License Application)

Review work incorporates FDA regulations, science and judgment

Chemistry
Animal toxicology
Statisticians
Physicians
Clinical Pharmacology
Plant inspectors

Public Advisory Committees that include patient perspective

Between IND & NDA: What are we looking at?

- Chemical composition
- Animal studies first
  - Is it safe to give to humans?
- How will you assure their safety?
  - What is the range of possible doses?
  - What are you trying to show?
- What are your plans for clinical trials?
  - How do you know you have the optimal dose?
  - How large should the clinical trials be?
  - What will you compare the drug to and what study endpoints?
- Multiple points of interface between FDA and industry sponsor
  - Every clinical trial is addressed in detail
  - Seek careful, well designed development program

The gold standard: Substantial Evidence of Effectiveness

Adequate and well-controlled study:

- Study has been designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation" (§ 314.126)

Adequate and Well-Controlled Study Design

- Permits a valid comparison with a control
  - Concurrent: placebo, no-treatment, active, dose-comparison
  - Historical
- Well defined patient population
- Adequate measures to minimize bias
- Methods of assessment of response are well-defined and reliable
- Analysis of the results is adequate to assess the effects of the drug itself
- This is straightforward when disease is well defined and has objective, established measures

Clinical trials matter – a lot

- Essential to assess the effect and safety of a drug
- Measures matter
  - Objective, easy to quantify, “signs”
    - Blood pressure; kidney function; viral counts in blood; MI; death
    - Available for most well understood diseases
  - Subjective, “symptoms”
    - Pain; fatigue; weakness; headache; depression
    - All involve how the patient feels or functions
    - Complex to measure and quantify

What also matters is the patient

- The disease frames scientific and regulatory considerations
  - Greater need calls for greater attention to detail
- Seriousness of disease shifts risk tolerance
  - Creative use of regulatory tools
  - It may call for utilization of novel endpoints in clinical trials – they still need to be rigorous and validated
- Regardless of disease, the standard of evidence is the same
  - Adequate and well controlled trials establish safety and efficacy

Agenda

- Panel 1—Drug Development: Innovation, Expedited Pathways, Regulatory Considerations
- Panel 2—Symptoms and Treatments: A View from Patients and Clinicians
- Panel 3—Clinical Trial Endpoints and Design
- Panel 4—Summary and Path Forward
- Closing Remarks

Thank You!

Panel 1:
Drug Development: Innovation, Expedited Pathways, Regulatory Considerations

Moderator:
RADM Sandra Kweder, MD
Deputy Director, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Background and Meeting Goals

Sandra Kweder, MD

Drug Innovation and Derisking Drug Discovery

Bernard Munos, MS, MBA
Founder
InnoThink Center for Research in Biomedical Innovation

How to energize innovation and de-risk drug R&D for CFS?

InnoThink

Bernard Munos
Founder

InnoThink Center For Research in Biomedical Innovation

Washington, DC, April 26, 2013

The challenge

How to develop treatments for a disease that is complex, poorly understood, and with multiple etiologies?

InnoThink

Traditional drug R&D has not risen to the challenge

- **Dearth of translatable research**
- **Lack of research infrastructure**
- **"Fuzzy" disease routinely misdiagnosed**
- **Treatments address symptoms**
- **Ill-equipped regulators**

InnoThink

CFS needs an innovation supply chain

Goal: make it easier, cheaper, and faster to work on CFS

- **Need data**
- **Need tools**
- **Need partners**
- **Need money**
- **Need leadership and passion**

InnoThink

Need data

There can't be any science without data

"If you think about the scientific revolutions in history, they've been driven by one thing -- the availability of data. From Copernicus to quantum mechanics, it's data that drives innovation."

InnoThink

Need data

- CFS is a complex disease. Disease heterogeneity magnifies data requirements
- Need lots of data
  - Patient registry (better international)
  - Natural history data to understand disease progression and identify midpoints and endpoints that can be used in future clinical trials
  - Genomic data
- Such data collection is unlikely to be funded by industry
- Technology makes it possible to collect high-quality data cheaply
  - TLS' patient monitoring
  - Patient-Like-Me
  - Biosensors to track effort/mobility
  - Phone/computer apps
- Data must be available in free open-access to scientists

InnoThink

If you build it, they will come

- Example: Multiple Myeloma Research Foundation
- Founded 1998
- Heterogeneous disease with many subtypes
- Has raised $225m, sequenced the myeloma genome, opened 45 trials of 23 drugs--6 of which have approved by the FDA-- which have doubled the life span of multiple myeloma patients
- Incidence: 4 per 100,000 (vs. 7 to 3,000 for CFS)

InnoThink

Need tools

There can't be much research without tools

Tools leverage the value of data

InnoThink

Need tools

- Tools + data make up the basic research infrastructure
- Need the tools of drug discovery, e.g.,
  - Tissue bank, animal models, biomarkers, assays
  - Networking tools
- Tool development is unlikely to be funded by industry
- Technology makes it possible, even for small disease foundations, to fund such effort
  - Chordoma Foundation
- Tools must be available in free open-access to scientists

InnoThink

If you build it, they will come

- Example: Open-Source Drug Discovery Project
- Launched 2008
- Over 6,000 scientists collaborating to develop new treatments for tuberculosis
- Generate 65% of the published papers on TB
- Runs on <$2m budget per year

InnoThink

Need partners

- **Scientists**
  - **Established scientific leaders**
  - **Young investigators**
  - **Physicians who treat patients**
- **Companies**
  - **Need to see IP and the outline of a drug**
- **Regulators**
  - **Need patients to help them understand the disease, assess risks and trade-offs, and improve the design of clinical trials**

InnoThink

If you ask them, they will respond

- 80% of the time and cost of research projects is generating high-quality data
  - The availability of such data is a major factor in de-risking R&D
- Passion shortens timelines, lower costs, and raises the probability of success
- It's more exciting to work with passionate people for whom failure is not an option

InnoThink

Need money

- Good news: it is getting cheaper!
  - New research models make it possible (indeed advisable) to run ambitious research programs on a shoestring
  - e.g., open-source, crowdsource, virtual pharma, public-private partnerships, prizes, drug repurposing, etc.
- CFS community is larger than many rare disease communities with successful drug development programs

InnoThink

Need leadership and passion

- It's already there!
- CFIDS created 1987
- Raised over $30m
- Has already created the networks and some of the infrastructure required

InnoThink

Thank you!

Questions?

(bhmunos@stanfordalumni.org)

Knowledge and Intuition to Reposition Drugs for CFS

Suzanne Vernon, PhD
Scientific Director
The CFIDS Association of America

The CFIDS Association of America

Leveraging patient-centered research to cure ME/CFS

Knowledge and Intuition to Reposition Drugs for CFS

Suzanne D. Vernon, Ph.D.
Scientific Director

Development of Safe and Effective Drug Therapies for Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME)

April 25-26, 2013

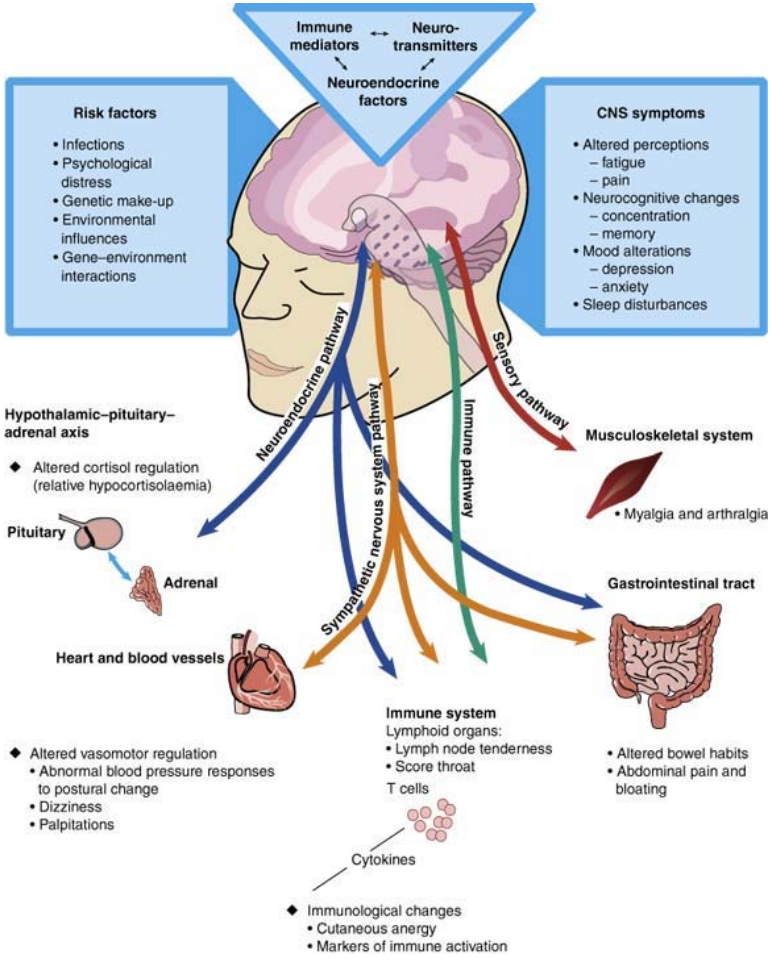
The CFIDS Association of America

- **Leader in ME/CFS Translational Research**
  - Strategic shift in 2008 to bridge the "Valley of Death"
  - Patient-centered research to de-risk and foster CFS drug R&D

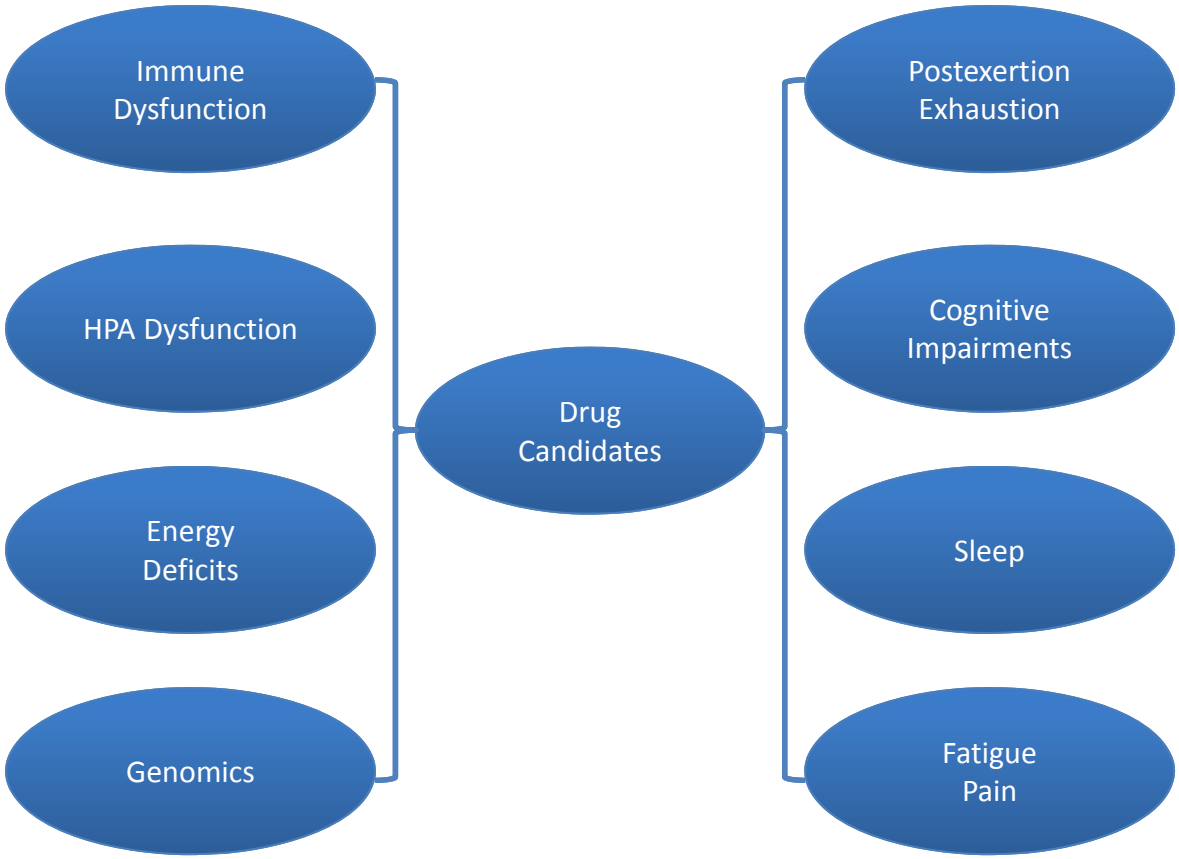
- **Our Innovation Pathway**
  - Build an infrastructure that makes it faster, easier and cheaper
    - SolveCFS BioBank – 800 ME/CFS and healthy controls; partnered with pharma and 8 academic investigators since 2010
    - Built a knowledgebase and data analysis/sharing platform
    - Our unique and extensive library, publications and knowledgebase
  - New research avenues – drug repurposing

Chronic Fatigue Syndrome (CFS)

- What's in a name?
  - CFS, ME, ME/CFS, CFS/ME, CFIDS
- 6,000 publications in PubMed describing all aspects of CFS
  - 1 million people in US, 17 million worldwide
  - Risk factors, pathophysiology described
  - $51 billion annual direct and indirect costs
  - FDA considers CFS a "serious condition"
- Over the past 25 years, >$150 million spent
  - Cause(s) have been elusive
  - Lack validated biomarkers for diagnosis and treatment
  - No regulatory framework for CFS
  - No FDA-approved treatment
  - No standardized, widely accepted clinical guidelines, symptom-based treatment

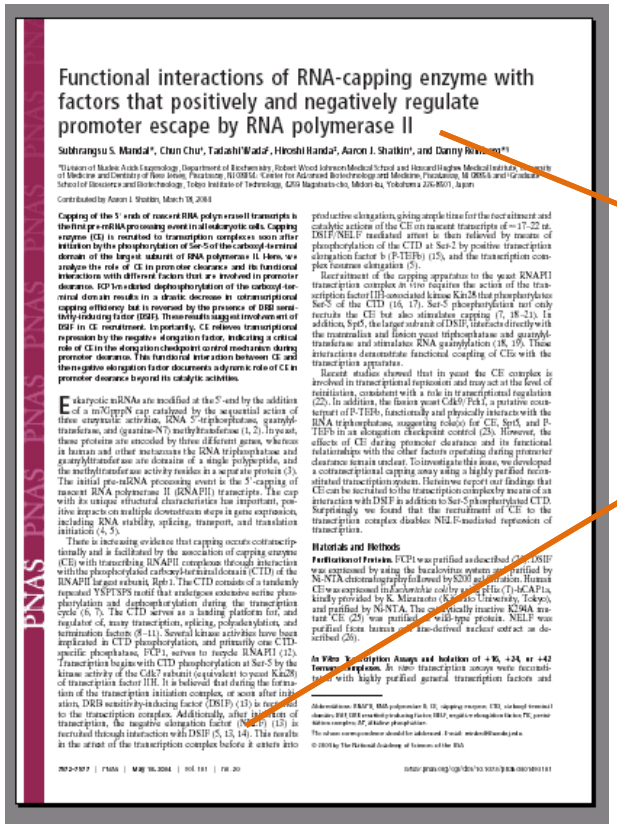


Drug Repurposing for CFS



- Well suited to multifactorial diseases
- Ideal for unmet medical need diseases where effective treatments are lacking and research spending is inadequate
- Drug safety is known, this accelerates development and reduces costs

Clinical Outcomes Search Space (COSS™)



Functional interactions of RNA-capping enzyme with factors that positively and negatively regulate promoter escape by RNA polymerase II

29,000 clinical outcomes
25,000 human targets
90,000 compounds

Extraction Engine

RNA polymerase II

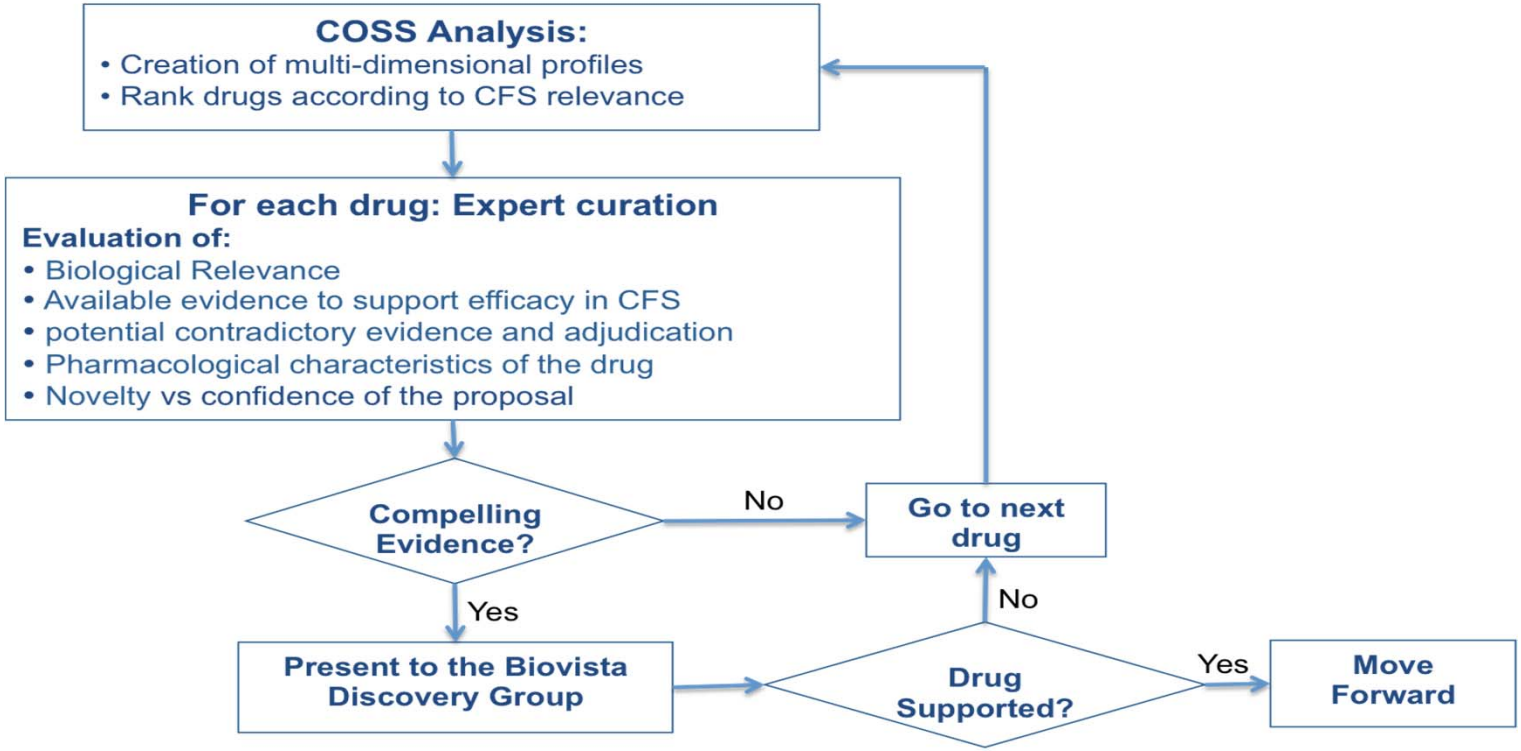
CTD phosphorylation

in some context

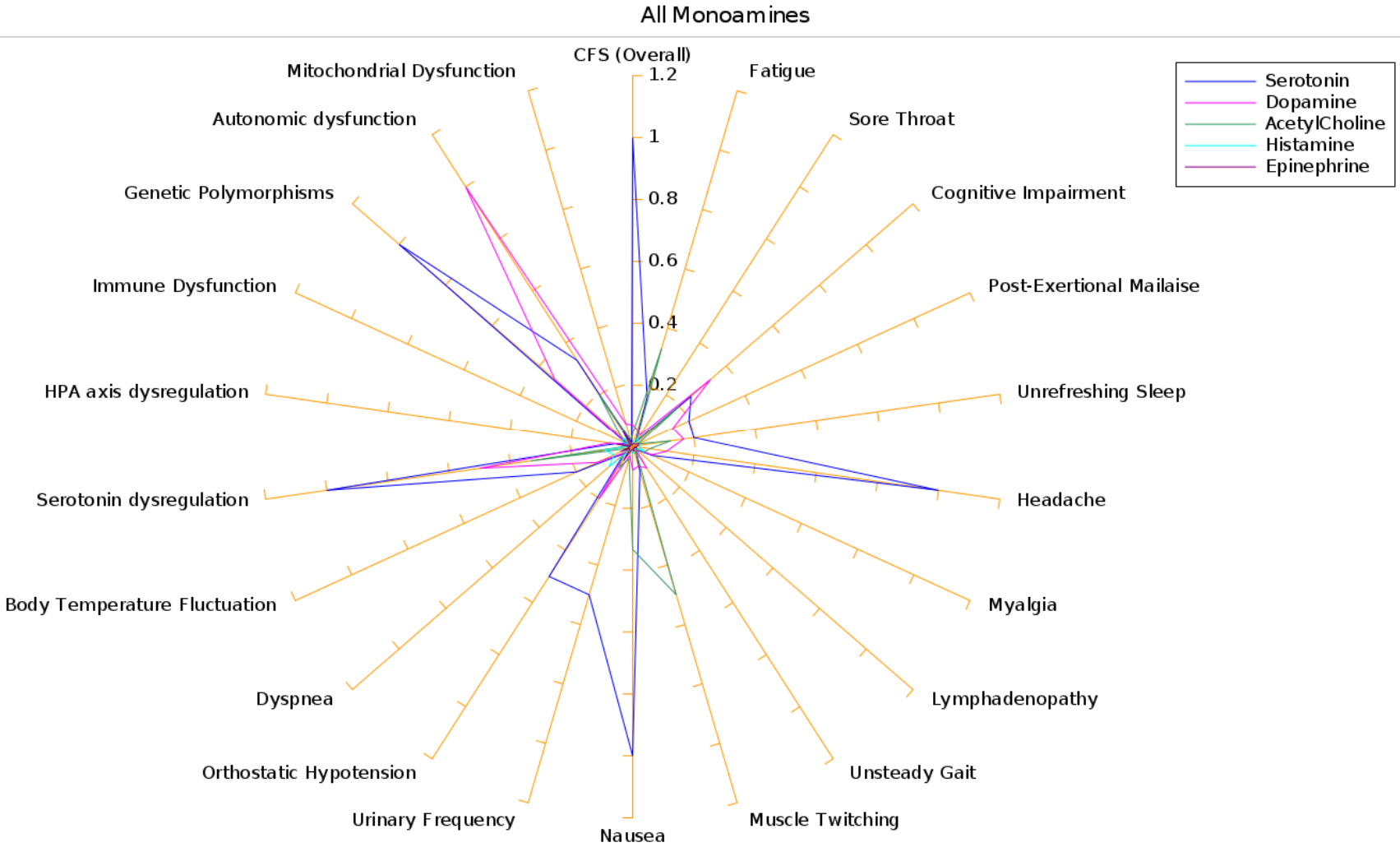
A Unique Profile

COSS™ for Repositioning for CFS

- Identify novel drug candidates for the treatment of CFS
  - Bibliographic knowledge on CFS pathophysiology and symptoms
- Identify biomarkers that may be used to monitor the response to treatment
  - Relevant to CFS pathophysiology and drug mechanism of action (MoA)
  - Use existing data including the SolveCFS BioBank to evaluate/validate

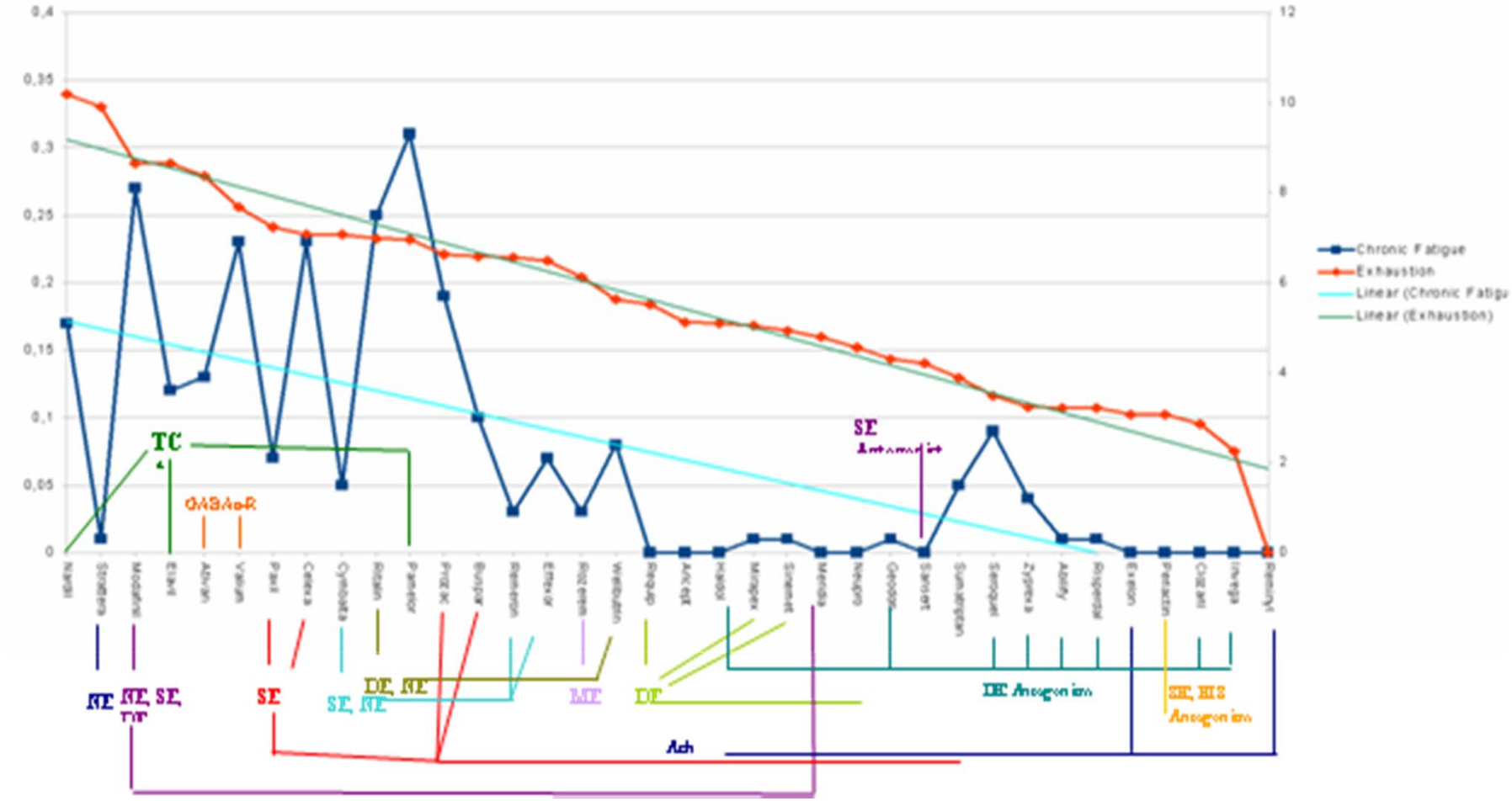


Correlation of Drugs with Symptoms



- The drugs that correlated with CFS symptoms and pathophysiological mechanisms that are related to the regulation of neurotransmitters (mostly monoamines)
- In order of decreasing bibliographical association: Serotonin > Dopamine > Acetylcholine > Histamine >= Epinephrine.

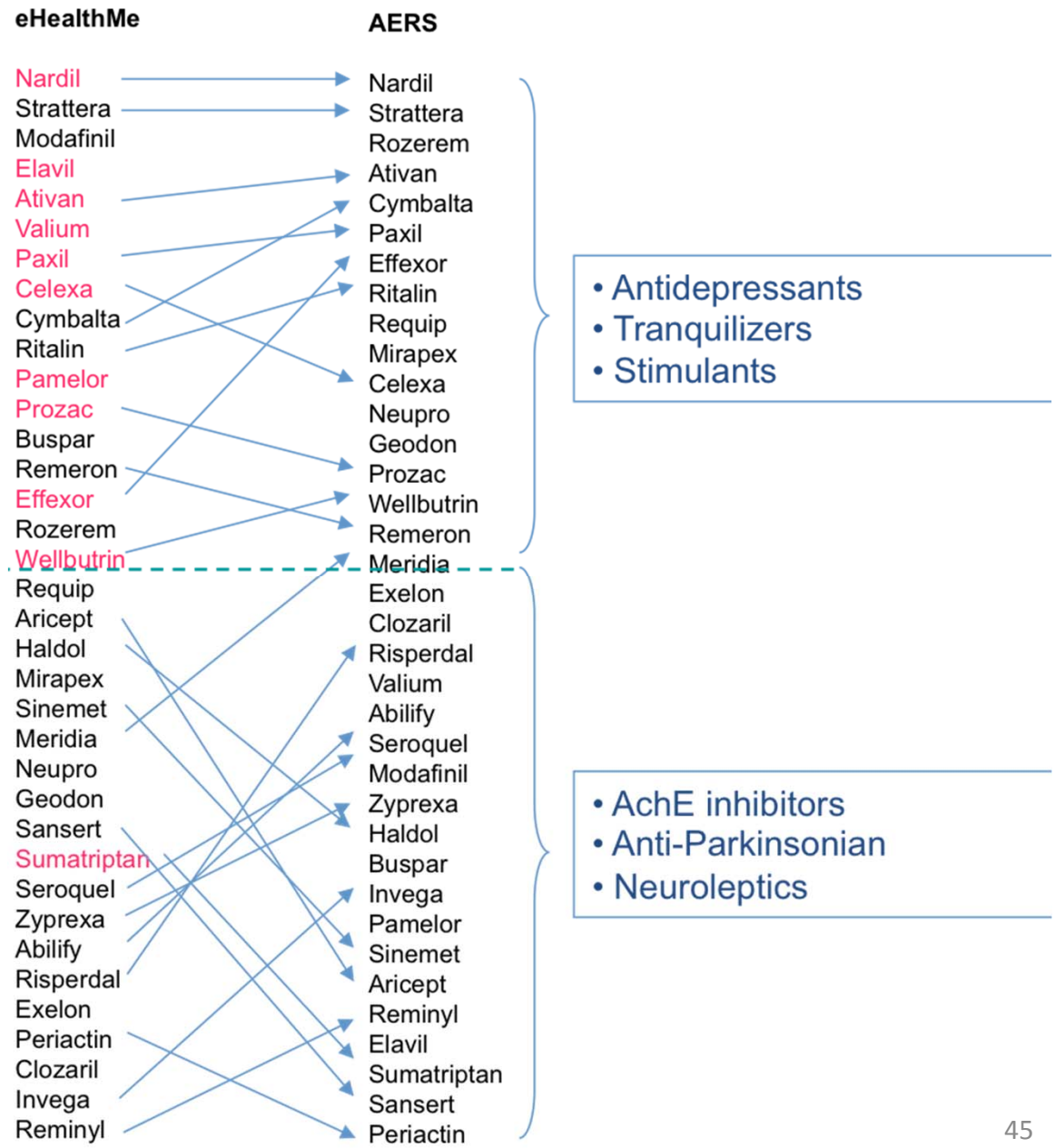
eHealthMe Adverse Events and Chronic Fatigue



- Serotoninergic & noradrenergic drugs associated with exhaustion
  - frequency of *exhaustion* co-reported with the drugs shown on the horizontal axis is represented by the *orange* graph (*right* vertical axis).
  - frequency of *chronic fatigue* that is co-reported with each drug is represented by the *blue* graph (*left* vertical axis)

Adverse Events and Chronic Fatigue

- Frequency of fatigue reports from eHealthMe and AERS for selected drugs
- Red indicates drugs that are used by CFS patients as reported in the SolveCFS BioBank



Summary of Results using COSS™

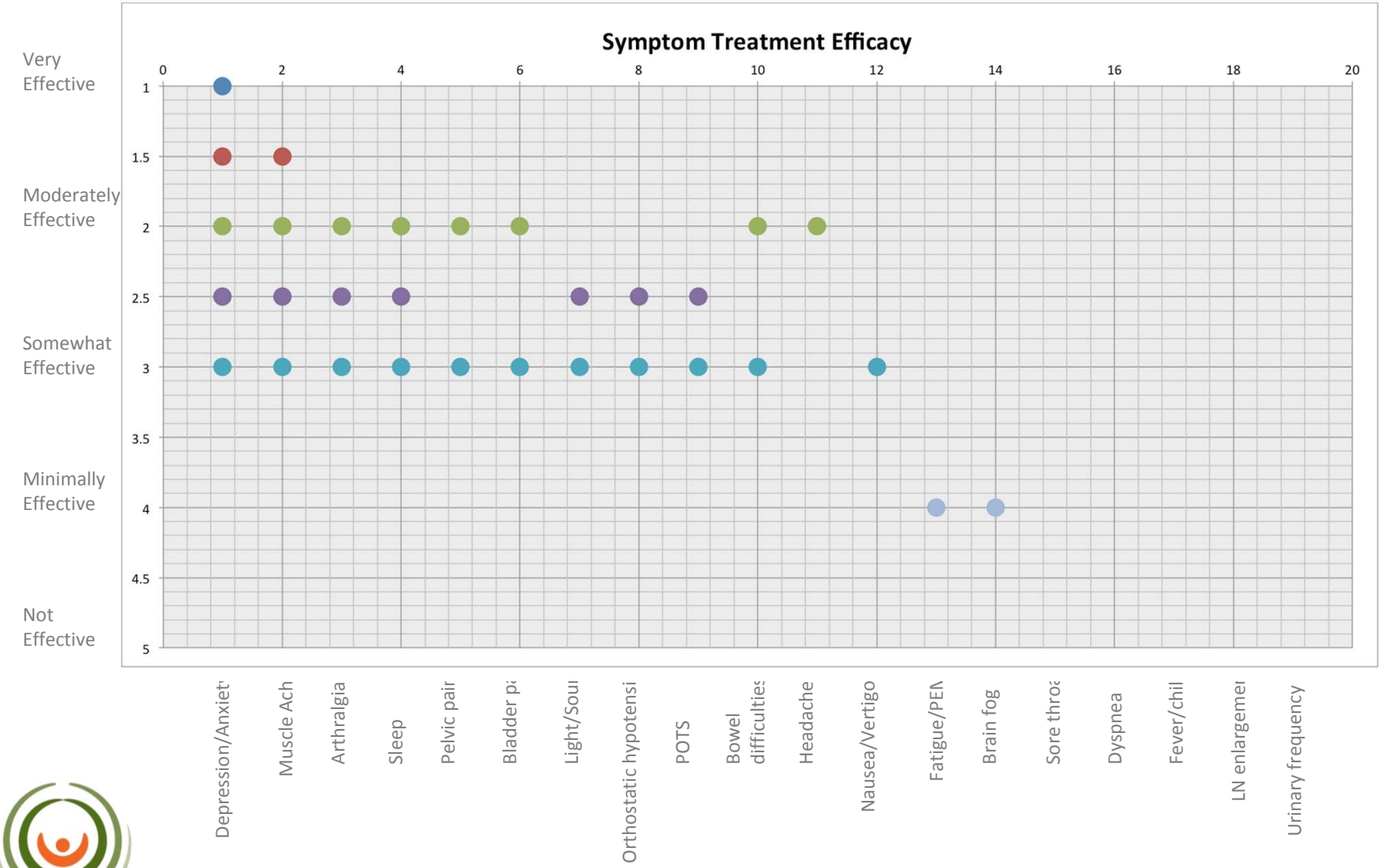
- CFS symptoms and pathophysiology correlate with the known mechanisms neurotransmitters as described in the biomedical literature
- *Counterintuitive observation*: Serotoninergic and noradrenergic drugs cause fatigue more frequently than neuroleptics. Fits with "Central Fatigue Hypothesis"
- Drug repurposing using the COSS™ platform has identified a two drugs that target at least 2 CFS symptoms
- The knowledge-based identification of these drugs was validated by patient-reported data from the SolveCFS Biobank data and clinical intuition data (shown next)
- Currently designing a proof-of-concept clinical trial to test these drugs as a combination therapy

Capturing Clinical Intuition

"…But the key is that a lot of the research in this to date have been out there on their own. They're clinicians who are following a series of patients for decades. And no one's been able to tap into the kind of information that they have …" – Dr. Kweder, 9/13/2012 Stakeholder Teleconference

- The CFIDS Association and Biovista created a web-based tool to investigate three main areas:
  - Efficacy of drugs currently used in the treatment of CFS symptoms
  - Alternative treatment options (nutritional supplements, fluids, pacings, etc.)
  - Treatment strategies: How are symptoms interrelated? Which symptoms are more important to treat first?

Clinical Intuition Results



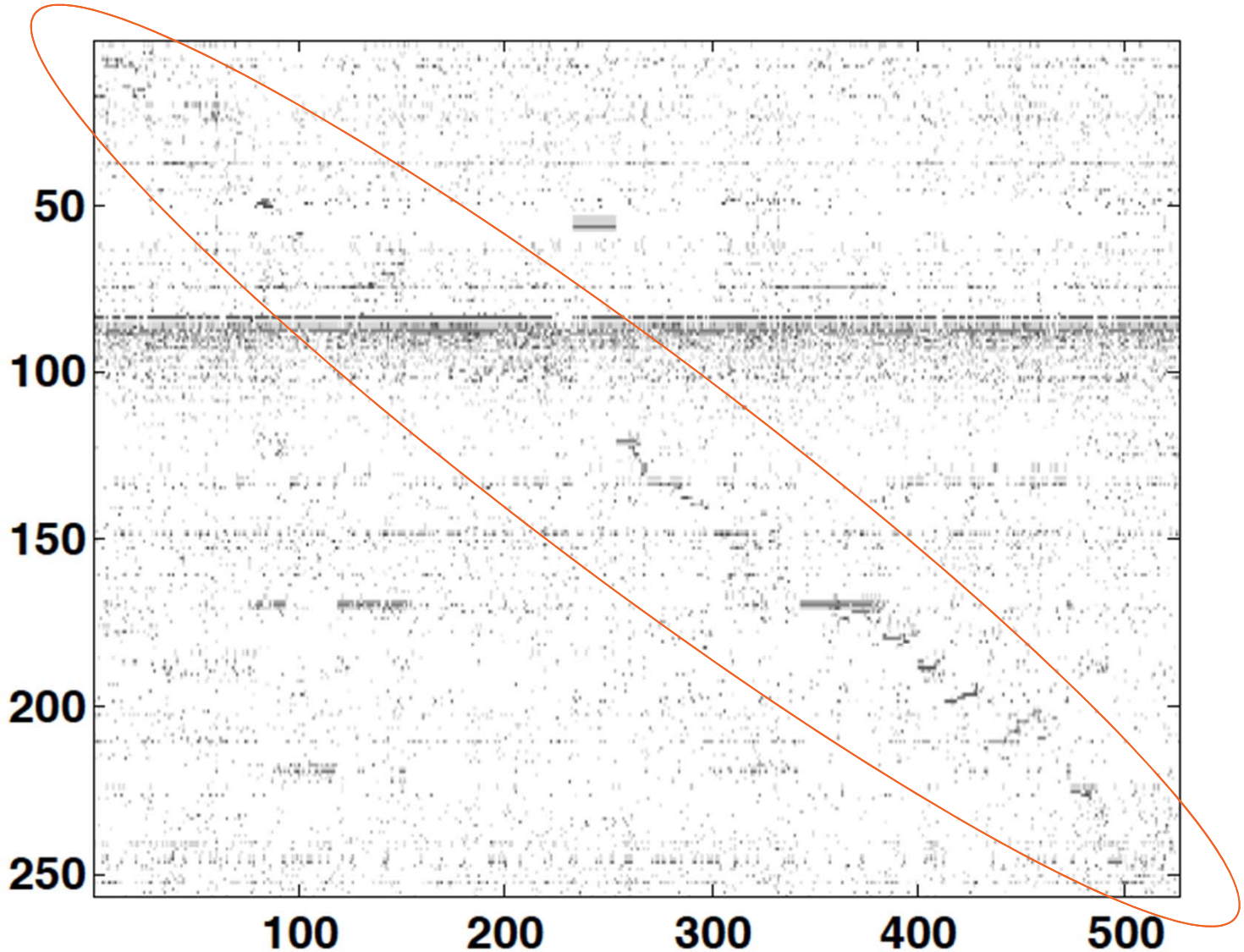
Clinical Intuition Validates Published Knowledge

- Drugs identified as moderate to very effective for treating specific symptoms (sleep, pain, fatigue) were those identified using the Biovista COSS™ platform based on correlations of symptoms and drug MoA.
- Vitamin B12 injections were reported as moderate to very effective for treating brain fog, although effect is transient
  - Gut microbiome differences between CFS and matched controls.
- Biovista COSS platform and clinicians identify 2 predominant CFS phenotypes:
  - **Immune** - sore throat, lymph node enlargement, fever and chills
  - **Autonomic** - fatigue, post-exertional malaise, non-restorative sleep, pain, headache, cognitive problems, and orthostatic intolerance are thought to be inter-related symptoms
  - *Clinicians identified young versus older CFS patients clear subtype*

Drug Development Survey

- Survey the patient community to gather responses to questions posed by the 20 questions posed by the FDA
  - open-ended text responses
- Questions were related to disease impact, symptoms and treatment
- Analyzed using Part-of-Speech parsing, word-sense disambiguation by matching UMLS concept IDs followed by PCA and bi-clustering.

Drug Development Survey



Pain
Muscle, lumbar, abdominal, facial, back eye, neck, chest, general body pain, joint, stomach

exhaustion
arthralgia
malaise
weakness, spasms, food sensitivities
sore throat

Non-drug therapies
Nutritional therapies
Diet modification
Anti-inflammatory drugs

Pain
Prednisone
Migraines

Activity modification

Next Steps

- Drug repurposing
  - Document preparation to request a pre-IND meeting for proof-of-concept (PoC) clinical trial for a combination therapy for ME/CFS
  - Use SolveCFS BioBank participants for PoC trial
- Optimize clinical intuition platform and expand use
  - Attempt to understand patient phenotype and co-morbid conditions
- Operationalize patient-centered passive and active data collection

The CFIDS Association of America

Leveraging patient-centered research to cure ME/CFS

The Physicians and Providers

ME/CFS Patients, Family and Friends

Thank you!

Drug Development and Review: FDA's Expedited Programs for Serious Conditions

Melissa Robb
Associate Director for Regulatory Affairs
Office of Medical Policy Initiatives
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Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. Food and Drug Administration
Protecting and Promoting Public Health

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Drug Development and Review: FDA's Expedited Programs for Serious Conditions

Melissa Robb
Associate Director for Regulatory Affairs
Office of Medical Policy Initiatives, CDER, FDA

CFS and ME Workshop
April 26, 2013

Disclosure

- I have no relevant financial relationships to disclose.

Background

Longstanding FDA goal to facilitate and expedite development and review of new drugs to address unmet medical need for serious conditions

- Existing Programs
  - Subpart E regulations (1988) - speeding the availability of new therapies for serious conditions with unmet medical need, while maintaining safety and efficacy standards
  - Accelerated Approval Regulations (1992)
  - Fast Track (1997)
  - Priority Review (1992)

FDASIA (2012) – Title IX

- Reinforces FDA commitment to expedited development
- Clarifies Accelerated Approval requirements
- Creates Breakthrough Therapy provision
- Requires FDA to issue draft guidance
  - On accelerated approval by July 2013
  - On breakthrough therapy designation by January 2014

How FDA Expedites Drug Development and Review

- Four expedited programs
  - Fast track designation
  - Breakthrough therapy designation
  - Accelerated approval
  - Priority Review

Common Terms

- **Serious conditions** - associated with morbidity that has substantial impact on day-to-day functioning. Includes life-threatening conditions.
- Seek to satisfy an **unmet medical need** by showing an advantage over **available therapy** (existing therapy, alternative treatment), if one exists.

Fast Track Designation

- Criteria
  - Serious condition
  - Nonclinical or clinical data demonstrate the potential to address unmet medical need
- Features
  - Actions to expedite development and review
    - Meetings with FDA to discuss study design and requirements for marketing approval
  - Rolling review allows for earlier submission and initiation of review

Breakthrough Therapy Designation

- Criteria
  - Serious Condition
  - Preliminary clinical evidence indicates the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development
- Features
  - Intensive guidance on efficient drug development
  - Organizational commitment
    - Involving senior managers and experienced review staff
    - Assigning a cross-disciplinary project lead to facilitate efficient review

Accelerated Approval

- Existing regulations- 21 CFR part 314, subpart H, and part 601, subpart E
- FDASIA provides additional flexibility and clarity to the accelerated approval pathway
  - Flexibility: Approval takes into account the availability or lack of alternative treatments
  - Clarity: Approval can be based on a clinical endpoint (intermediate clinical endpoint) that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit.

Accelerated Approval

- Criteria
  - Serious condition
  - Meaningful therapeutic benefit over available therapies
  - Demonstrates an effect that is reasonably likely to predict clinical benefit or an effect on an endpoint that can be measured earlier that is reasonably like to predict an effect
- Features
  - Shortens time to approval

Accelerated Approval

- Uses
  - Long disease course and extended period of time to measure clinical benefit of drug
  - Effect on surrogate or intermediate clinical endpoint occurs rapidly
- Examples
  - Cancers
  - HIV
- Requirements
  - Promotional materials
  - Postmarketing confirmatory trials

Priority Review Designation

- CDER Criteria
  - Demonstrates potential to be a significant improvement in safety or effectiveness
- Features
  - Marketing application reviewed in 6 months (compared to 10 months for priority review)

Tools and Approaches for Expedited Development

- Early communication between sponsor and FDA
- Flexible drug development programs that enable shorter, smaller, or fewer studies
- Emphasis on regulatory science

Looking Forward

- Anticipate draft guidance will publish July 2013
- Comment period
- Develop final guidance (FDASIA goal dates)

Resources

- Fast Track, Accelerated Approval and Priority Review
  http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm
- Fact Sheet: Breakthrough Therapies
  http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm
- FY 2012 Innovative Drug Approvals
  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM330859.pdf

Panel 1:
Audience Question and Answer Period

All Panelists

CHERRY BLOSSOMS ON THE TIDAL BASIN

Panel 2:
Symptoms and Treatments:
A View from Clinicians and Patients

Moderators:

Nancy Klimas, MD, FACP, FIDSA

Chair, Department of Clinical Immunology
Director, Institute of Neuro-Immune Medicine
Nova Southeastern University

Theresa Michele, MD

Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Panel 2:
Symptoms and Treatments: A View from Clinicians and Patients

- Lucinda Bateman, MD
  - Fatigue Consultation Clinic, Salt Lake City, Utah
- Lisa Corbin, MD, FACP
  - Associate Professor, Division of General Internal Medicine, University of Colorado Denver School of Medicine
- Lily Chu, MD, MSPH
  - International Association for CFS/ME, Patient
- Jose Montoya, MD, FACP, FIDSA
  - Professor of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine
- Jennifer Spotila, JD
  - Patient
- Christine Williams, MEd
  - Patient

Panel 2: Question 1

- What were your key takeaway messages from the discussion yesterday on the most significant symptoms experienced by patients with CFS and ME?
  - Please describe any significant differences in your experiences as clinicians and patients compared to yesterday's discussion.

Panel 2: Question 2

- Based on your expertise as clinicians and experience as patients, which symptoms of CFS and ME could be identified as valid, quantifiable and reliable outcome measures or endpoints in clinical trials to evaluate potential drugs to treat CFS and ME?

Panel 2: Question 3

- What are the key factors you take into account when making decisions to prescribe (as clinicians) or use (as patients) therapies to treat symptoms associated with CFS and ME?

Panel 2: Question 4

- Are there candidate agents that you think particularly warrant exploration in clinical trials?
  - If so, what endpoints do you think would be most valuable to study in association with the product(s)?

Panel 2:
Audience Question and Answer Period

All Panelists

CHERRY BLOSSOMS ON THE TIDAL BASIN

Panel 3:
CFS and ME Clinical Trial Endpoints and Design

Moderators:

Jordan Dimitrakoff, MD, PhD

Assistant Professor
Tufts University
Boston, MA

Edward Cox, MD, MPH

Director
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Clinical Trial Designs in CFS

Peter Rowe, MD
Professor of Pediatrics
Johns Hopkins University School of Medicine
Director
Chronic Fatigue Clinic
Johns Hopkins Children's Center

Clinical Trial Design in CFS

Peter C. Rowe, MD
Professor of Pediatrics
Sunshine Natural Wellbeing Foundation Professor
of Chronic Fatigue and Related Disorders
Director, Pediatric CFS Clinic
Johns Hopkins University School of Medicine, Baltimore, MD

JOHNS HOPKINS
MEDICINE

- Clinical trials in CFS from 1988-2013:
  - What has and hasn't worked?
  - Lessons from specific trials
- What is the ideal patient population?
  - Lessons from other illnesses
  - Lessons from CFS and FM studies
- What is the ideal endpoint?
- Potential designs to decrease heterogeneity

ACYCLOVIR TREATMENT OF THE CHRONIC FATIGUE SYNDROME

Lack of Efficacy in a Placebo-Controlled Trial

Stephen E. Straus, M.D., Janet K. Dale, R.N., Martin Tobi, M.B., Ch.B., Thomas Lawley, M.D., Olivia Preble, Ph.D., R. Michael Blaese, M.D., Claire Hallahan, M.S., and Werner Henle, M.D.

- Randomized crossover study of 27 with CFS (8M/19F)
- Mean duration of CFS 6.8 years
- All underwent clinical evaluation at NIH
- Subjects had to meet 1988 CDC criteria for CFS
- To select a group with an improved likelihood of treatment response, eligible subjects had to have titers $\geq$ 1:40 of antibodies to EBV EA.

INTERVENTION

- Each received IV acyclovir q8h for 7 days (500 mg/M^2) or placebo, then 30 days of outpatient therapy with 800 mg q8h or placebo.

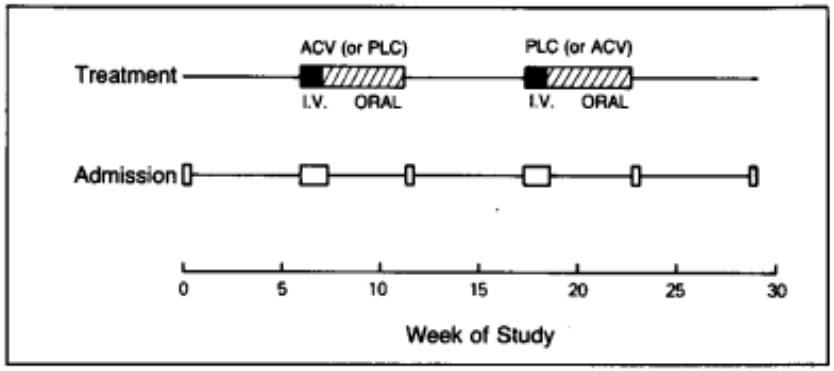


Figure 1. Design of the Placebo (PLC)-Controlled Acyclovir (ACV) Trial.

- Outcomes: daily energy level, wellness score (0-100), temp; weekly POMS for fatigue, vigor, anger, depression, anxiety

RESULTS

- 3/27 developed renal failure with IV acyclovir and were withdrawn
- 21/24 who completed the study rated themselves as improved during one stage of the study or the other
- 11 felt better during acyclovir phase, 10 during placebo
- Anxiety, depression significantly worse during acyclovir treatment phase
- Wellness score worse during acyclovir phase (mean difference of -1.08 ± 3.01; $P > .5$)

SYSTEMATIC REVIEWS OF TREATMENT

Whiting P, et al. JAMA 2001;286:1360-8
Chambers D, et al. J Royal Soc Med 2006;99:506-20.

- By 2006, 56 randomized and 14 non-randomized controlled clinical trials were included in review

Category	Examples
Behavioral	CBT, GET, Rehab
Immunological	Acyclovir, IVIG, Staph toxoid, Inosine pranobex, Terfenadine
Corticosteroids	Hydrocortisone, fludrocortisone
Other pharmacologic	Fluoxetine, galantamine, NADH, GH, Dextroamphetamine
Complementary	Massage, EFA, carnitine, liver extract

SYSTEMATIC REVIEWS OF TREATMENT: MAIN FINDINGS

Chambers D, et al. J Royal Soc Med 2006;99:506-20.

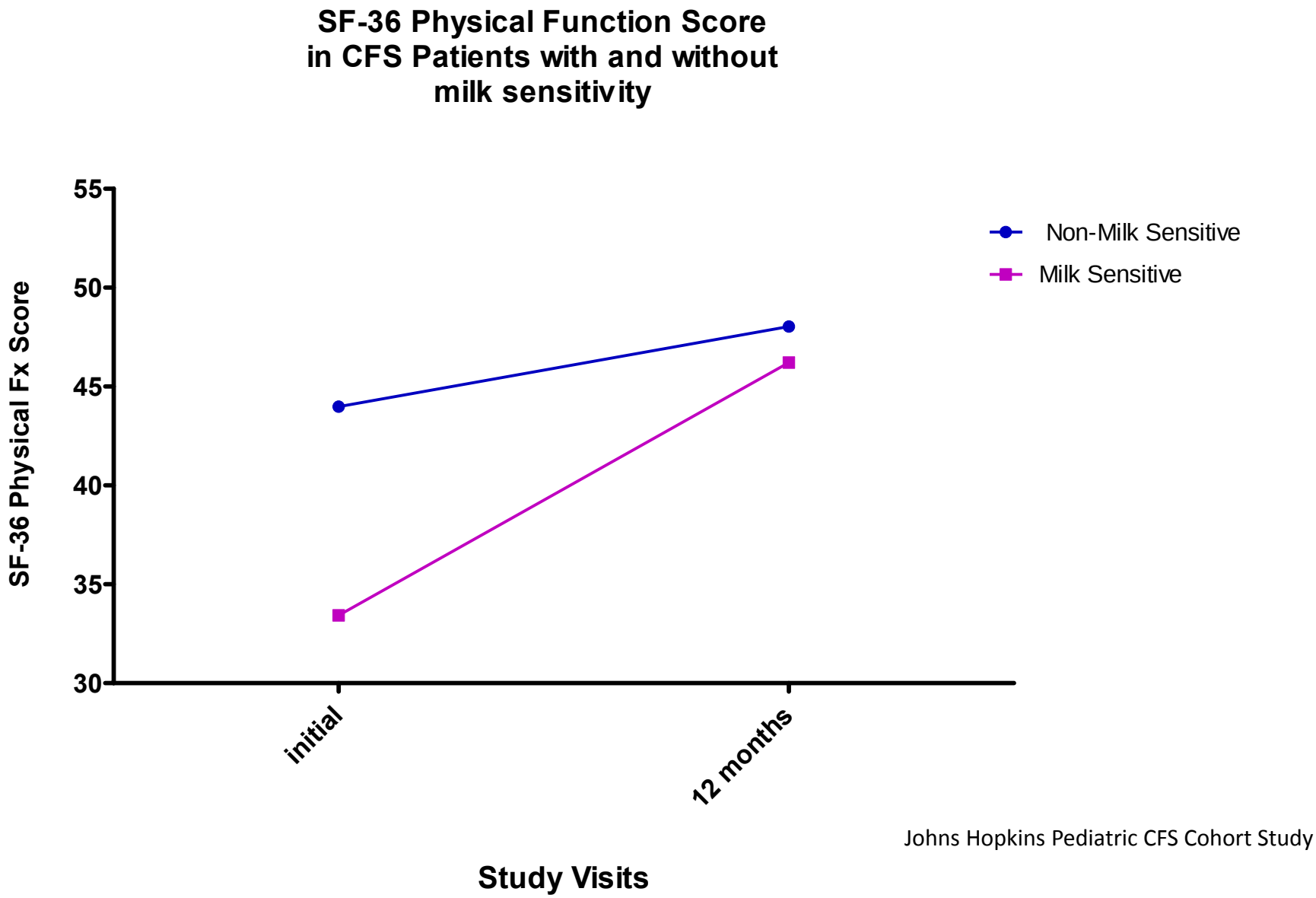
- A number of RCTs suggest that CBT, GET, and rehab may reduce symptoms and improve physical function
- Immunologic and anti-viral treatments may have beneficial effects but also can be associated with harmful side effects
- Most pharmacological treatments have not shown beneficial effects

CFS TRIALS: THE CHALLENGE OF HETEROGENEITY

Onset	Abrupt/infectious
	Gradual
Co-morbidities	Pain/FM
	Migraine, IBS, TMD, dysmenorrhea
	Allergies
	Orthostatic intolerance
	Joint hypermobility
	Anxiety/depression

CFS TRIALS: THE CHALLENGE OF HETEROGENEITY

- Heterogeneity can be reduced by careful subject selection, clear case definition and eligibility criteria (especially for subsets)
- Flares in co-morbid illnesses can occur in RCTs and have the potential to obscure treatment effects
- Given the heterogeneity of CFS and OI, studies of single agents will need large sample sizes



Johns Hopkins Pediatric CFS Cohort Study

SAMPLE SIZES IN EARLY NEGATIVE TRIALS

• Acyclovir	Crossover	N=27 (24) per group
• IVIG	RCT	N=15 per group
• IVIG	RCT	N= 23 IVIG, 26 placebo
• Terfenadine	RCT	N=15 per group
• HC	RCT	N=35 per group
• HC	Crossover	N=32 per group
• Phenelzine	RCT	N=12 per group
• Fludrocort	Crossover	N=25 per group

SAMPLE SIZE IN POSITIVE TRIALS

Pregabalin in FM

N=529

131 – placebo

132 – pregabalin 150 mg daily

134 – pregabalin 300 mg daily

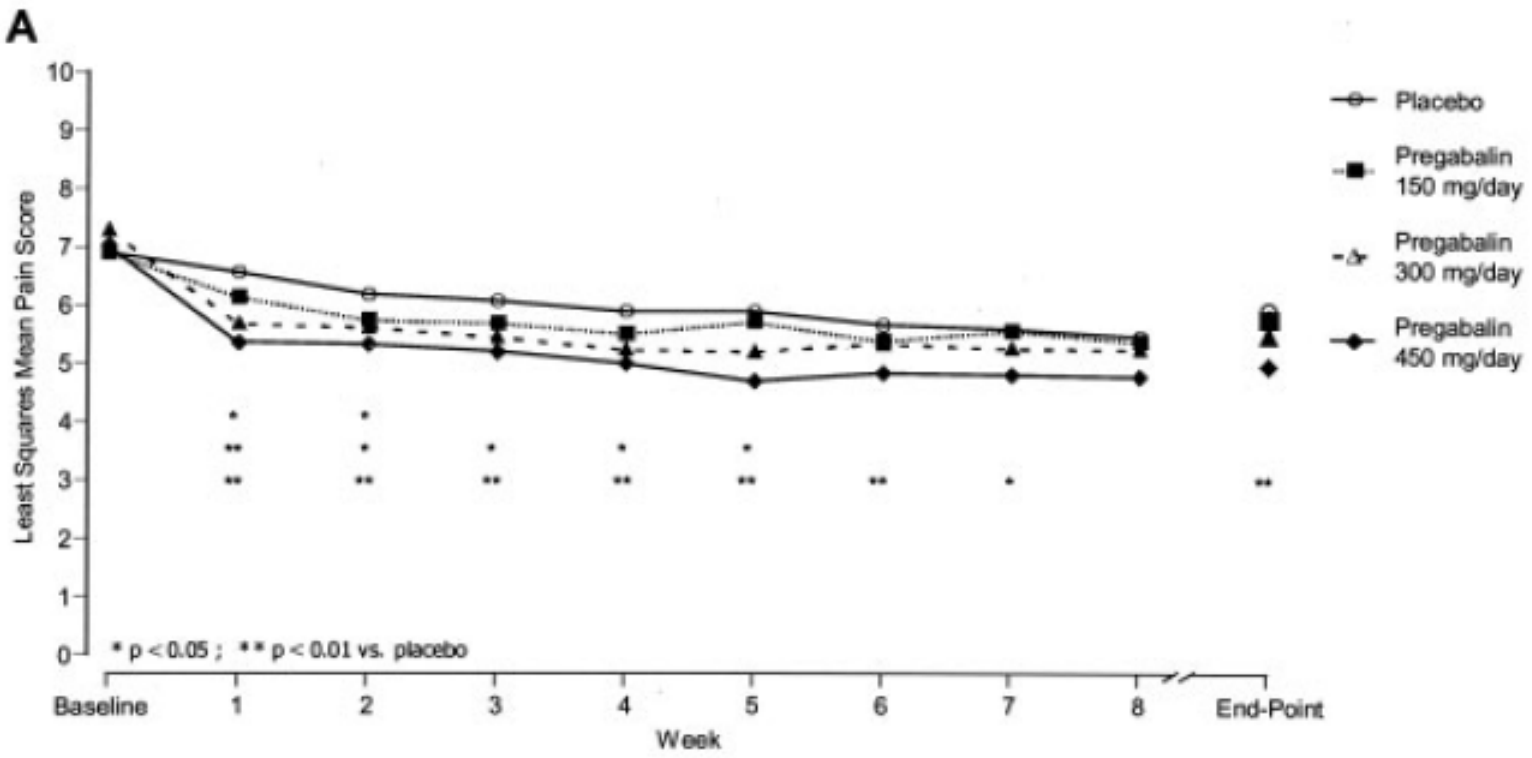
132 – pregabalin 450 mg daily

1° outcomes:

Daily pain scale (0-10)

21.4% had > 30% improvement (P < .003)

Pregabalin for the treatment of fibromyalgia syndrome: Results of a randomized, double-blind, placebo-controlled trial



Arthritis & Rheumatism
Volume 52, Issue 4, pages 1264-1273, 7 APR 2005 DOI: 10.1002/art.20983
http://onlinelibrary.wiley.com/doi/10.1002/art.20983/full#fig2

SAMPLE SIZE IN SUCCESSFUL TRIALS

PACE study N=641, ~ 160 per group

1° outcomes:

SF-36 physical function (0-100)
Chalder fatigue scale (0-33)

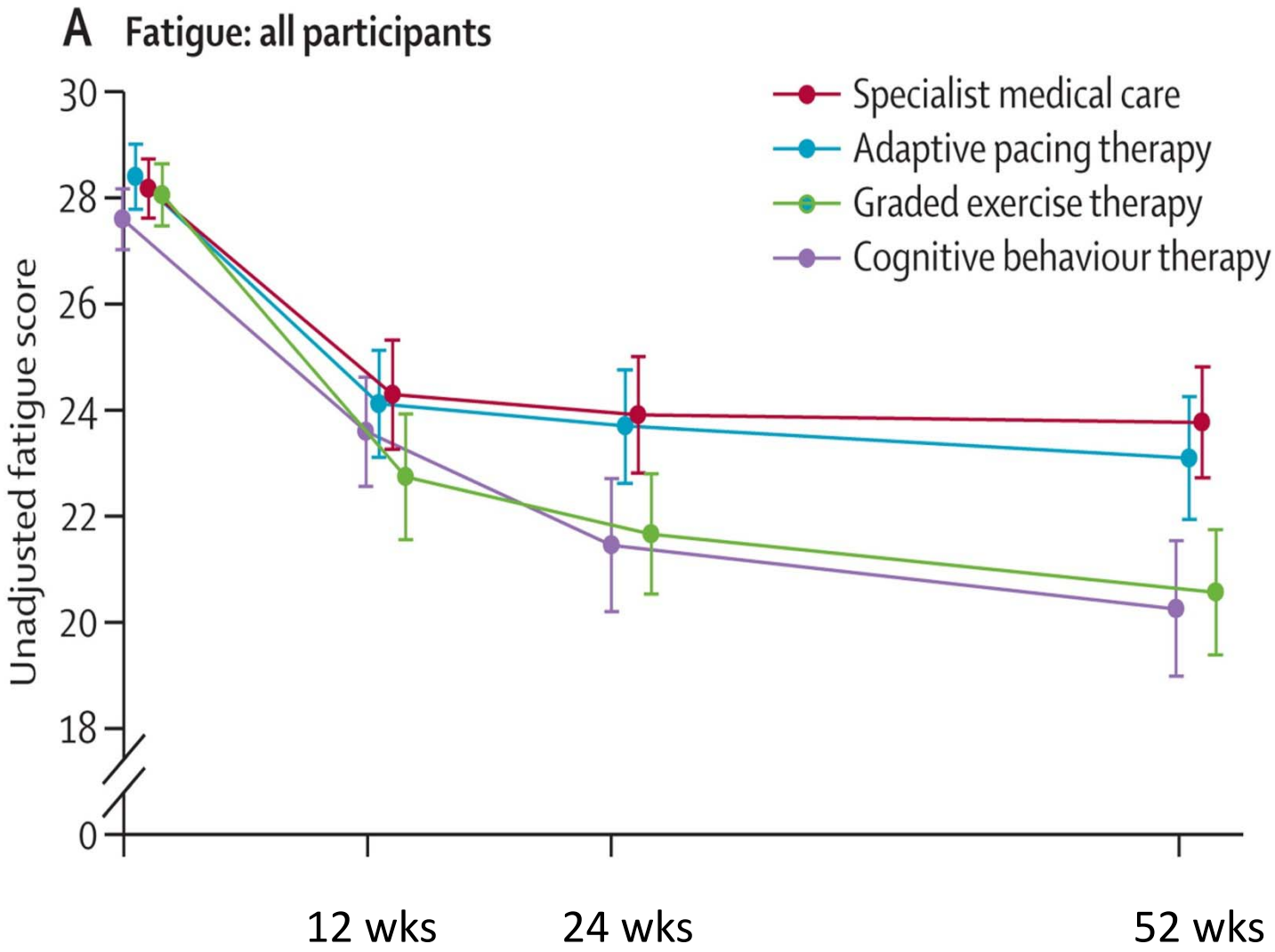
2° outcomes:

Clinical Global Impression Scale
Work and Social Adjustment
6 minute walk
Sleep, HADS, CFS symptoms, PEM

PACE TRIAL RESULTS

Specialist Medical Care (SMC) vs. SMC + CBT

	SMC	SMC + CBT	P
FATIGUE			
Baseline	28.3	27.7	
52 weeks	23.8	20.3	
Mean Difference		- 3.4	< .001
% improved by 2 points	65%	76%	
SF-36 PHYSICAL FUNCTION			
Baseline	39.2	39.0	
52 weeks	50.8	58.2	
Mean Difference		+ 7.1	.001
% improved by 8 points	58%	71%	



White PD et al. PACE trial. Lancet 2011

Fludrocortisone Acetate to Treat Neurally Mediated Hypotension in Chronic Fatigue Syndrome

A Randomized Controlled Trial

JAMA. 2001;285:52-59

JHU: PC Rowe, K DeBusk, H Calkins, S Snader

NIH: R McKenzie, G Sharma, N Soto, P Hohman, B Cuccherini, S Straus

Supported by grant AI 39500 (Dr. Rowe), GCRC RR00052, and the CFIDS Assoc. of America to the JHU investigators

16 year old with fatigue

Healthy and active until 9 mo. before visit

Insidious onset of fatigue

Sleeps 12 hrs per night, awakens unrefreshed

Has to lie down after showering

Has to lie down the day after an active day

Difficulty concentrating, muscles sore, HA, LH

Unable to attend school

16 year old with fatigue

- On exam: Acrocyanosis
- Standing test: HR 80 → 121 in 10 min
- Tilt test: Symptoms: fatigue, warmth, LH, nausea, diaphoresis
  Presyncope at 17 minutes
  BP 117/81 →78/48 (HR 70)
- Diagnosis: CFS, POTS, NMH
- Treatment: Increased salt and fluid intake
  Fludrocortisone, potassium

16 year old with CFS: Early Follow-up

- Improvement in all symptoms within 2 wks
- Began working 2 jobs, feeding livestock at family farm, able to spend time with friends
- Full school attendance
- Fatigue only after 45 minutes of swimming
- Standing test on Florinef:

  HR 76 to 86 after 10 min

STUDY QUESTION

Will individuals with CFS and NMH have a greater improvement in

(1) self-reported well being

(2) objective orthostatic tolerance

9 weeks after starting treatment with fludrocortisone than they will after starting placebo?

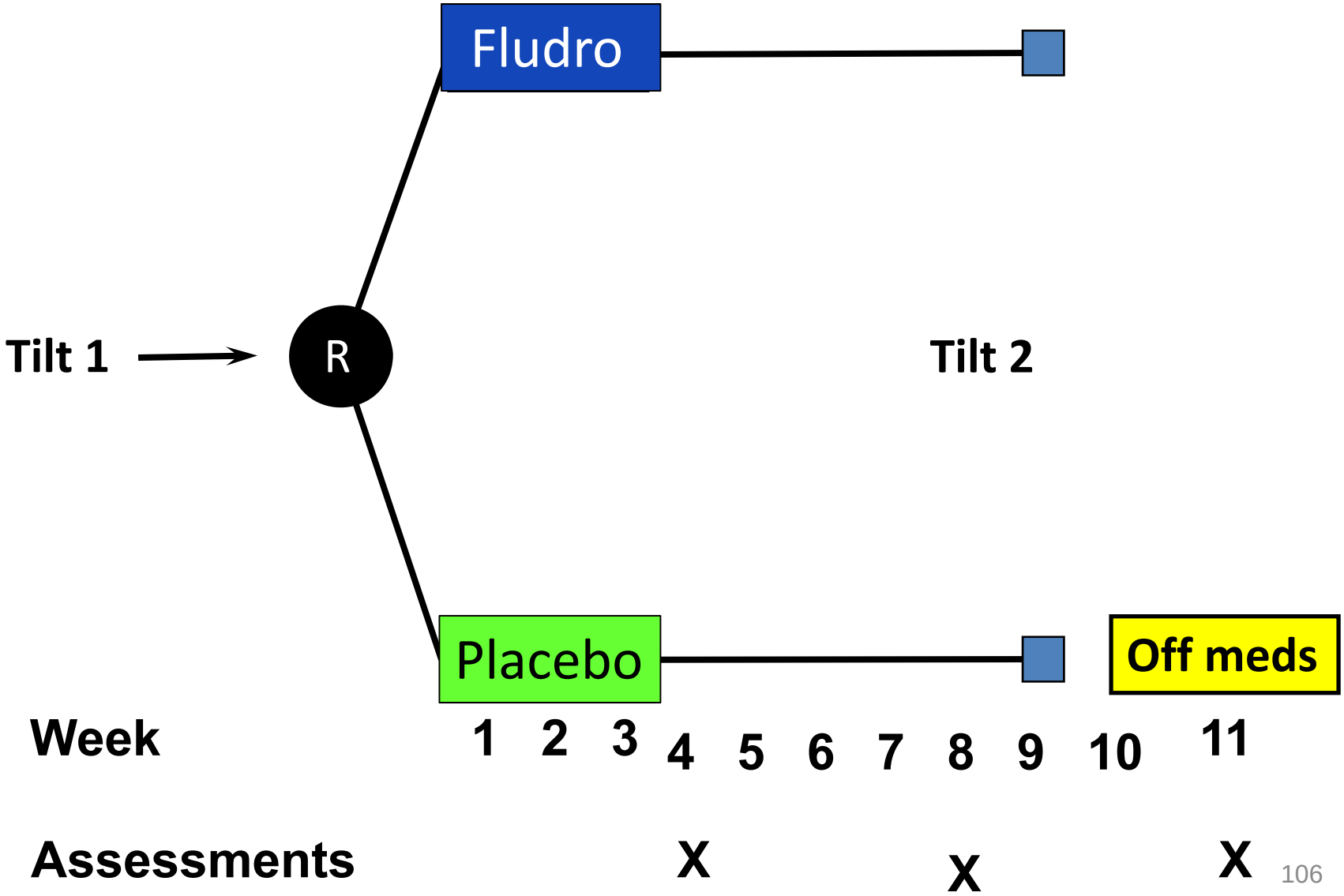
INCLUSION CRITERIA

- Age 18-50 yrs
- Satisfy 1994 Fukuda criteria for CFS
- Have undergone an evaluation to exclude other causes of chronic fatigue
- Hypotension during stage 1 or 2 of HUT
- At least moderate severity of symptoms at baseline
- Able to walk without assistance

STUDY DESIGN

- Randomized, placebo-controlled, double-blinded
- Stratified by center and by disease duration
  (< 3 yrs vs ≥ 3 yrs)
- Fludrocortisone 0.025 mg/d for week 1, then 0.05 mg for week 2, then 0.1 mg/d X 7 weeks.
- Fluid intake 2 L/d
- All patients received potassium chloride 10 mEq/d, and were asked to remain on usual sodium intake

STUDY DESIGN



OUTCOME MEASURES: PRIMARY

- % with a clinically important 15 point improvement in well being, as measured by the global Wellness Score:

  "How have you felt over the past 24 hours?"

  "For the wellness score, record a number between 0 and 100 (0=dying, 100=the best you can imagine a person to feel)."

- Recorded <u>daily</u> throughout the study

OUTCOME MEASURES: SECONDARY

- Changes in symptom scores
  - Profile of Mood States
  - Wood Mental Fatigue Inventory
  - Duke Activity Status Index
  - Beck Depression Inventory
  - SF-36
- % tolerating one further stage of tilt
- Adverse effects

SAMPLE SIZE ASSUMPTIONS

- 15-point change in global Wellness score is clinically meaningful
- 35% with 15-point improvement in treatment group
- 10% with 15-point improvement in control group
- alpha 0.05, Beta 0.20
- Sample size: N=100; 50 per group

CLINICAL FEATURES AT ENTRY

Characteristic	Placebo	Fludrocortisone	P
	N=50	N=50	
Age	37.3 (9.3)	36.2 (7.4)	.50
Female (%)	66	66	1.00
Working (%)	53	56	.84
Duration of CFS	6.0 (4.9)	6.9 (6.4)	.40
CFS > 3 yr (%)	72	70	.83

RESULTS: PRIMARY OUTCOMES

Improvement in Wellness	Placebo	Fludro	P
5-point	34%	28%	.52
10-point	12%	18%	.58
15-point	**10%**	**14%**	**.76**
20-point	6%	10%	.72
Mean change	2.7 (10.0)	3.8 (11.5)	.71

RESULTS: SECONDARY OUTCOMES

No differences between groups in:

WMFI, BDI, DASI

POMS vigor or fatigue subscales

SF-36 physical function or mental health

Supine HR, SBP, DBP at 2nd tilt

Normal tilt in week 9 (9/41 vs 4/33)

Outcome by center

Adverse events

CONCLUSION

- Fludrocortisone is not efficacious when used alone for treating NMH in adults with CFS

The PI returns to the clinic . . .

16 yr old with CFS: 10 year Follow-up

- After RCT, any attempt to wean Florinef was associated with the return of impressive fatigue, despite good level of exercise and physical conditioning
- Off Florinef: wellness 50-70/100

  On Florinef: wellness 85-90/100

How to reconcile the study results and the clinical observations?

CLINICAL FEATURES AT ENTRY

Characteristic	Placebo	Fludrocortisone	P
	N=50	N=50	
Age	37.3 (9.3)	36.2 (7.4)	.50
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Working (%)	53	56	.84
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CFS > 3 yr (%)	72	70	.83

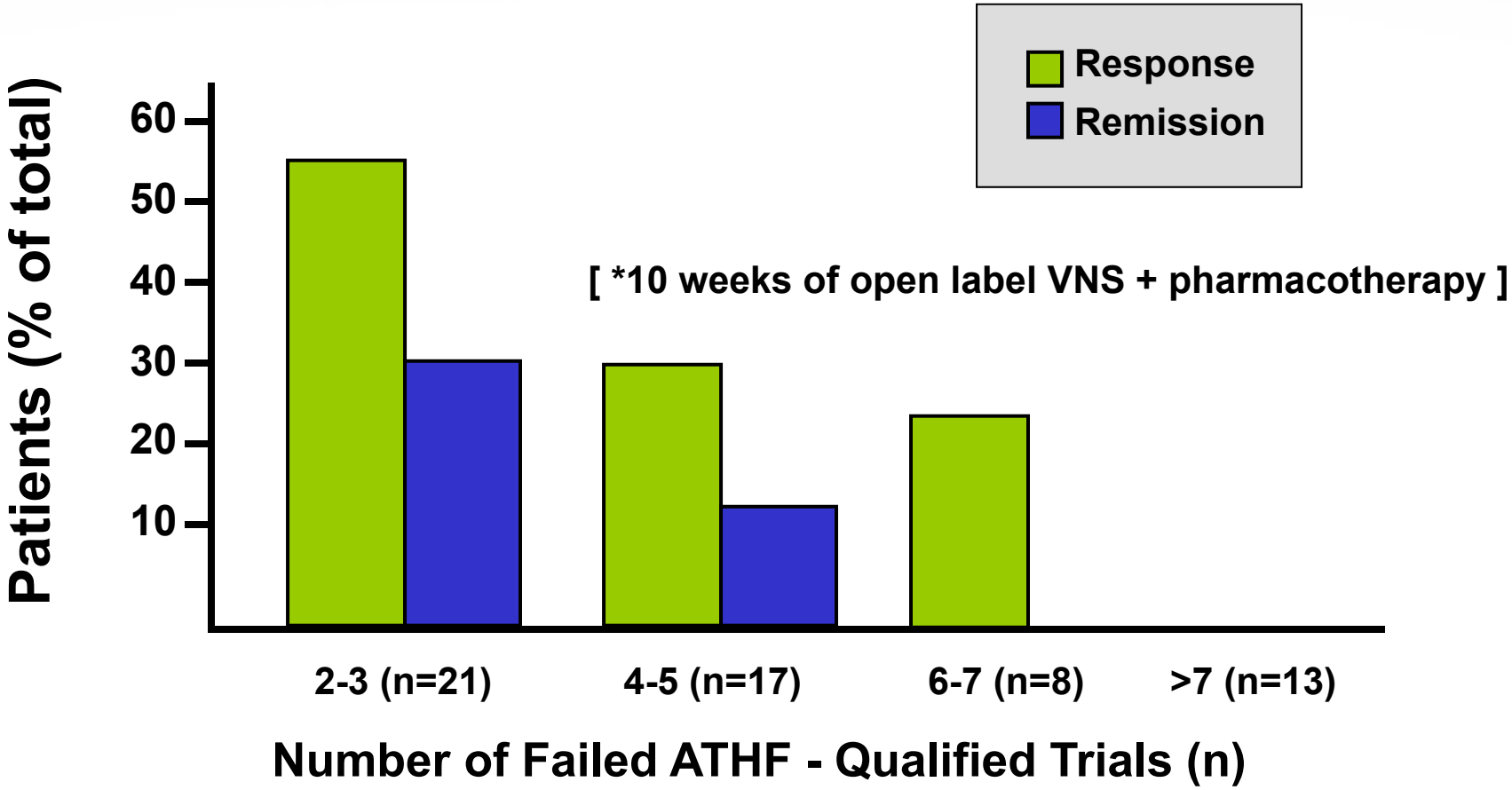
RESULTS: SUBGROUP ANALYSES (defined before unblinding)

	N with 15-point improvement	
Feature	Placebo	Fludrocortisone
CFS < 3 yrs	0/14	4/15
Age < 30 yrs	0/9	3/12

Patients with prolonged CFS may be more refractory to treatment; 71% had CFS > 3 years.

- Clinical trials in CFS from 1988-2013:
  - What has and hasn't worked?
  - Lessons from specific trials
- What is the ideal patient population?
  - Lessons from other illnesses
  - Lessons from CFS and FM studies
- What is the ideal endpoint?
- Potential designs to decrease heterogeneity

Influence of Past Treatment Resistance on Future Treatment Response*

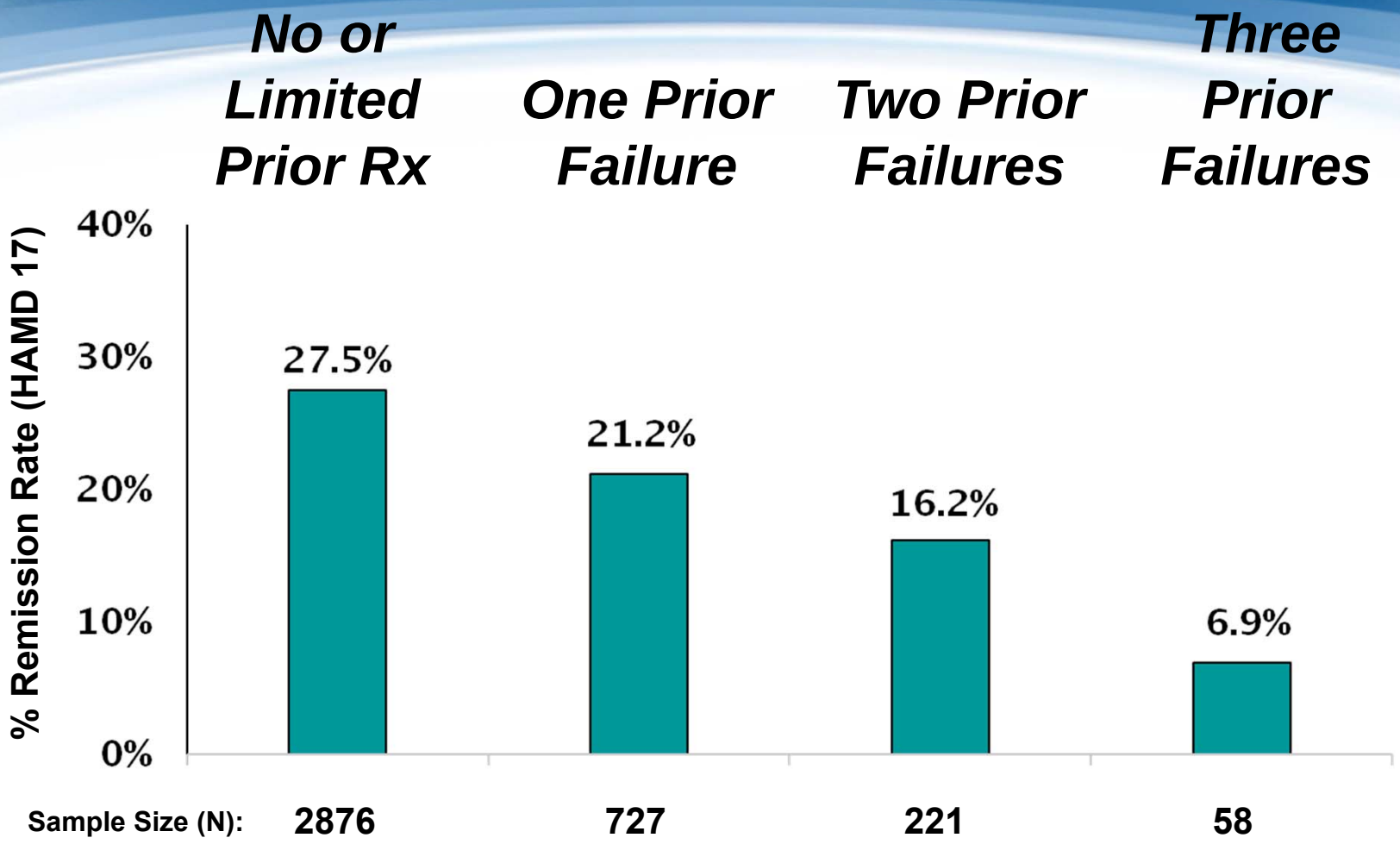


Sackeim, et al (2001)

Slide courtesy of MA Demitrack

NEURONETICS

Acute Outcome Worsens with Increasing Number of Prior Treatment Failures



Slide courtesy of MA Demitrack

Trivedi et al. (Am J Psychiatry, 2006); Rush et al. (NEJM, 2006);
Fava et al (Am J Psychiatry, 2006); McGrath et al (Am J Psychiatry, 2006)

NEURONETICS

CFS STUDY SUBJECTS

"…because CFS by definition develops after a substantial period of time has elapsed, and as many treatment studies have obtained treatment samples based on self or clinician referral to tertiary care medical centers, the populations under study often represent patients who are among the more refractory to any further treatment intervention."

Demitrack MA, Pharmacogenomics 2006;7 (3):521-8.

NEW ONSET CASES FOR CFS STUDIES?

observations from studies with positive findings

STUDY	DURATION OF ILLNESS
PACE trial (CFS)	2.7 yrs (1.3-5.7)
Rituximab trial (CFS)	5.1 yrs Rituximab 8.1 yrs placebo (P=.09)
Dextroamphetamine trial (CFS)	7.1 yrs Dexamphet 5.6 yrs placebo
Pregabalin (FM)	8.5 yrs
Milnacipran (FM)	4.1 yrs

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- What is the ideal endpoint?
- Potential designs to decrease heterogeneity

OPEN ACCESS Freely available online

PLoS one

Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study

Øystein Fluge[1]*, Ove Bruland[1,2], Kristin Risa[1], Anette Storstein[3], Einar K. Kristoffersen[4], Dipak Sapkota[1], Halvor Næss[3], Olav Dahl[1,5], Harald Nyland[3], Olav Mella[1,5]

1 Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway, **2** Department of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway, **3** Department of Neurology, Haukeland University Hospital, Bergen, Norway, **4** Department of Immunology and Transfusion Medicine, Haukeland University Hospital, and The Gade Institute, University of Bergen, Bergen, Norway, **5** Institute of Internal Medicine, Section of Oncology, University of Bergen, Bergen, Norway

October 2011 | Volume 6 | Issue 10 | e26358

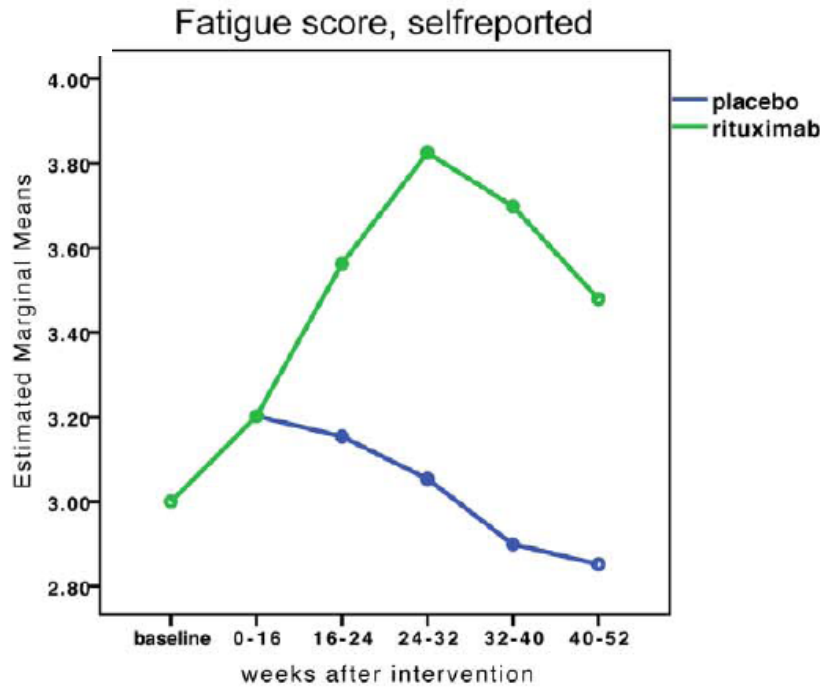
OUTCOME MEASURES: PRIMARY

- Baseline VAS symptoms

1= no symptom, 10=very severe symptom

- Follow-up VAS of change in last 2 weeks vs. baseline:
  - 0 Major worsening
  - 1 Moderate worsening
  - 2 Slight worsening
  - 3 No change
  - 4 Slight improvement
  - 5 Moderate improvement
  - 6 Major improvement

- Fatigue score calculated as mean VAS for Fatigue, Post-exertional exhaustion, need for rest, daily functioning



Rituximab - Placebo						
difference:	0.00	0.00	0.41	0.77	0.80	0.63
95% CI, lower:		-0.31	-0.28	0.16	0.16	-0.09
95% CI, upper:		0.31	1.10	1.38	1.44	1.34
p-values:		1.00	0.23	0.016	0.016	0.083
p-values, adj.:		1.00	0.46	0.08	0.064	0.25

Clinical responses in the Rituximab and Placebo groups, and response durations for patients with significant responses, derived from self-reported fatigue scores during 12 month follow-up.

		Rituximab N=15	Placebo N=15	P
Clinical responses	Major	9 (60%)	1 (7%)	.002
	Moderate	1 (7%)	1 (7%)	
	Overall (%); 95% CI	10 (67%) (41-85%)	2 (13%) (4-38%)	.003
Response duration in wks, mean (range)		25 (8 - > 44) n=10	41 (34 - > 48) n=2	

CFS STUDY ENDPOINTS

- VAS scores of fatigue and specific CFS symptoms (including frequency and severity/impact)
- Fatigue scale
- Measures specific to outcome of interest
- General QOL measure
- Activity measure (questionnaire or mean # steps/day)
- Functional measure (work/school attendance)
- Global Clinical Measure of Change (patient)
- Global Clinical Measure of Severity (clinician)

- Clinical trials in CFS from 1988-2013:
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- What is the ideal patient population?
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- What is the ideal endpoint?
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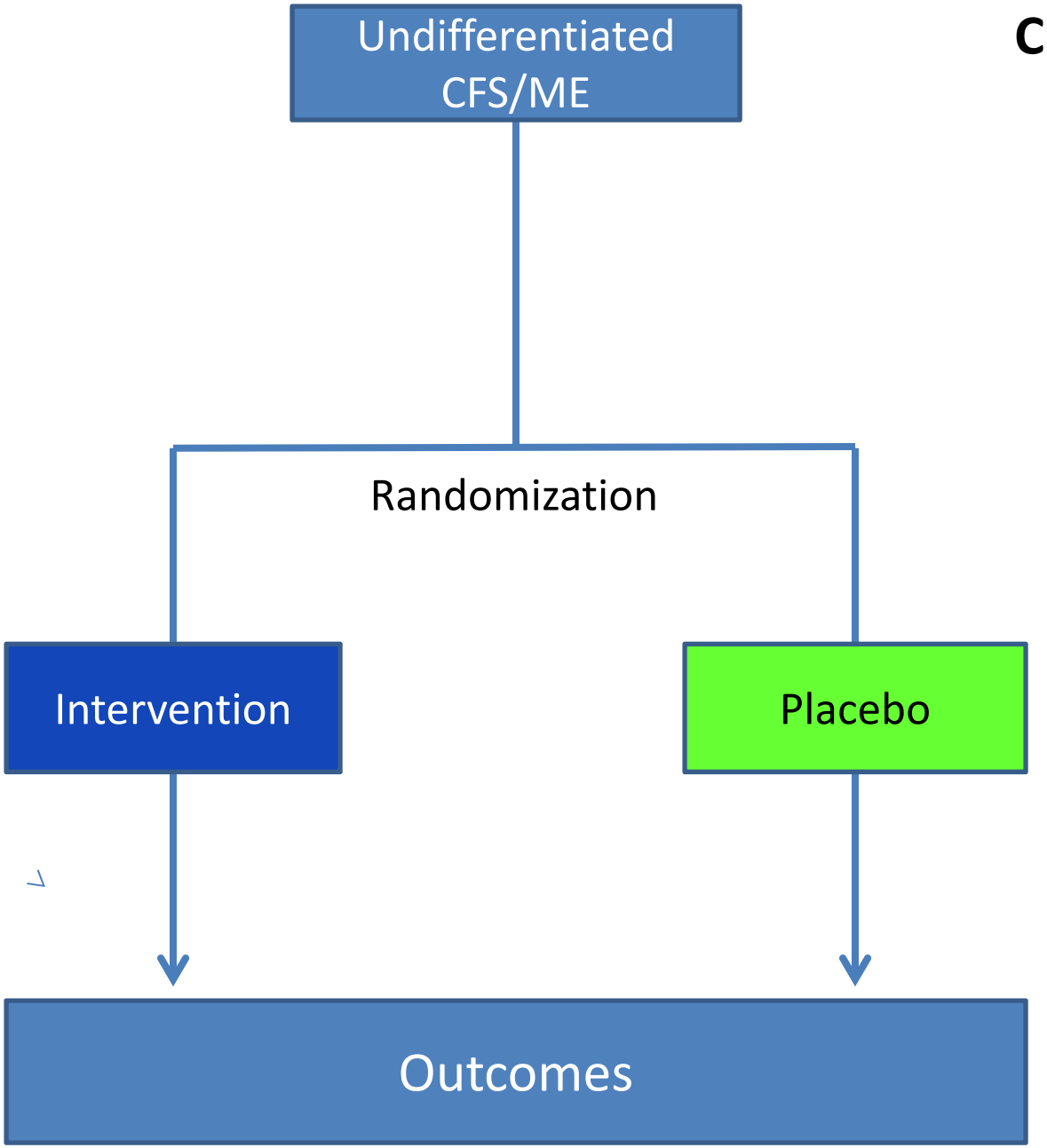
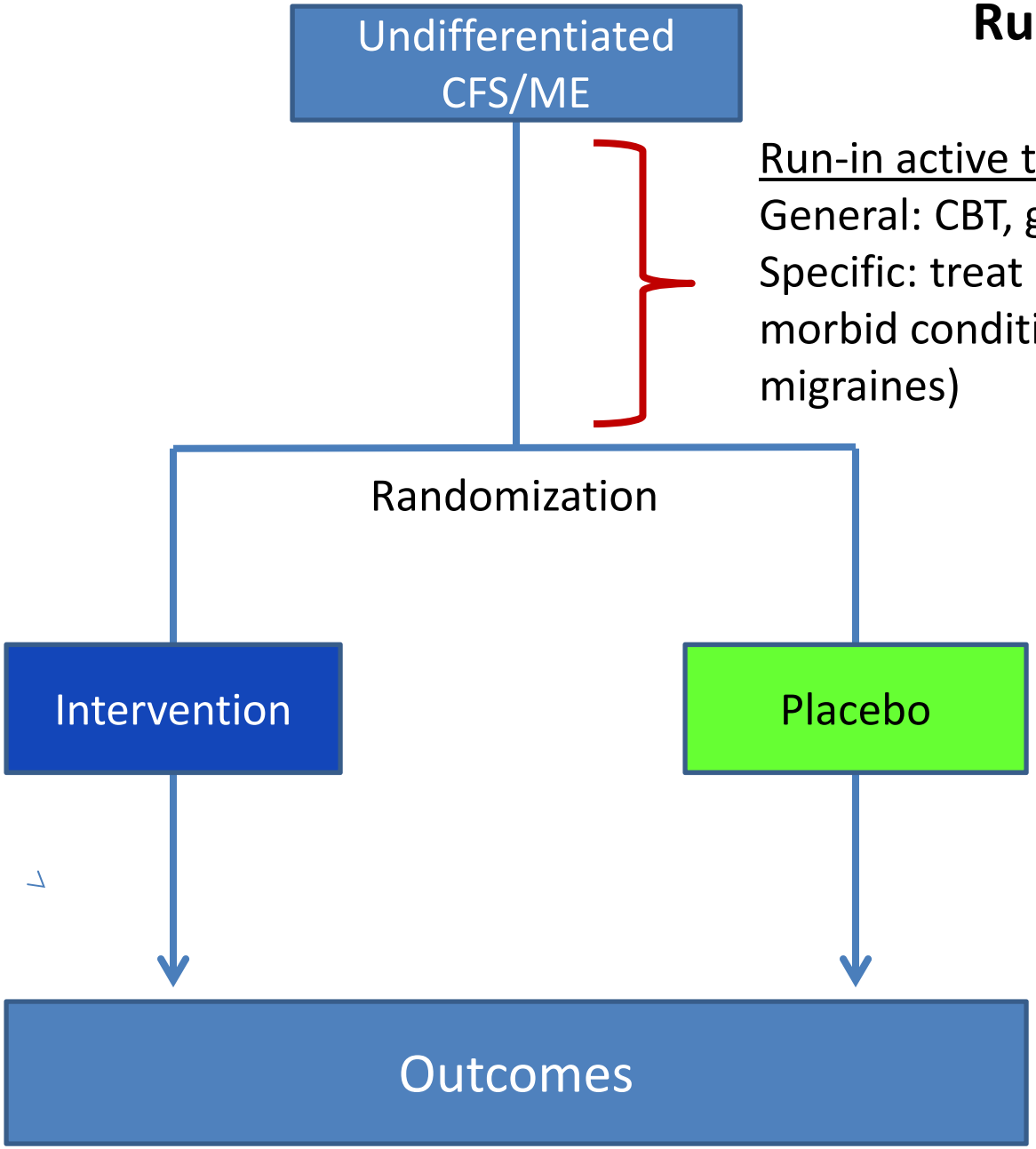
DESIGNING CFS TRIALS TO ACCOUNT FOR PHENOTYPIC HETEROGENEITY

- Larger studies needed to detect signal from noise caused by co-morbid disorders
- Different trial strategies
  - Stratification to address duration of illness, subsets
  - Run-in periods for treating co-morbid disorders or identifying responders
  - Randomized trials of <u>withdrawing</u> ostensibly effective therapies
  - Crossover designs
  - N-of-1 trials

Current approach



Run-in treatment

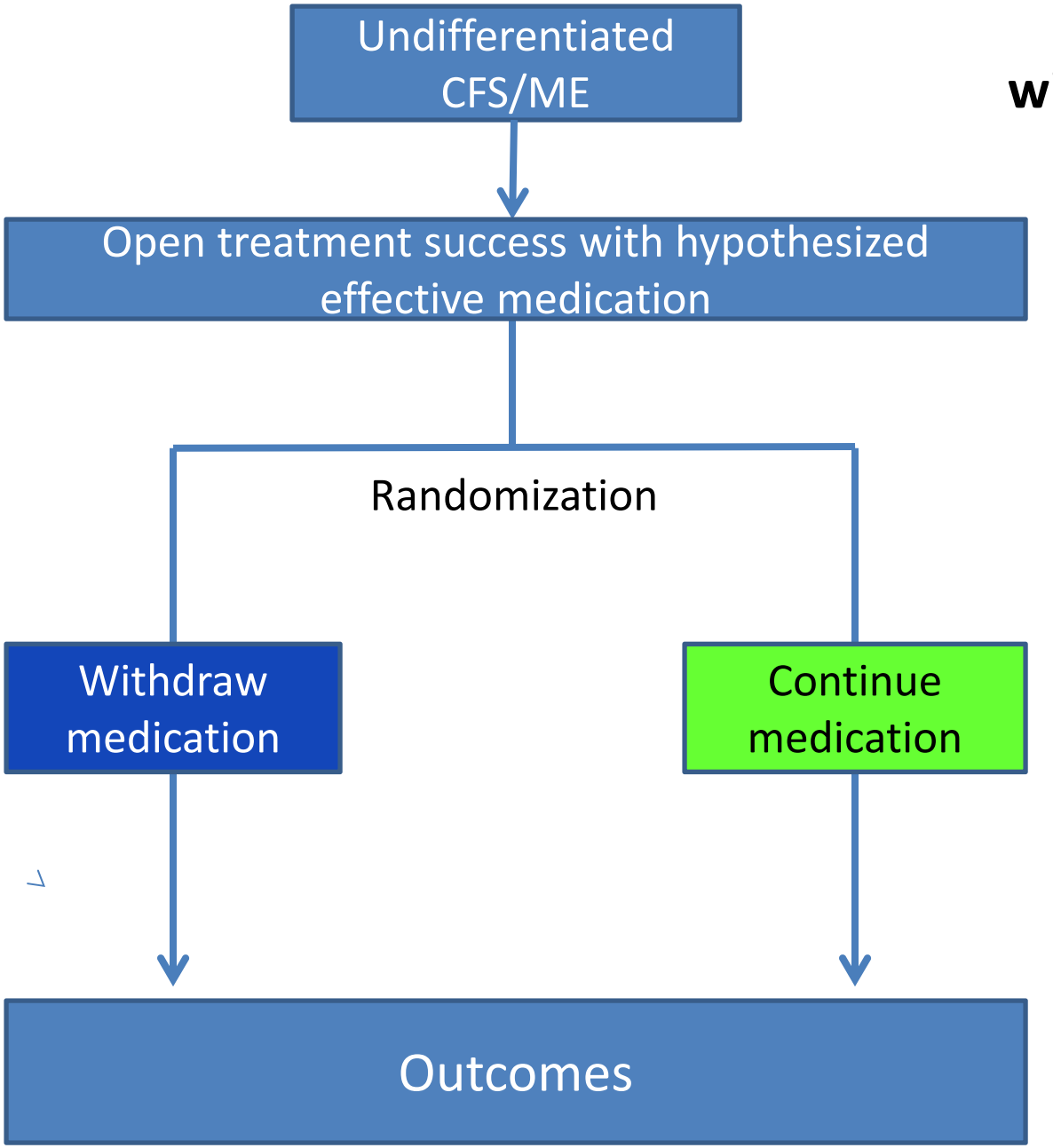


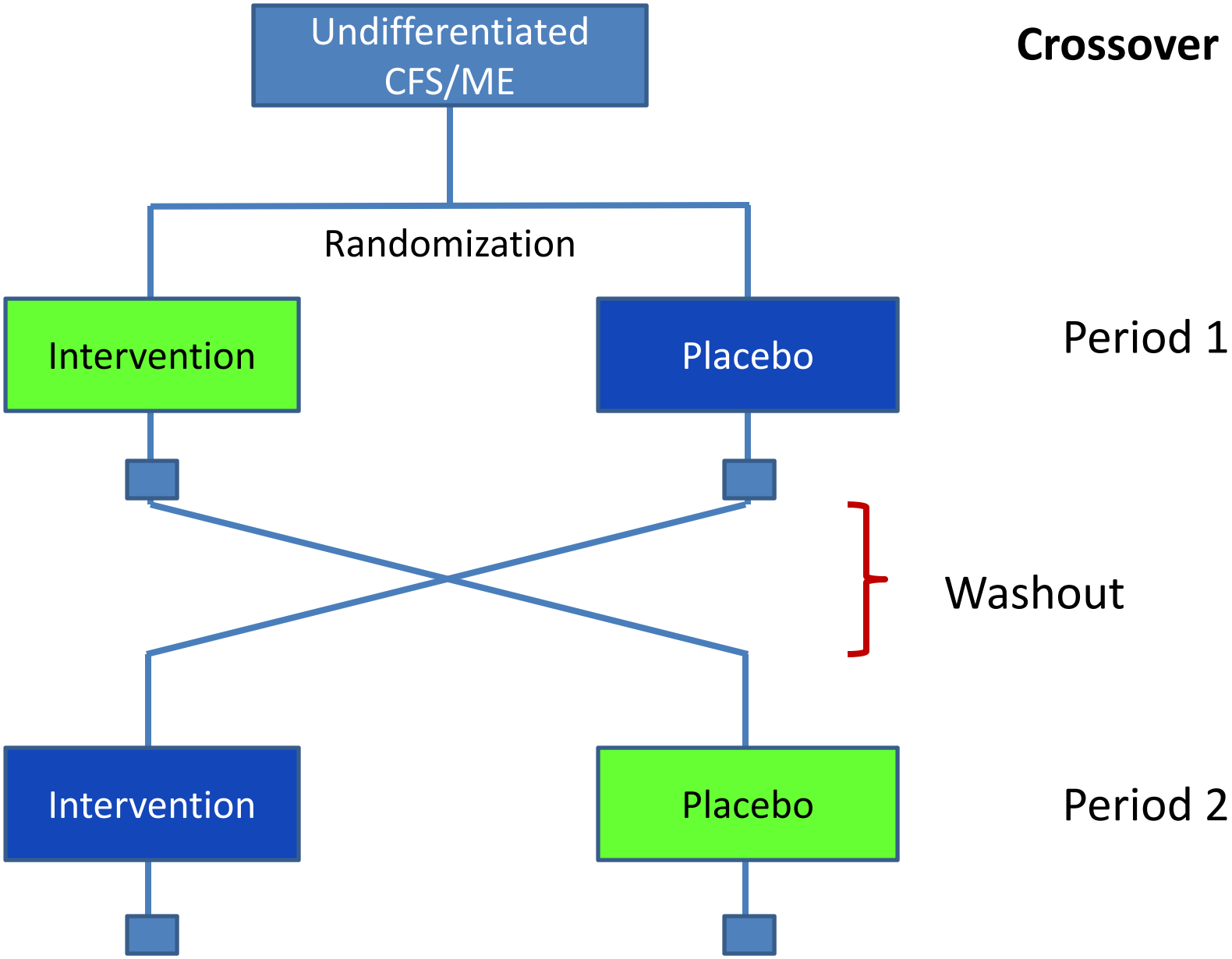
Run-in active treatment period

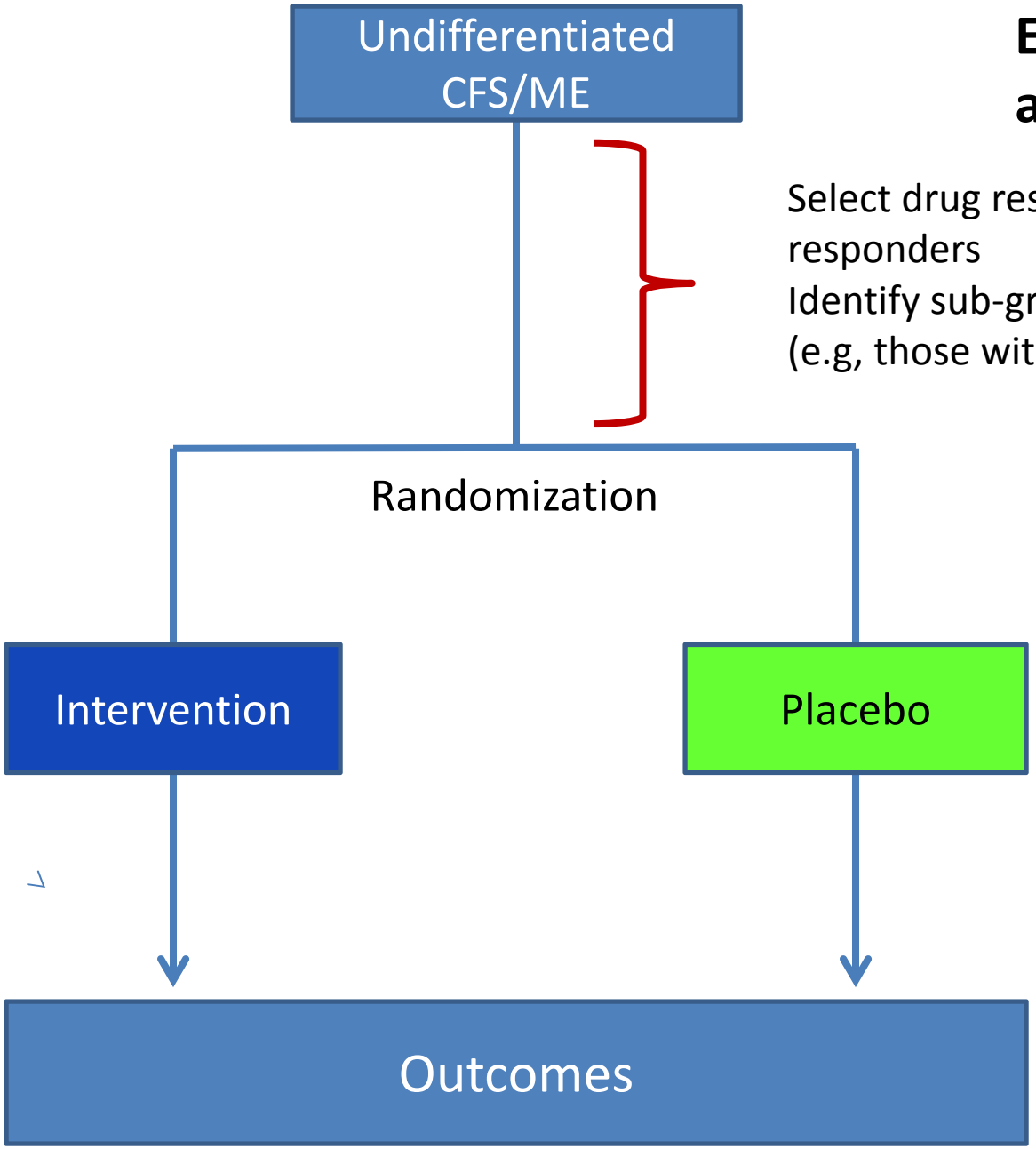
General: CBT, graded exercise

Specific: treat and stabilize co-morbid conditions (e.g, allergies, migraines)

Randomized withdrawal of meds




Crossover
Undifferentiated CFS/ME
Randomization
Intervention
Placebo
Period 1
Washout
Intervention
Placebo
Period 2



Enrichment approaches

Select drug responders, placebo non-responders
Identify sub-groups expected to respond (e.g, those with OI, infectious onset)

SELECTED REFERENCES

- Robert Temple. Enrichment strategies. FDA/DIA Statistics Forum. April 25, 2012.

  http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-orgs/documents/document/ucm303485.pdf

- Demitrack MA. Clinical methodology and its implications for the study of therapeutic interventions for chronic fatigue syndrome: a commentary. Pharmacogenomics 2006;7:521-8

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- Sunshine Natural Wellbeing Foundation (endowed Chair)
- Volunteer RA Colleen Marden
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston)
- Many families and patients:
  - Special thanks to the following:

    Boies, Cornell, Smith, Caldwell, Newbrand, Kelly, Kiely, McFerron
  - Megan Lauver, Hannah Vogel

Repeated CPET Results as Clinical Endpoints for ME/CFS Research

Christopher Snell, PhD
Professor
Health, Exercise and Sport Sciences
University of the Pacific

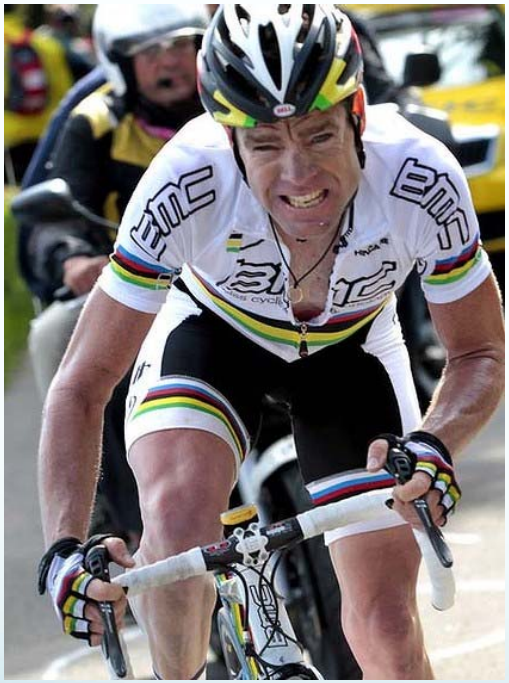
Repeated CPET Results as Clinical Endpoints for ME/CFS Research

Christopher Snell, PhD., Staci Stevens, MA., Mark VanNess, PhD. & Brian Moore, PhD.

Workwell Foundation Clinical Services

www.workwellfoundation.org

Assessing Function



Vs

Asking the Right Questions

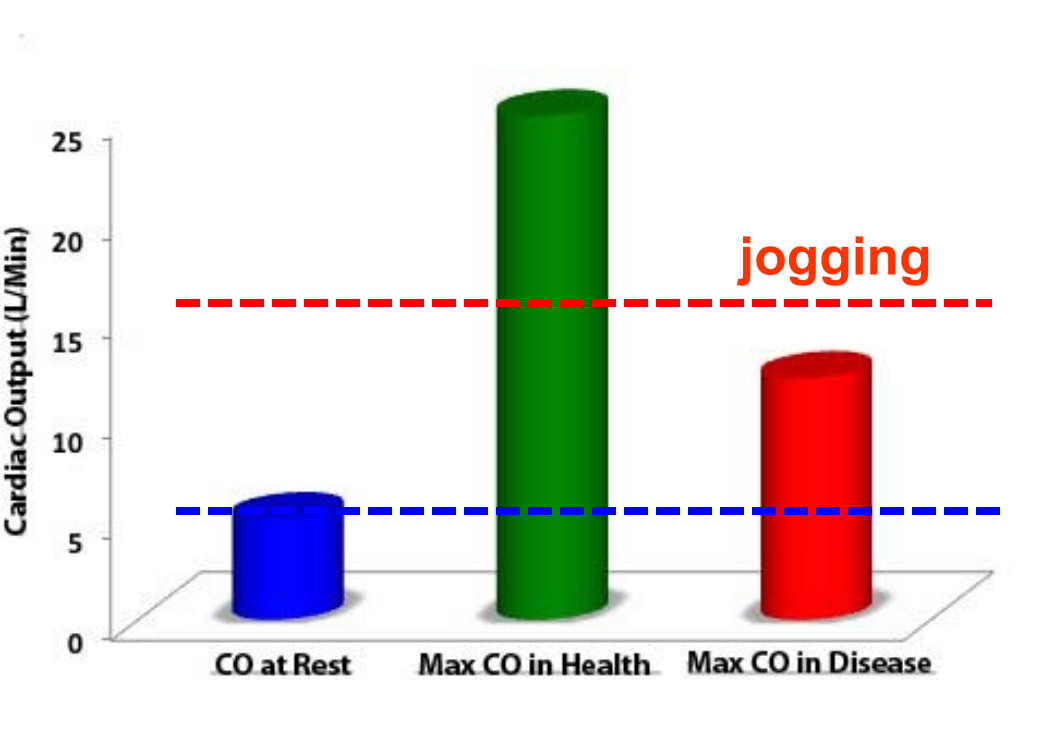
Exercise testing is a noninvasive procedure that provides diagnostic and prognostic information and evaluates an individual's capacity for dynamic exercise.

American Heart Association

Value of Exercise Testing

- Organs and organ systems have built-in reserve capacity
- Disease states reduce this capacity
- In the absence of stress, reduction in functional capacity isn’t always seen
- Exercise is an effective way to induce stress

Stressing the System



What is goal of exercise testing?

- Assess function of the cardio-respiratory system

- Determine functional capacity
  - Focus on aerobic capacity

Energy Production

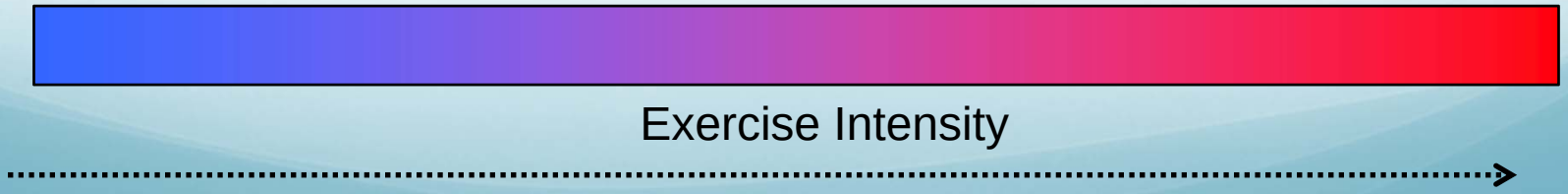
Two Main Energy Liberation Systems:

Aerobic Metabolism

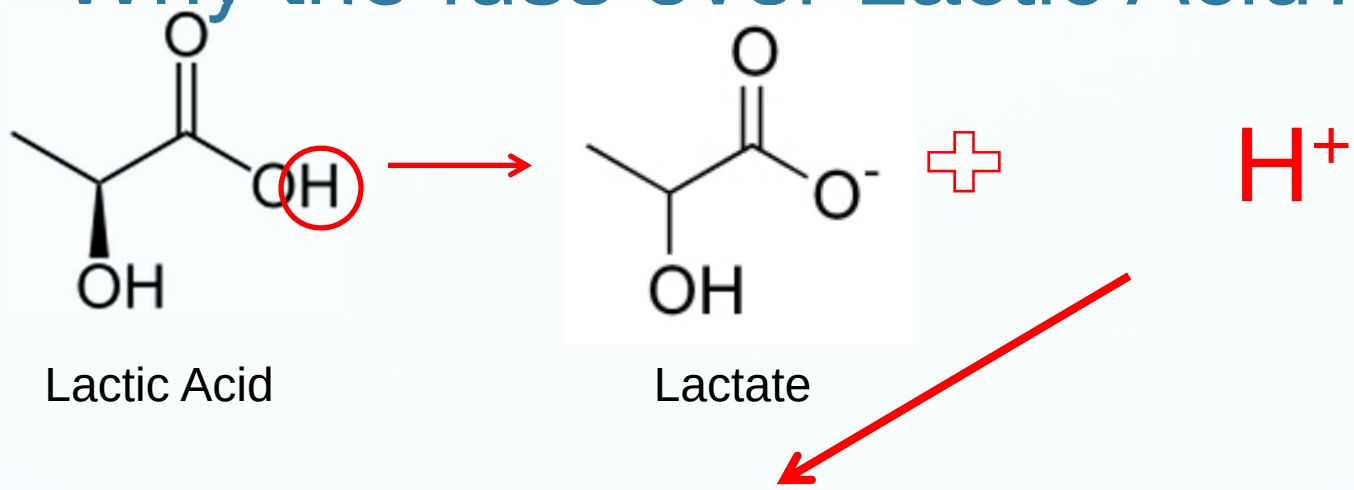
- oxygen dependent
- very efficient
- time intensive
- predominates at lower workloads
- CO_2 is byproduct

Anaerobic metabolism

- No oxygen needed
- Contributes more at higher workloads
- 2 ATP per glucose vs. 30-36
- Lactic acid is byproduct



Why the fuss over Lactic Acid?



Lactic Acid

Lactate

Altered muscle and blood pH!

- Pain
- Reduced muscle function
- Altered enzyme activity
- Cessation or reduction in activity

Quantifying Aerobic Capacity

VO2 MAX	Anaerobic Threshold
Maximum amount of oxygen system can deliver and combust (L/min). AKA maximal oxygen consumption.	The level of exercise oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms.

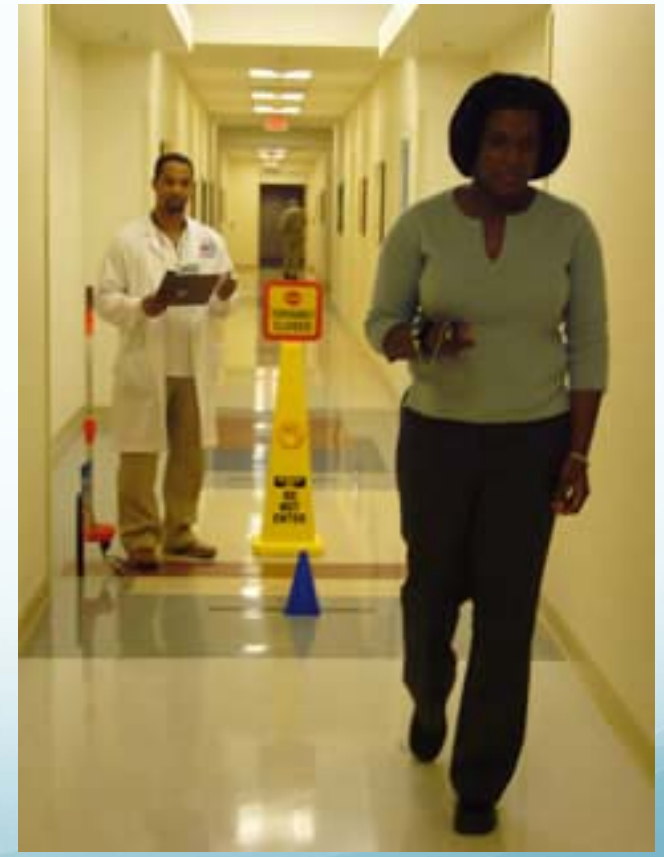
Both VO_2Max and Anaerobic Threshold (AT) can be determined:

1) **Directly** measured during a graded exercise test
   - Gas exchange techniques
   - Measurement of blood lactate levels
2) **Indirectly** estimated by recording HR response or onset of fatigue during a graded exercise test and apply regression equations developed from study populations

Modes of Testing Aerobic Capacity with a Graded Exercise Test

- Field tests
  - Cooper 12-minute test
  - Rockport One-Mile Fitness Walking Test
  - 6 minute walk test
- Step tests
- Treadmill tests
- Cycle ergometer tests

Field Tests



Field Tests

- Advantages
  - Easy to administer
  - Ability to test many individuals at once
  - Require minimal equipment
- Disadvantages
  - Unmonitored BP and HR
  - Aerobic capacity is estimated.
  - May result in inadvertent max testing in some populations
  - Motivation and pacing plays a big role in results

Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial*

6-min walking test n=110 (69%)

Baseline distance 341 yards

52-week distance 414 yards

1.9-2.3 mph

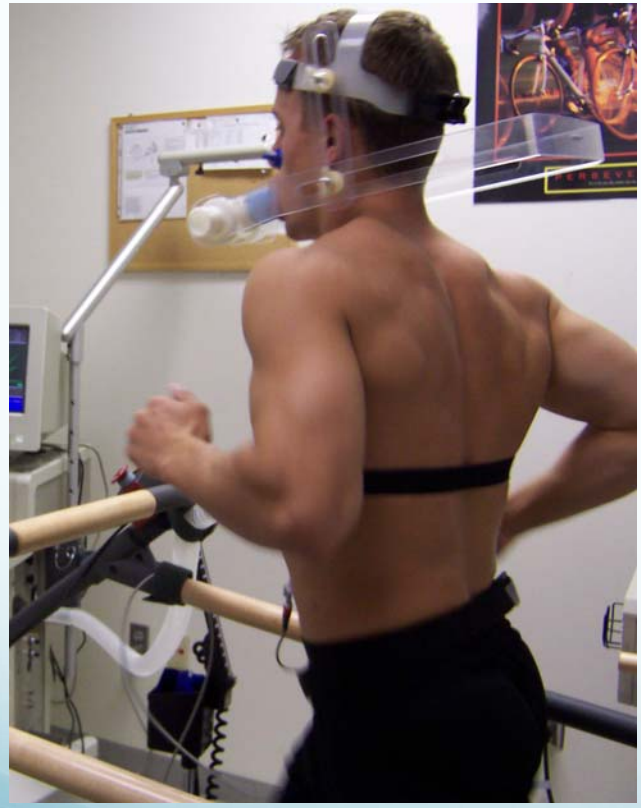
**White, et al. The Lancet, 377:9768, 823-836, March 2011*

1.9 mph
vs
2.3 mph

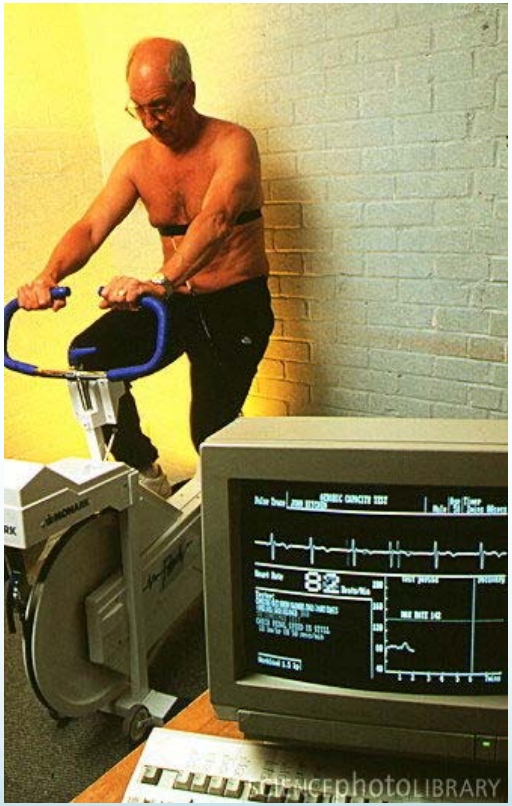
2 Mets =
7ml/min/kg O_2

Weber/NYHA
Severely
Disabled

Treadmill



Cycle Ergometer



Step Test

Indirect Estimation of Aerobic Capacity

Employ regression equations derived from experimental data to estimate Vo_2max and anaerobic threshold from performance on field tests, step tests, treadmill or ergometer

Limitations of Indirect Assessment

- May not apply to special populations/disease states
- Biased by tested population
- Biologic variability of heart rate response to exercise
- Dangers of using regression models outside tested values
- Assumptions must be made
  - Steady state of HR achieved during exercise
  - Linear relationship between measured variable and VO_2
  - Response for given age group is uniform
  - Mechanical efficiency is same for every individual
  - Individual is not on medications that affect measured variable

May not apply in Disease

- "Mild exercise led to rapid fatigue, with hyperventilation and disproportionate tachycardia."
  - Cardiovascular and Metabolic Responses to Exercise in a Patient with McArdle's Syndrome, Daniel Porte, Jr., M.D., N Engl J Med 1966; 275:406-412August 25, 1966
- "In conclusion, the association of an abnormal stress response with nonmetabolic factors, including backscatter and blunted peak heart rate…"
  - Usefulness of at rest and exercise hemodynamics to detect subclinical myocardial disease in type 2 diabetes mellitus. Jellis CL, Am J Cardiol. 2011 Feb 15;107(4):615-21. Epub 2010 Dec 31.

Biologic Variability of Heart Rate

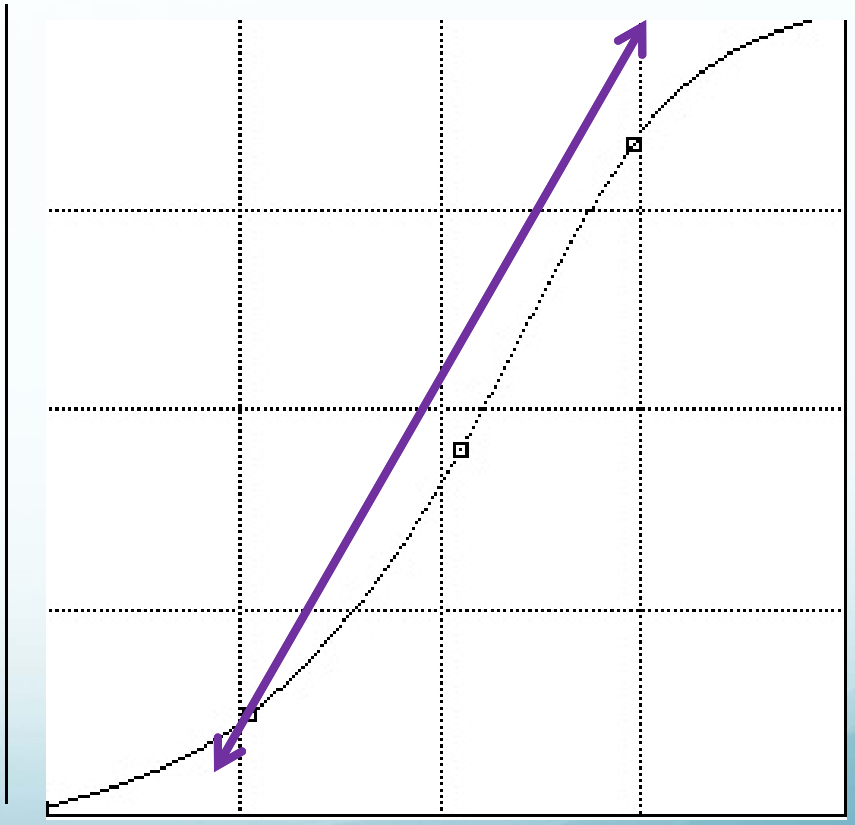
- "SRBD is associated with reduced physical working capacity and a modified hemodynamic response to exercise."
  - The heart rate response to exercise is blunted in patients with sleep-related breathing disorder. Grote L. Cardiology. 2004;102(2):93-9. Epub 2004 Apr 19
- Variables affecting heart rate response
  - Medications
  - Ambient temperature
  - Environmental noise
  - Body temperature
  - Elevation
  - Time of day
  - Illness

Biased by Tested Population

- "These findings demonstrate that a novel treadmill-based PRET can yield predictions of VO2max that are acceptably reliable and valid amongst young, healthy, and active adults."
  - The validity and reliability of predicting maximal oxygen uptake from a treadmill-based sub-maximal perceptually regulated exercise test. Morris M, Eur J Appl Physiol. 2010 Jul;109(5):983-8
- "These results indicate that a four minute aerobic dance test provides a valid and reliable sub-maximal protocol for estimating VO2max and providing an index of aerobic fitness in apparently healthy 18 to 40 yr old females."
  - A test to estimate VO2max in females using aerobic dance, heart rate, BMI, and age.Olson MS, J Sports Med Phys Fitness. 1995 Sep;35(3):159-68.

Regression Modeling Limitations

- Linear relationship may break down outside of a specified range



Direct Assessment of Aerobic Capacity

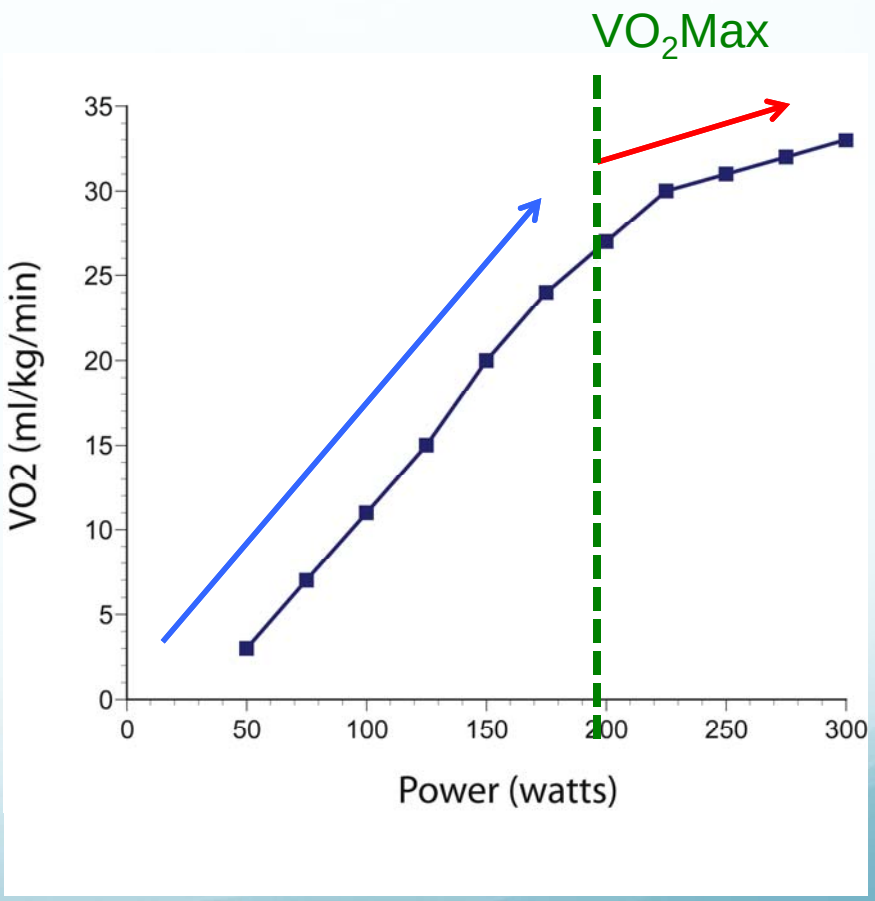
- Maximum Oxygen Consumption (VO_2max)
- Anaerobic Threshold (AT)

Principles of Gas Exchange

- Aerobic metabolism burns O_2 and produces CO_2
- By measuring the difference between inspired and expired gases, it can be determined how much O_2 is consumed and how much CO_2 is produced

Maximal Oxygen Uptake

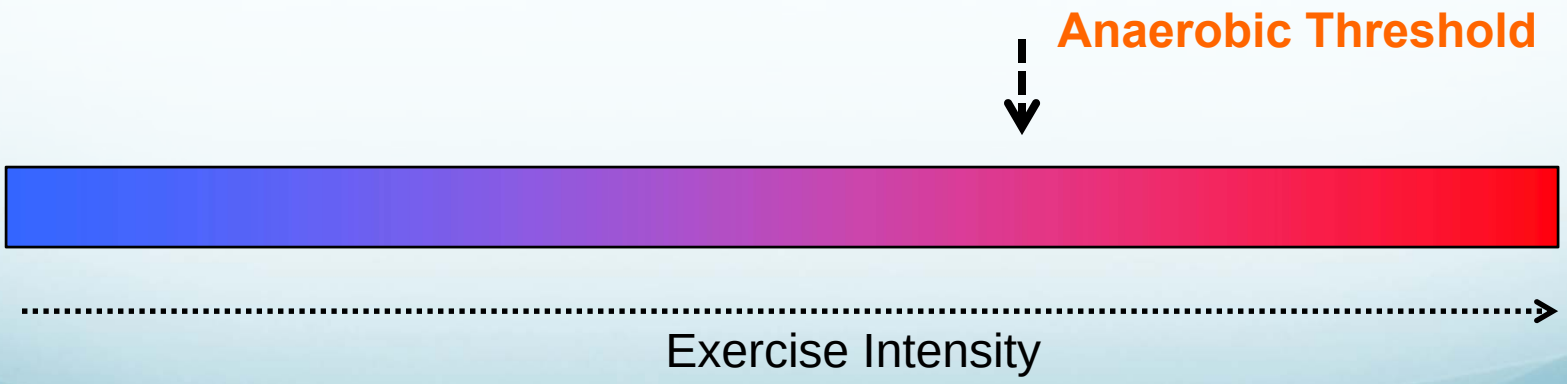
- VO_2 max is strongly correlated with endurance performance capability
- Dependent on cardiovascular limitations; ability of heart, lungs, and circulatory system to deliver O_2 to working muscle



Anaerobic Threshold

- Exercise intensity above which aerobic metabolism is significantly supplemented by anaerobic energy production.

- Can be identified through measuring gas exchange

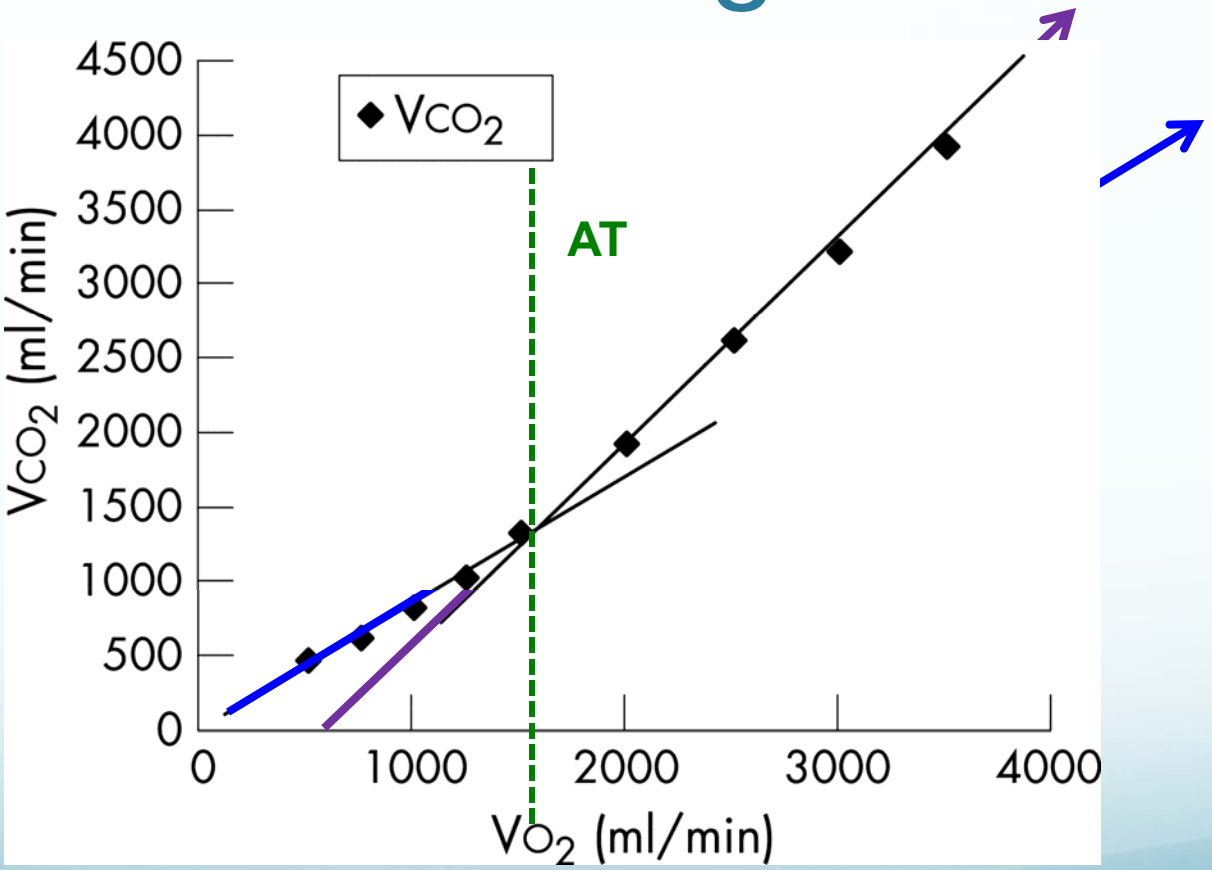


Measuring AT with Gas Exchange

- Respiratory Exchange Ratio RER (R)

$$\frac{CO_2 \text{ Produced}}{O_2 \text{ Consumed}}$$

Measuring AT with Gas Exchange



Accuracy of Direct vs Indirect Measurements of Aerobic Capacity

- Indirect estimates of VO_2max can routinely vary by $\pm$ 25%
- Ventilatory threshold is highly correlated to blood lactate threshold and aerobic performance.
- Measuring gas exchange allows you to accurately and reliably determine effort

Respiratory Exchange Ratio (VCO_2:VO_2)

This physiological response to exercise is consistent in apparently healthy subjects and all patient populations, which makes peak RER the most accurate and reliable gauge of subject effort. A peak RER of 1.10 is generally considered an indication of excellent subject effort”

***Circulation*. 2010;122:191-225.** © 2010 American Heart Association, Inc.

Summary

- Determining aerobic capacity is crucial when assessing level of function.
- Oxygen uptake and anaerobic threshold are two parameters that are closely correlated to aerobic performance.
- Direct measurements of aerobic capacity are much more accurate, especially in special populations and disease states.

Moderate to Severe Impairment in CFS/ME

Severity of Impairment	Peak VO_2 (ml/kg/min)	# of patients	Group VO_2 (ml/kg/min)	Predicted VO_2 (ml/kg/min)
None to Mild	>25	33	29.5 ± 0.9	38.6 ± 1.2
Mild to Mod	20-25	72	22.1 ± 0.2	35.3 ± 0.8
Mod to Severe	15-20	**77**	17.2 ± 0.2	34.2 ± 0.6
Severe	<15	**21**	12.1 ± 0.5	33.0 ± 0.6

Reduced Functional Capacity

- Riley et al., 1990
- Demitrack et al., 1998
- DeBecker et al., 2000
- VanNess et al., 2003
- Vermulen et al., 2010
- Jones et al, 2011

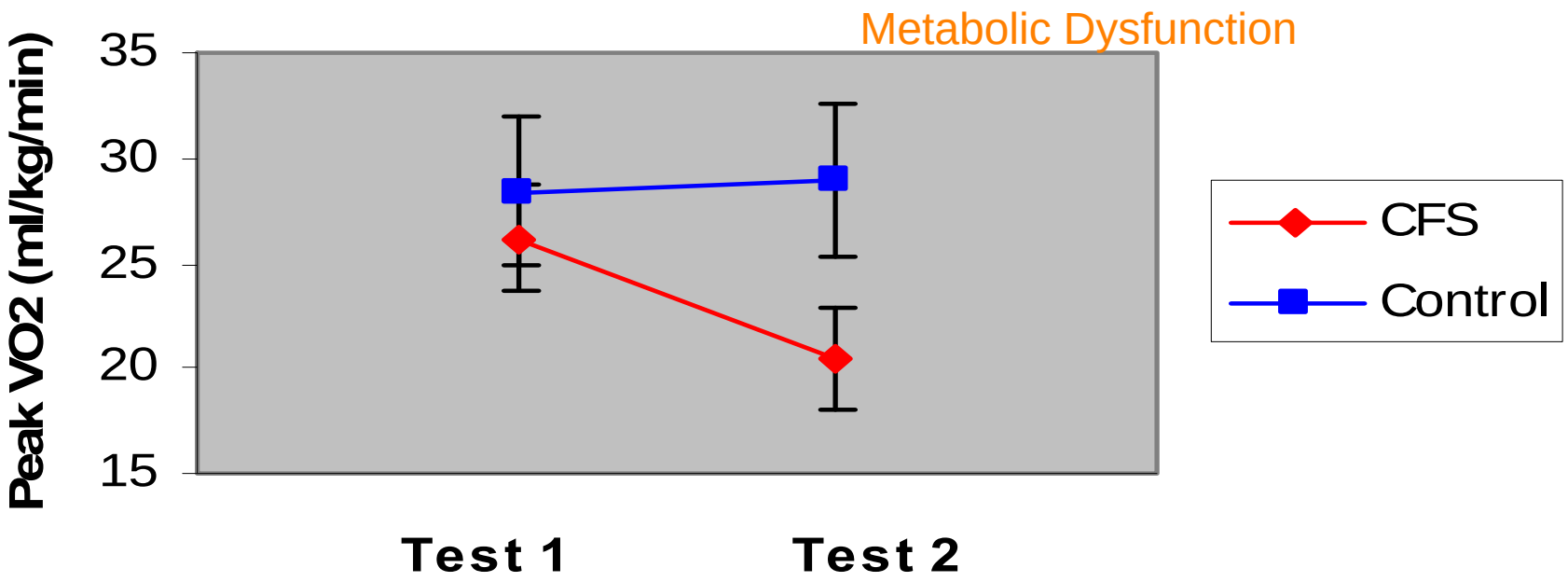
*Difficult to separate “CFS effects” from detraining

Exercise Test-Retest Paradigm

- Waxing and waning of symptoms
- Fluctuations in fatigue levels

*“Induced” Post-Exertional Effect

Reduced Ability to Utilize Oxygen in the Post-Exertional State



VanNess, J.M., C.R. Snell and S.R. Stevens. J of CFS, 14(2):77-86, 2007.

Repeated Exercise Tests

- Demonstrates the effect of post-exertional malaise
- Quantifies the magnitude of the post-exertional effect (Fatigue Effect)
- Informs the mechanisms of the response
- Reproducibility?

The Abnormal Stress Test: Objective Evidence of PEM?

Decline in VO_2peak/AT/workload values:

1. Atypical recovery response
   Abnormal stress test
   Post-exertional malaise
2. Distinguishes CFS from other illnesses

CFS 24.5% decrease.

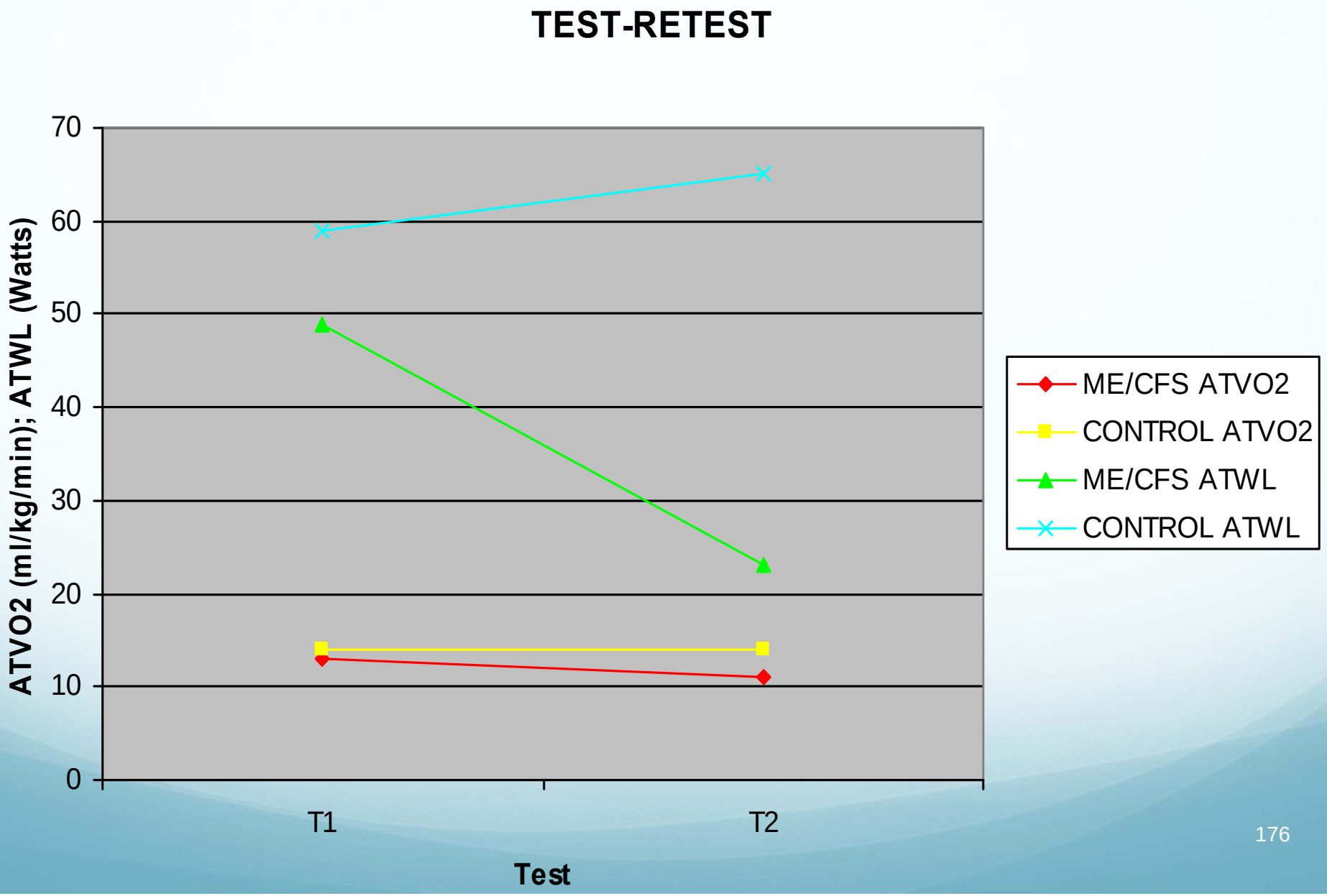
VanNess et al. 2007

Other illnesses 7.28% variability.

Clinical Exercise Testing (Weisman & Zeballos), p.28

	Test 1		Test 2	
	CFS n=51	Controls n=10	CFS n=51	Controls n=10
$VO_{2\ peak}$[1]	21.51	25.04	20.44	23.96
VTO_2[1]	12.74	13.83	11.36	14.12
WL_{peak}[2]	109.57	137.20	101.63	140.00
VTWL[2]	49.51	58.00	22.20	63.50

[1] ml/kg/min; [2] watts.


TEST-RETEST
70
60
50
40
30
20
10
0
ATVO2 (ml/kg/min); ATWL (Watts)
T1
T2
Test
ME/CFS ATVO2
CONTROL ATVO2
ME/CFS ATWL
CONTROL ATWL

Failure to Reproduce?

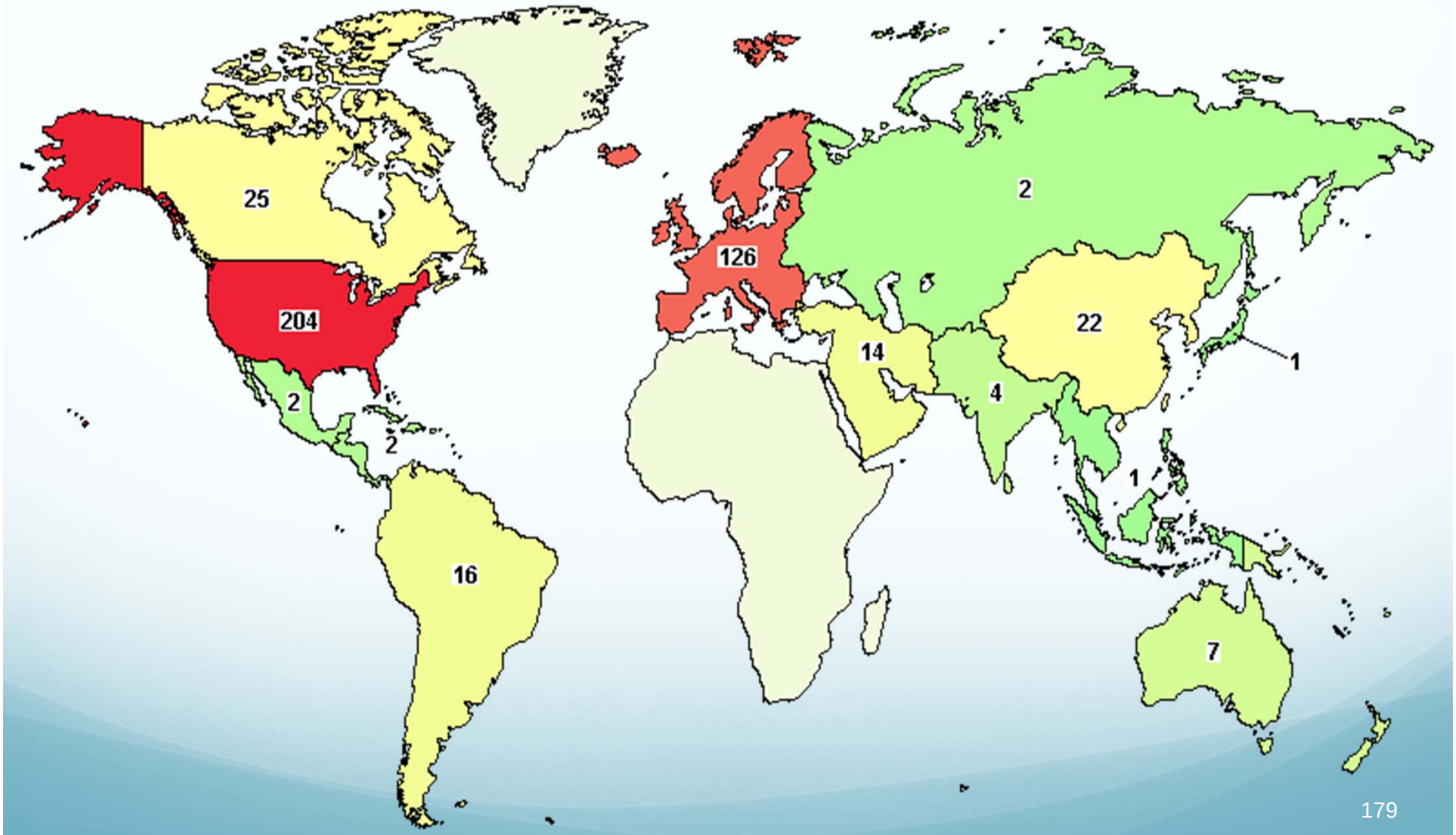
- Inflammatory cytokine elevation (Klimas et al., 2007)
- Neuroendocrine dysfunction
- Cardiovascular abnormalities
- Mytochondrial abnormalities (Whister et al., 2006, Wong et al.,1992)

Conclusions

- Cardiopulmonary exercise testing can provide objective measures of fatigue in CFS/ME (functional endpoint for clinical trials; disability assessment)
- As a quantifiable stressor, CPET has the capacity to reveal abnormalities across multiple systems
- Availability of the RER, a measure exclusive to analysis of expired gases, provides the most accurate and reliable gauge of subject effort
- A single exercise test may be insufficient to distinguish between CFS/ME and sedentary controls

CPET AROUND THE WORLD

Clinicaltrials.gov



Measures of CFS in a Multi-site Clinical Study

Elizabeth Unger, PhD, MD
Chief
Chronic Viral Diseases Branch
Division of High-Consequence Pathogens and Pathology
Centers for Disease Control and Prevention

Measures of CFS in a Multi-site Clinical Study

Elizabeth R. Unger PhD, MD
Chief, Chronic Viral Diseases Branch

FDA Scientific Drug Development Workshop
April 26, 2013

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for Emerging and Zoonotic Infectious Diseases
Division of High Consequence Pathogens and Pathology

Background

- **Physicians world-wide recognize CFS with similar features**
- **Different case definitions in use**
- **Heterogeneity of patients in clinical trials and research studies could confound results**
  - Duration of illness
  - Severity of and types of symptoms
  - Co-morbid conditions
  - Medications
  - Demographics (age, race, sex, BMI, socio-economic, etc.)

Study Objectives and Design

- **Capitalize on clinical expertise of physicians experienced in care and treatment of CFS patients**
- **Collect standardized data on major illness domains of CFS from patients in these practices**
  - Describe heterogeneity of CFS patients between practices
  - Evidence-based data to address case definition and CFS-subgroups
- **Enrollment criteria: Any patient (18-70 years old) diagnosed with CFS in participating clinics**
  - Exclusions: HIV +, age at diagnosis older than 62 years

Participating Clinics

- **Beth Israel Medical Center, New York City NY**
  - Benjamin Natelson, MD
- **Center for Neuro-Immune Disorders, Miami FL**
  - Nancy Klimas, MD

Open Medicine Institute Consortium

- **Fatigue Consultation Clinic, Salt Lake City UT**
  - Lucinda Bateman, MD
- **Hunter-Hopkins Center, Charlotte NC**
  - Charles Lapp, MD
- **Open Medicine Clinic, Mountain View CA**
  - Andreas Kogelnik, MD
- **Richard Podell Medical, Summit NJ**
  - Richard Podell, MD
- **Sierra Internal Medicine, Incline Village NV**
  - Daniel Peterson, MD

Protocol

- **Developed by participating clinics and CDC**
  - Fit into clinic routine as much as possible
  - Minimize burden to patients
- **IRB approved**
- **Phase 1 – Cross-sectional data**
  - Physical examination at time of clinic visit (or within one year)
  - Questionnaires for self-reported measures of illness
    - Patient completed
  - Data abstraction of medical records by clinic personnel

Data Abstraction Forms – Not Standardized

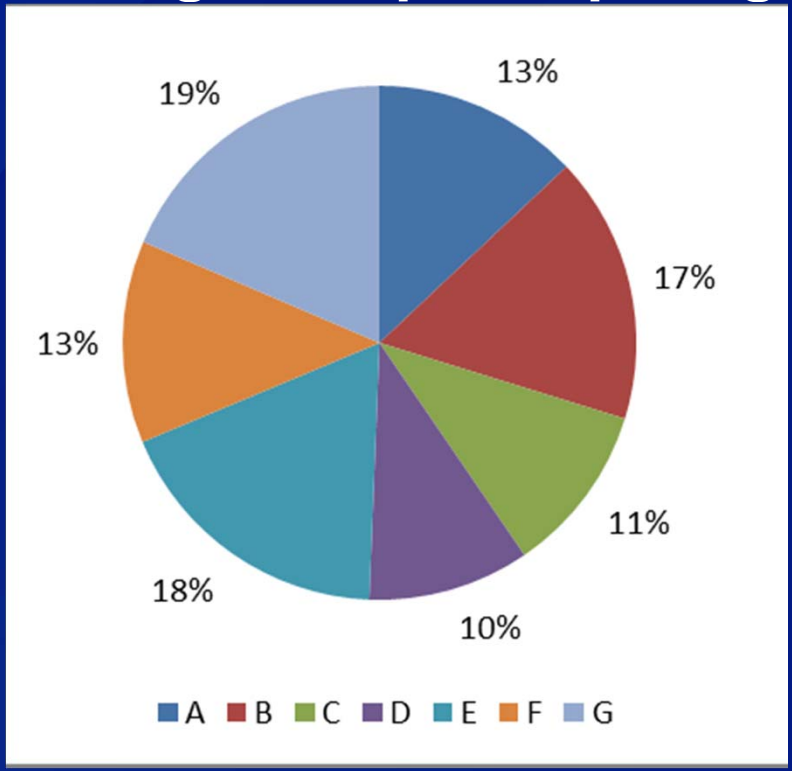
Data Collected by Clinic Personnel
New patient intake form (scanned)
Basic demographics
Detailed medical history
History of present illness
Current medication list
Lab and other diagnostic tests
Family history
Infection/immunization history
Physical Examination

Data Collection Instruments – Patient Self-reported

Patient Health Questionnaire Depression Scale (PHQ-8)
Generalized Anxiety Disorder 7-item Scale (GAD-7)
Self-Rating Depression Scale (SDS)
CDC Symptom Inventory (CDC-SI)
Medical Outcomes Study 36-Item Short-Form (MOS SF-36 v2)
Multidimensional Fatigue Inventory-20 (MFI-20)
Questions from DePaul symptom inventory (DSQ)
PROMIS Forms – Fatigue, Sleep (Disturbance and Impairment), Pain (Behavior and Interference)
Sleep Questions
Brief Pain Inventory (BPI)

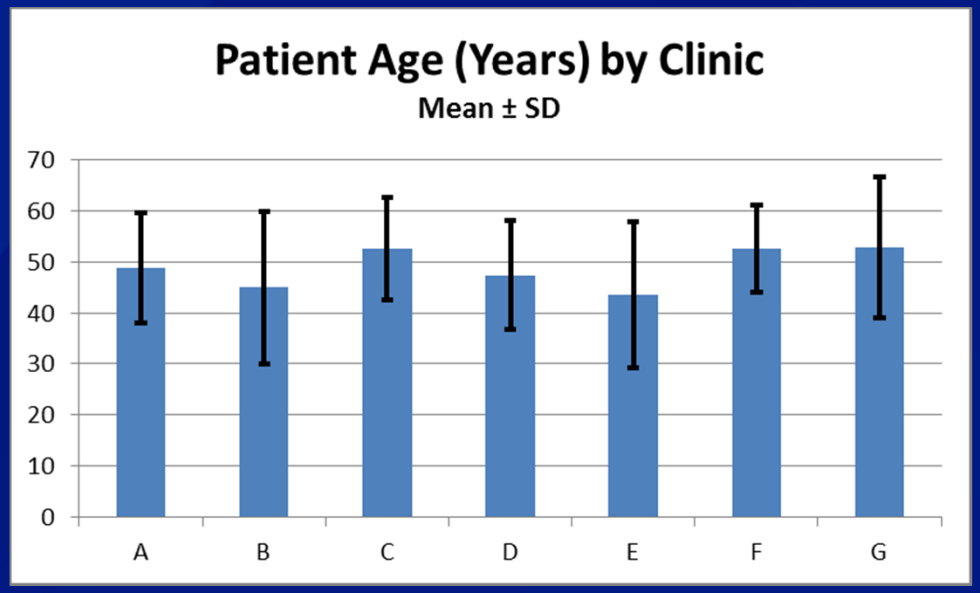
Interim Data Analysis

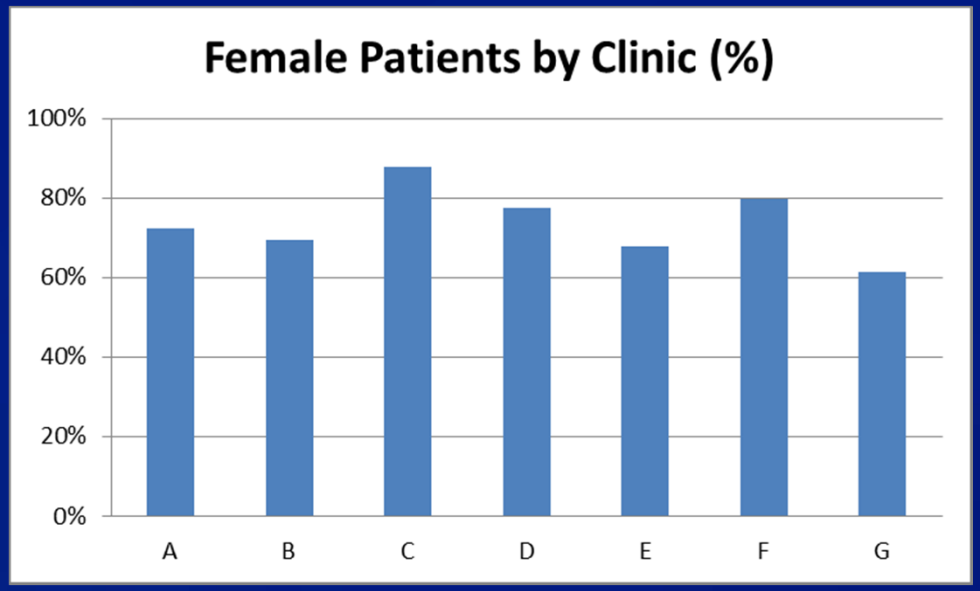
- **Data from 393 participants ready for analysis**
  - Final enrollment of 450 anticipated
- **Distribution among the 7 participating clinics:**



Overall Patient Demographics

- Mean age 48.6 yrs*
- 71.0% Female*
- 95.4% White*
- Mean BMI 27.2*
- 58.1% Married*
  - 16.1% Previously married
  - 25.7% Never married
- 78.3%≥College educ.*
- 97.8% Insured*
- 75.4% Not working
  - 15.4% Unempl. Benef.

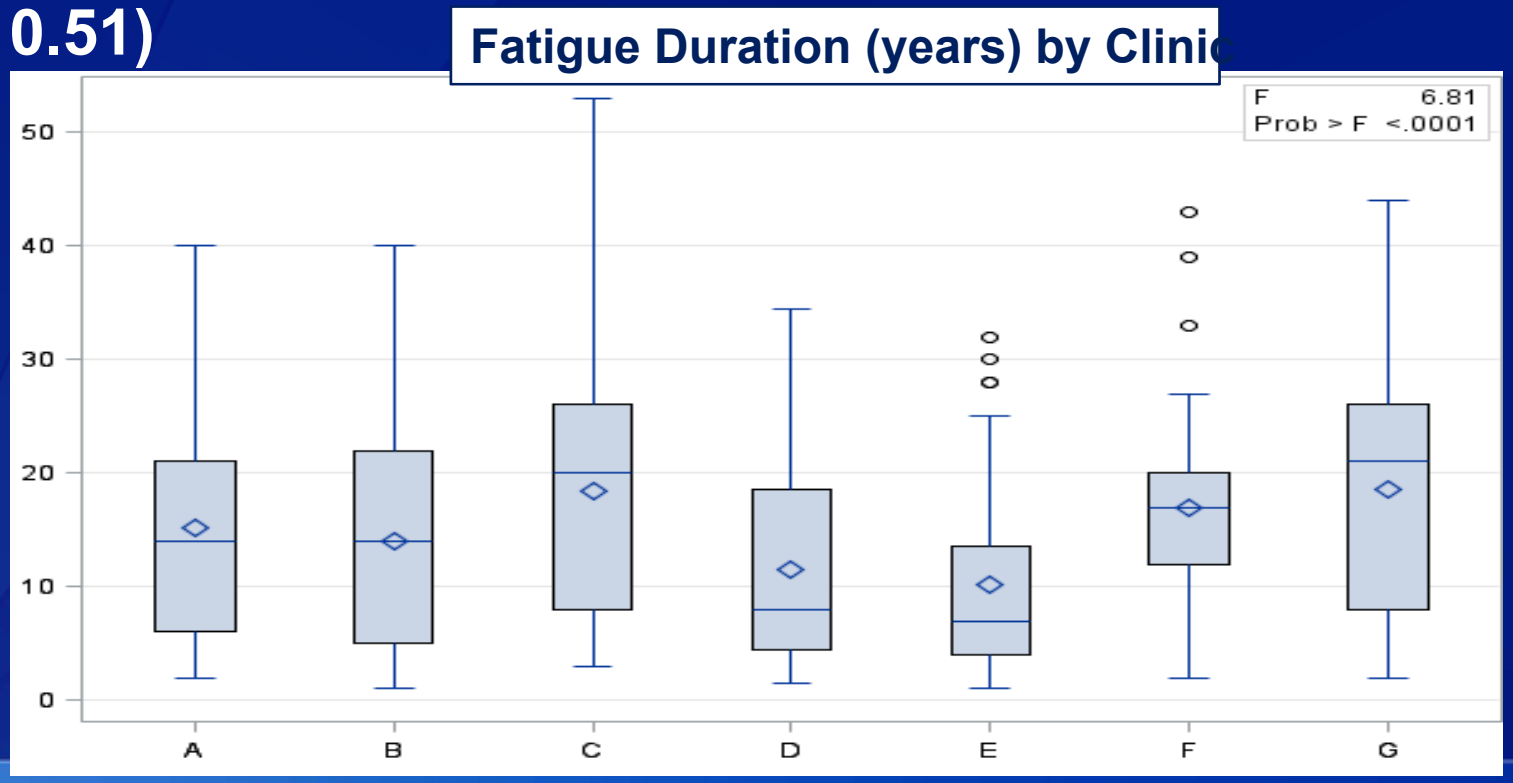




*Differs by clinic

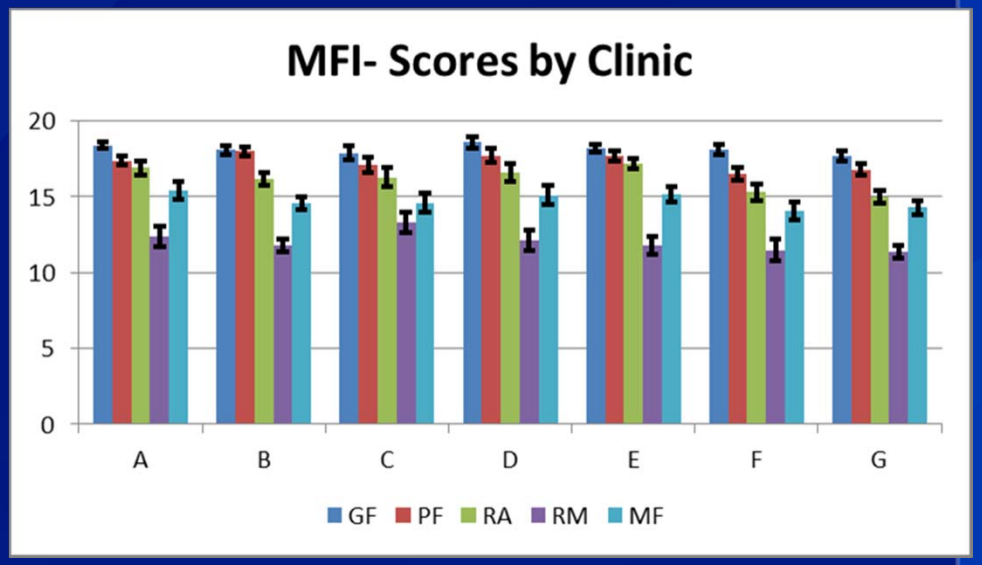
Illness Onset

- Mean age at diagnosis - 38.2 yrs (SEM 0.62)
  - 66.7% Sudden onset (range by clinic 52.3-76.1%; p<0.1)
- Mean duration of illness (fatigue) – 15.0 yrs (SEM 0.51)



Measures of Fatigue

- **PROMIS Score = 68.3 ± (0.36)**
  - Scores by clinic similar
- **MFI-RA differs by clinic**
  - Other MFI scores similar
- **MFI-GF shows ceiling effect (37.5% at max)**
- **PROMIS Fatigue correlates well with 3 MFI subscales**

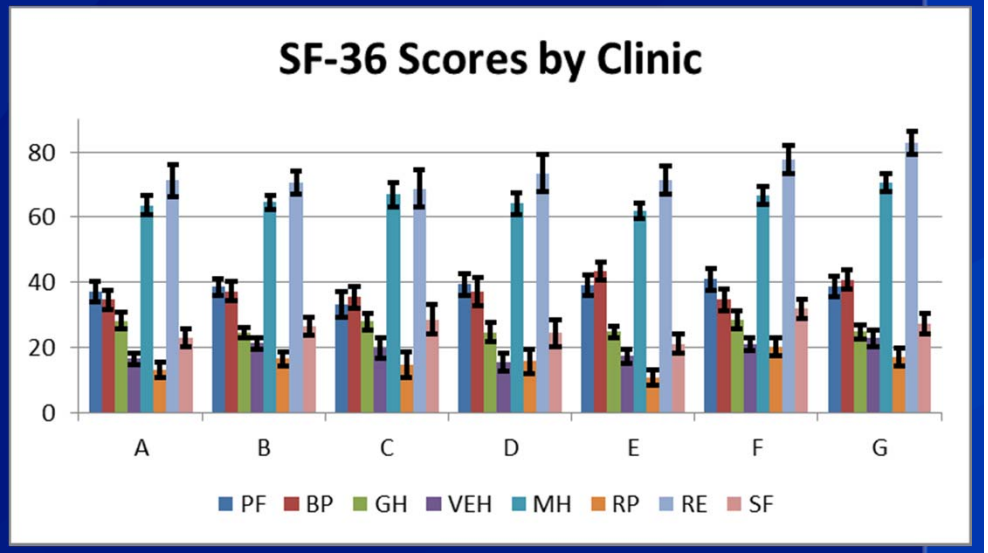


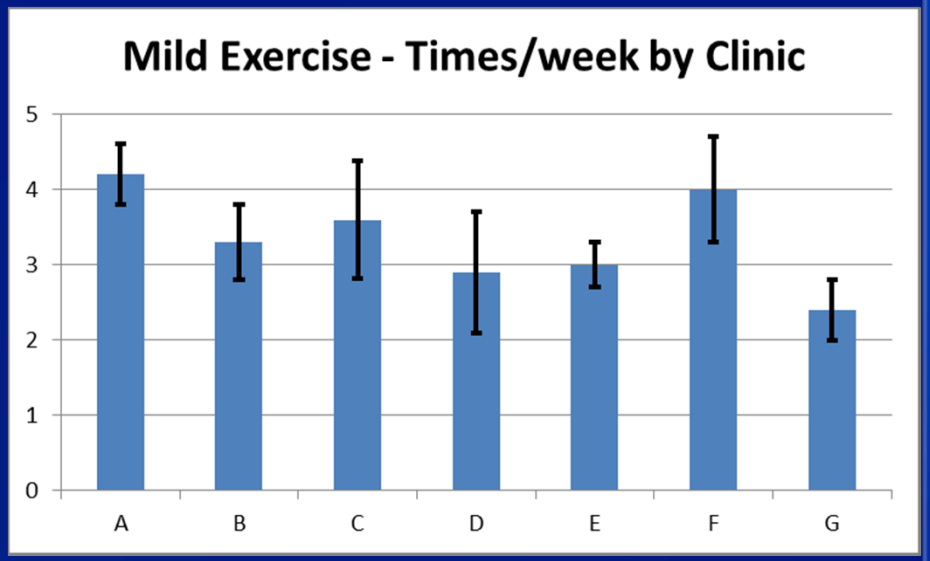
Correlation PROMIS and MFI					
	MFI Subscales				
	GF	PF	RA	RM	MF
PROMIS Fatigue	0.63	0.61	0.6	0.31	0.45

GF-General Fatigue RM-Reduced Motivation
PF-Physical Fatigue MF-Mental Fatigue
RA-Reduced Activity

Measures of Function

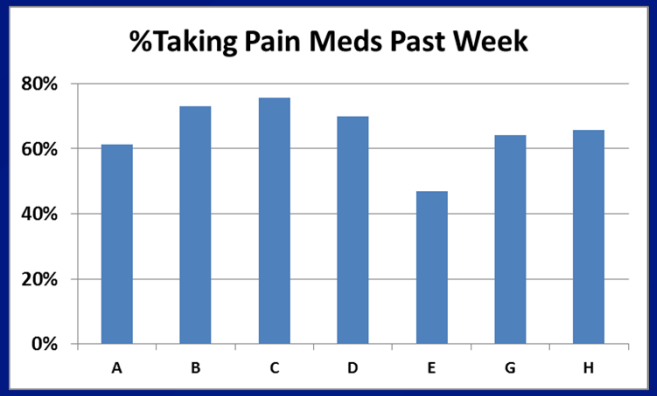
- **SF-36 indicates relative preservation of Mental Health and Role Emotional**
  - Lowest scores on Vitality and Role Physical
  - No significant variation by clinic
- **Daily activity hours-vertical (mean±SEM) = 7.6±0.2**
- **Daily activity hours-horizontal (mean±SEM) = 12.8±0.2**
  - Differs by clinic
- **Mild exercise times per week, overall (mean±SEM) = 3.4±0.21**
  - Differs by clinic

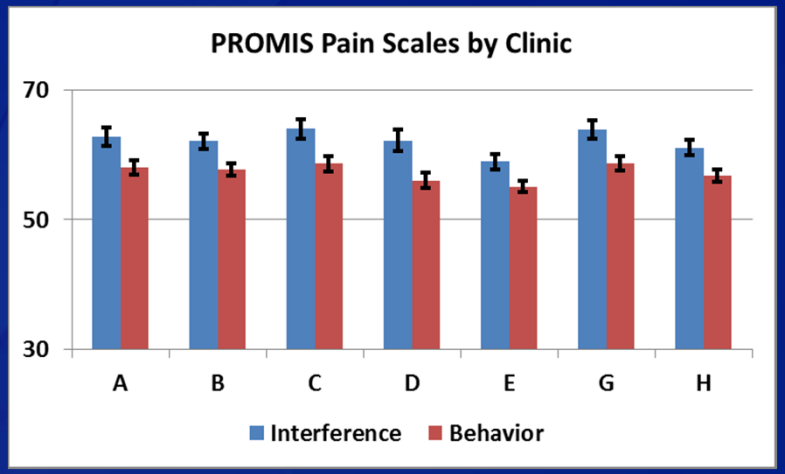


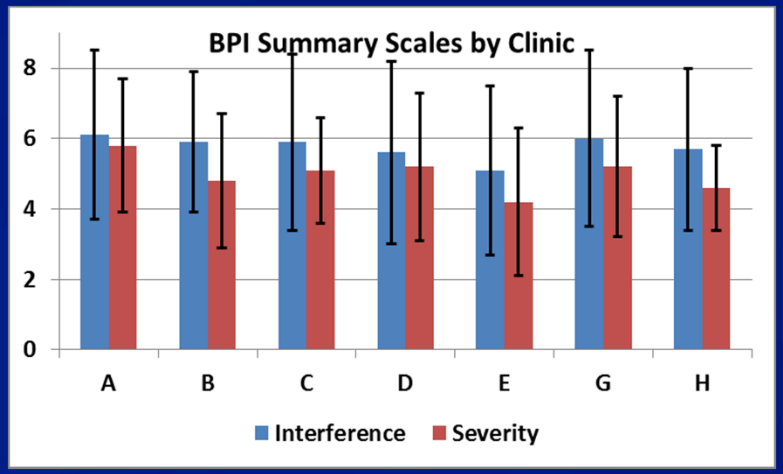


Measures of Pain

- **BPI – Overall 80% had pain in last week**
  - %Taking pain medication differed by clinic
  - Severity score differed by clinic
- **0.75 Correlation between PROMIS Interference and BPI Interference**

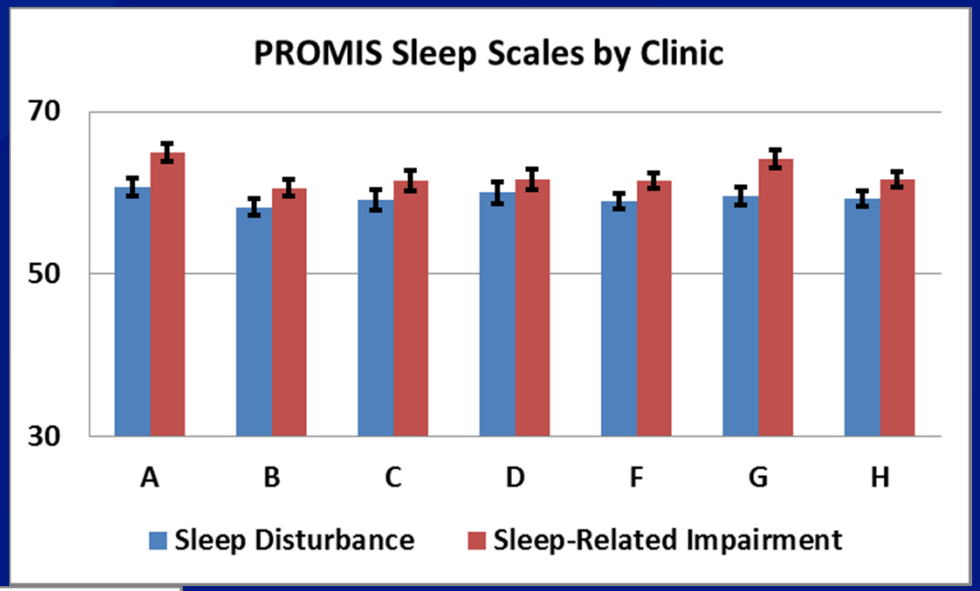


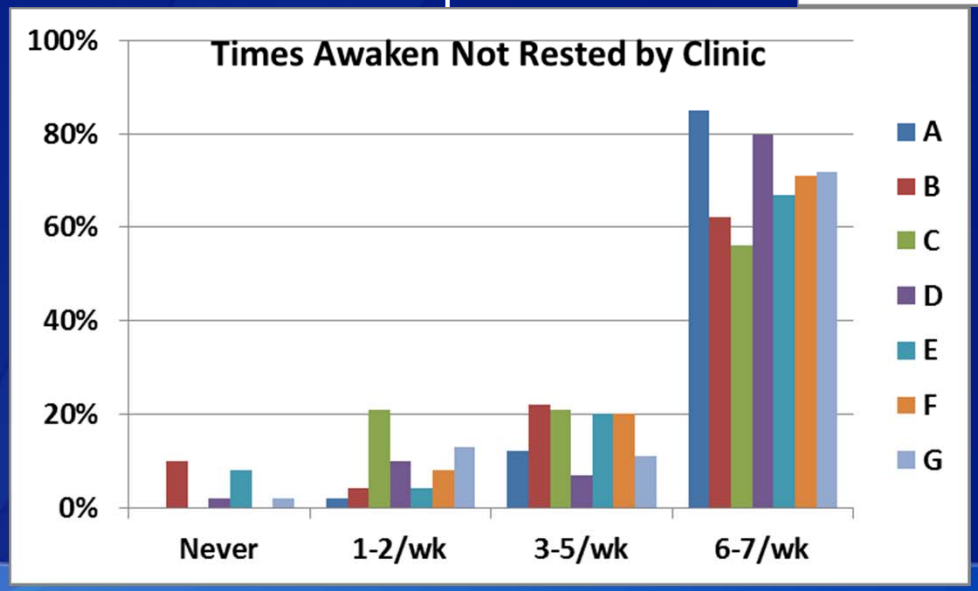




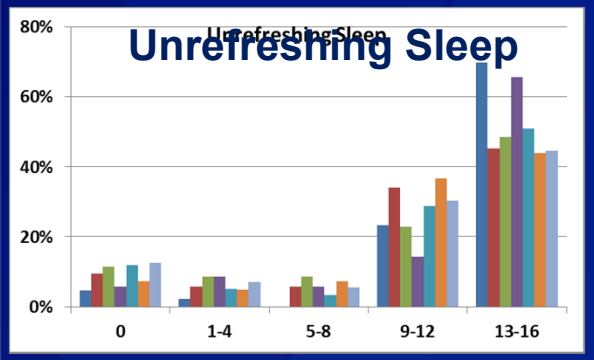
Measures of Sleep

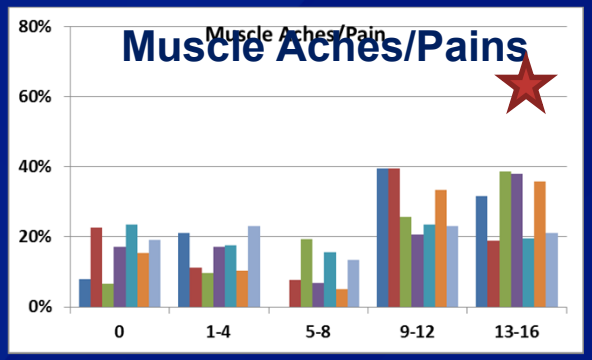
- **Severe sleep impairment noted in PROMIS, Sleep questions and CDC-SI**
  - Differences by clinic in PROMIS Sleep-Related Impairment

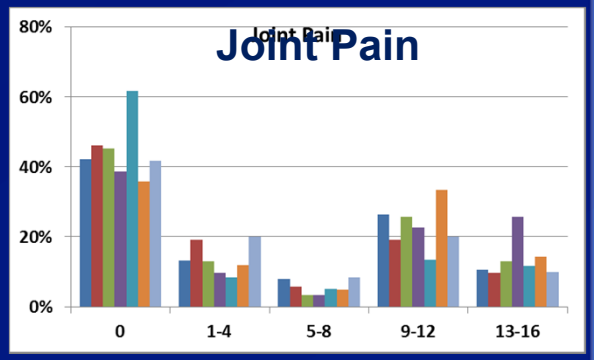


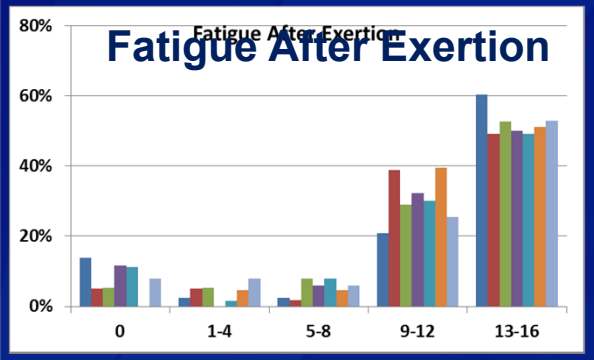


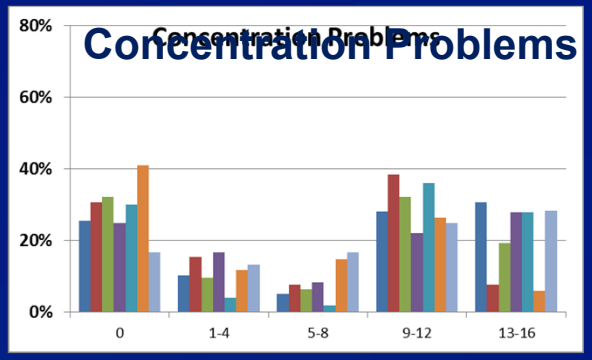
Distribution of CDC SI- Scores by Clinic

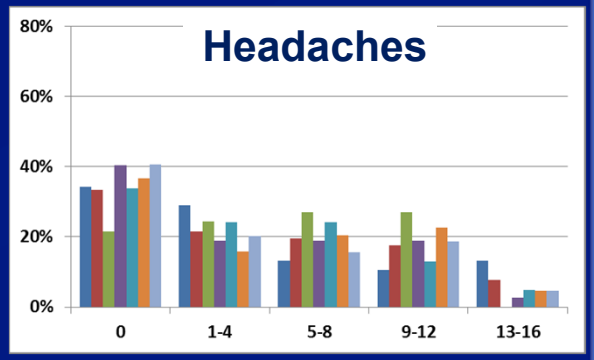


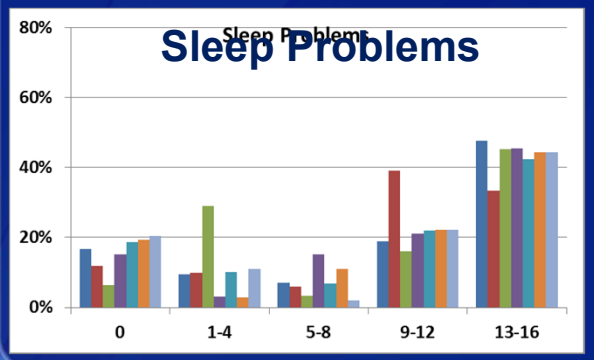


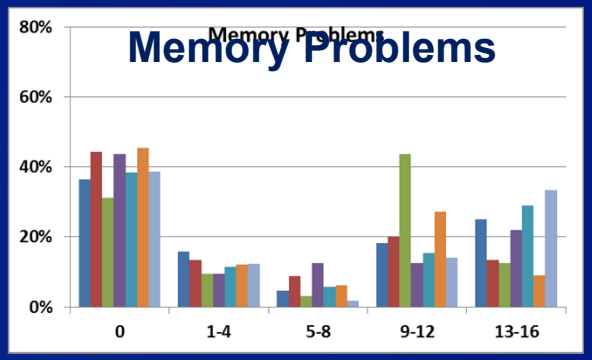


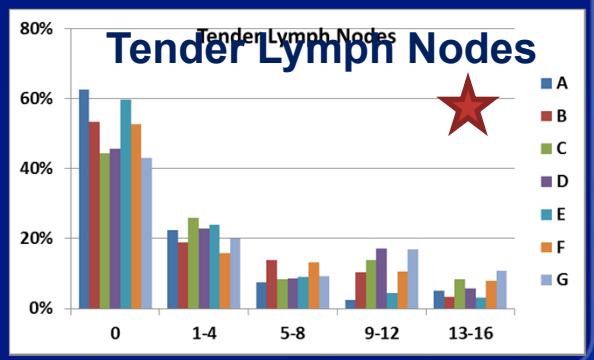




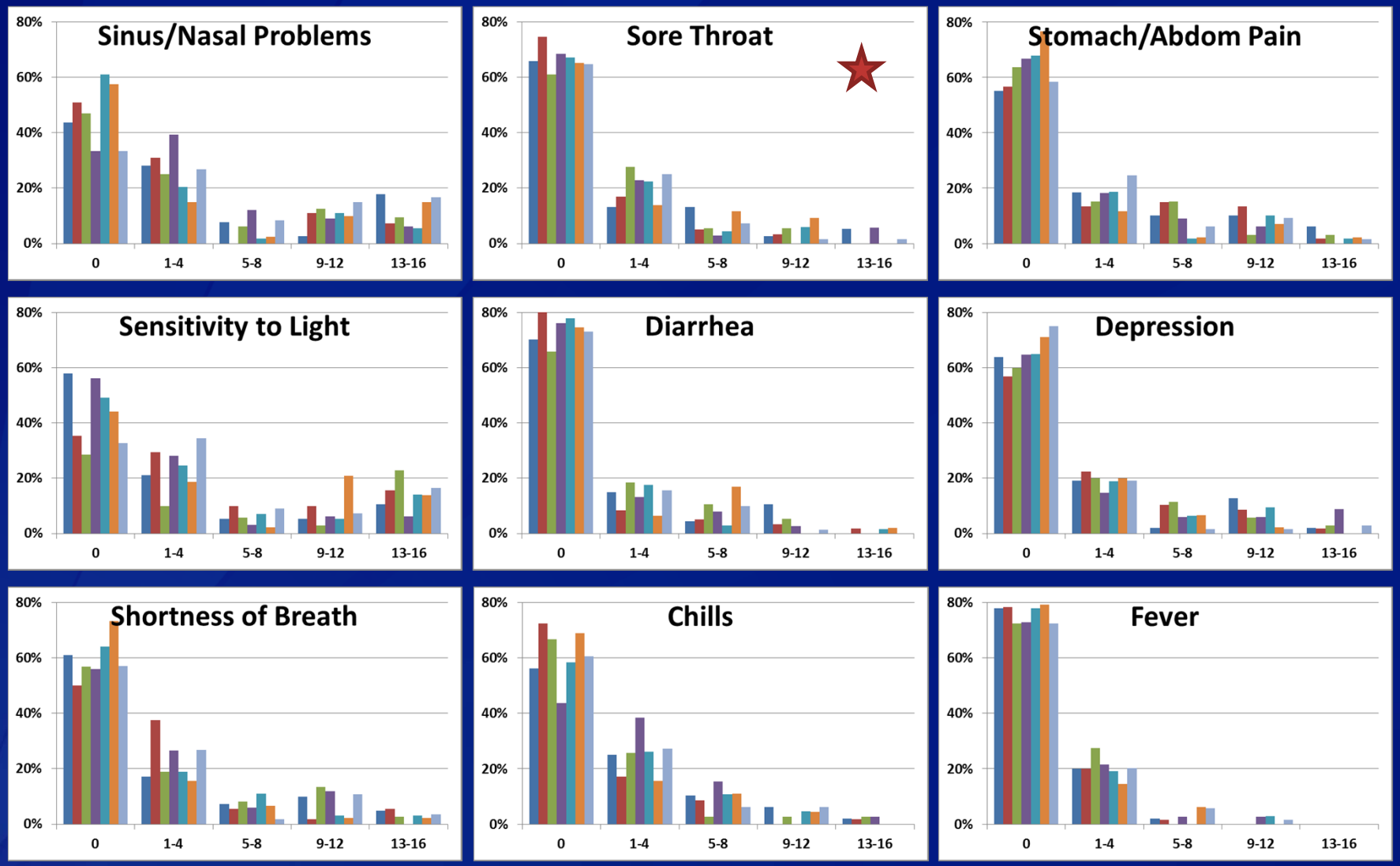




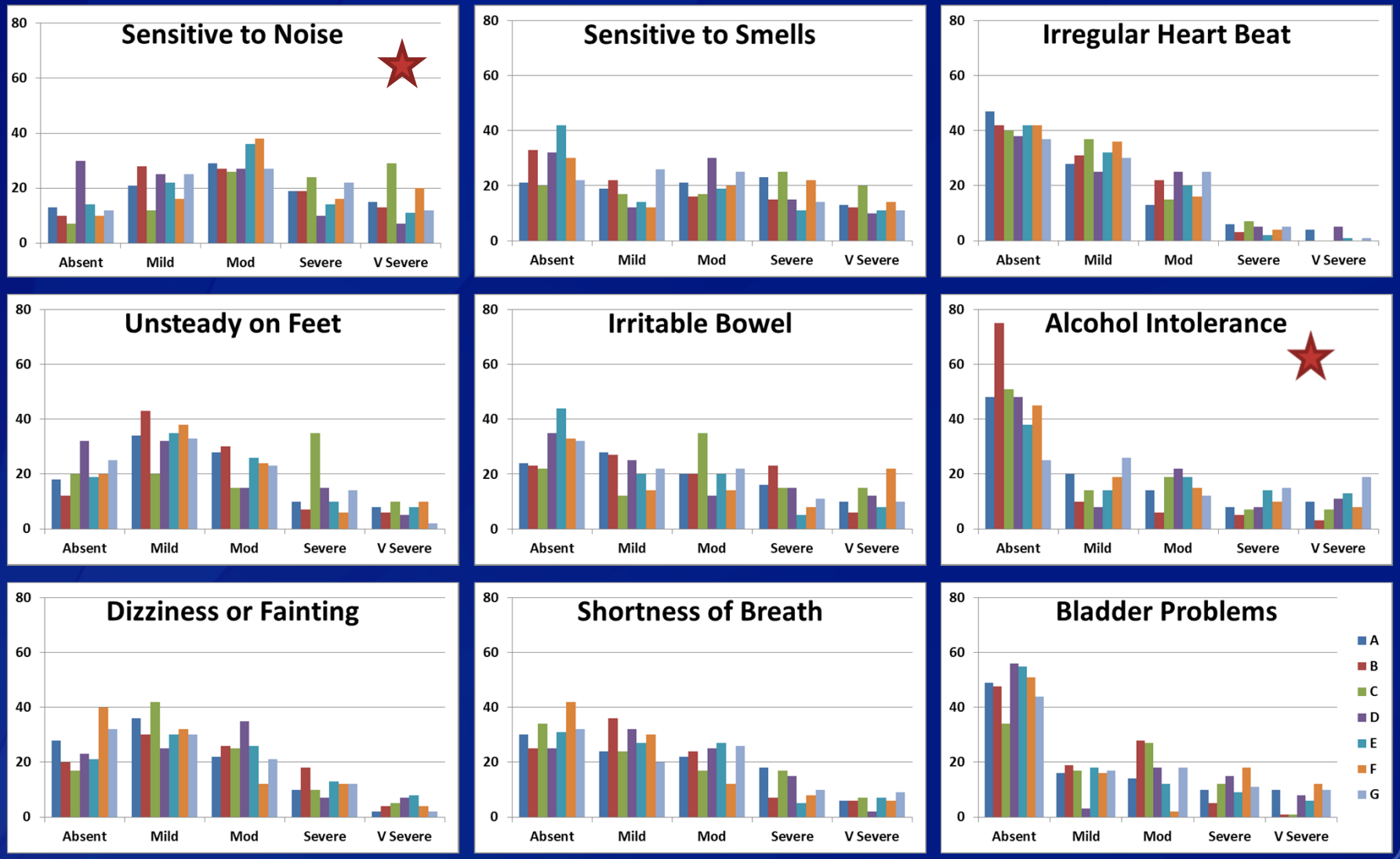




Distribution of CDC SI –Scores by Clinic



Distribution of DSQ- Severity by Clinic



Mean PROMIS T-Scores (SD)

Patient Sample	Fatigue	Sleep Disturbance	Sleep Related Impairment	Pain Interference	Pain Behavior
CFS – This Study	68. 3 (7.2)	59.3 (8.2)	62.2 (8.1)	61.9 (9.9)	57.2 (7.6)
[1]Chronic Pelvic Pain	56.0 (8.0)	59.0 (10.0)			60.0 (6.0)
[2]Spinal cord injury	52.4 (7.7)	52.6 (9.7)	49.8 (9.7)	56.8 (8.3)	
[2]Muscular Dystrophy	56.1 (8.2)	51.8 (9.1)	52.0 (9.6)	54.3 (8.8)	
[2]Post-polio syndrome	58.7 (7.2)	51.6 (9.1)	49.7 (8.7)	58.0 (7.9)	
[2]Multiple Sclerosis	58.2 (8.4)	52.4 (10.1)	53.3 (9.5)	56.4 (8.4)	

[1]J Minim Invasive Gynecol (2011) 18:189; [2]Arch Phys Med Rehabil (2012) 93:1289

Conclusions and Future Work

- **Interim analysis indicates heterogeneity of CFS population as a whole as well as between clinic**
  - However phenotypic measures appear limited in their ability to identify subgroups
  - Limitation of MFI-GF scale identified for CFS patients in specialty clinics
- **Final dataset will allow comparison of instruments measuring domains of CFS illness**
  - Follow-up important to correlate measures with course of illness
- **Additional measures of cognition and exercise capacity are planned in a subset of this study population**

Acknowledgements and Thanks

CFS Patient Study Participants

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Nancy Klimas
Elizabeth Balbin

Open Medicine Institute Consortium
Fatigue Consultation Clinic
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Hunter-Hopkins Center
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Wendy Springs
Open Medicine Clinic
Andreas Koglenik
Catt Phan
Richard Podell Medical
Richard Podell
Trisha Fitzpatrick
Sierra Internal Medicine
Daniel Peterson
Gunnar Gottschalk

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James Jones
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***Meredith Philyaw**
Ashish Rai
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Ashley Hagaman
Alex Pao
Lulu Tian

Clinical Outcome Assessments to Evaluate Treatment Benefit in Clinical Trials for CFS and ME

Ashley Slagle, MS, PhD
Oak Ridge Institute for Science and Education (ORISE) Fellow - Contractor
Study Endpoints and Labeling Development Staff
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

CLINICAL OUTCOME ASSESSMENTS TO EVALUATE TREATMENT BENEFIT IN CLINICAL TRIALS FOR CFS AND ME

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DISCLOSURES

- I have no conflicts to declare
- I am not speaking on behalf of the FDA
- The views expressed are my own based on my experience during my fellowship with the FDA
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EVIDENTIARY STANDARDS TO DOCUMENT TREATMENT BENEFIT

- Documented by "Substantial evidence" (21 CFR 201.56(a)(3))
- Evidence from "Adequate and well-controlled clinical trials"
- The methods of assessment are "well-defined and reliable" (21 CFR 314.126)

WELL-DEFINED AND RELIABLE METHODS OF ASSESSMENT

- Measures are well-defined and reliable when
  - Empiric evidence demonstrates that the score quantifies the <u>concept of interest</u> in the targeted <u>context of use</u>

ASSESSING TREATMENT BENEFIT IN CFS AND ME

- The impact of a treatment on how patients *feel, function,* or *survive*

- Outcome assessment options to evaluate treatment benefit include:
  - Measures of survival
  - Biomarkers
  - Clinical Outcome Assessments (COA)

ASSESSING TREATMENT BENEFIT USING BIOMARKERS

- Biomarker: an objective measure of biologic process, pathologic process, or biologic response to therapeutic intervention
  - Examples: VO2 max/anaerobic threshold; immune function markers
- Biomarkers do not directly reflect how patients feel, function, or survive
- May serve as indirect assessment of benefit, by showing biologic response to treatment
- Association ("replacement value") between the indirect assessment and how patients feel or function in daily life will need to be understood
  - For example what do circulating antibody levels tell us about how a patient feels or functions in daily life?

CLINICAL OUTCOME ASSESSMENTS (COA)

- Any assessment that may be influenced by human choices, judgment, or motivation
- Depends on the cooperation, implementation, interpretation, and reporting by one of the following:
  - A patient (PRO)
  - A clinician (ClinRO)
  - An observer (ObsRO)
- Comprised of:
  - A measure that produces a score
  - Clearly defined methods and instructions for administering the clinical outcome assessment
  - Clearly defined methods for assessing response
  - A standard format for data collection
  - Well-documented methods for scoring, analysis, and interpretation of results in the targeted patient population

CLINICAL OUTCOME ASSESSMENT CONSIDERATIONS

- Not all patient reported, clinical-reported, or observer-reported assessments are appropriate Clinical Outcome Assessments
  - May be useful for other purposes:
    - Diagnostic
    - Prognostic
    - Trial eligibility and trial enrichment
    - Epidemiologic or population studies
  - Measures used successfully for these other purposes will not necessarily be appropriate outcomes assessments (i.e., they may not be able to reliably detect treatment benefit in clinical trials)
- Clinical outcome assessments may be used independently in clinical trials
  - While biomarkers and clinical outcome assessments may be used together to identify patients or assess treatment benefit in clinical trials, there is no requirement to identify and use a biomarker in parallel with a clinical outcome assessments
  - Requirement is that assessment is well-defined and reliable

CONSIDERATIONS FOR SELECTING A CLINICAL OUTCOME ASSESSMENT

- Context of Use
- Concept of interest (the *thing* we want to measure)
- Conceptual Framework
- Other (e.g., recall period; length of questionnaire, measurement properties)

SELECTION OF A CLINICAL OUTCOME ASSESSMENT

- Depends on a particular Context of Use
  - Disease definition (explicit and specific to the clinical trial population)
  - Disease characteristics (e.g., severity, duration)
  - Clinical characteristics (e.g., co-morbidities)
  - Demographics (e.g., age group)
  - Setting (i.e., inpatient or outpatient if applicable)
  - General plan for study design (e.g., superiority or non-inferiority; randomized and blinded)
  - Endpoint positioning (i.e., how does this assessment fit in with the other endpoints selected for the study?)
  - Type of claim sought (e.g., symptomatic improvement vs. delay to onset of acute episode)

CONTEXT OF USE CHALLENGE IN CFS AND ME

- In CFS and ME, the disease definition is still unclear
  - For clinical trials, that's OK – investigators will need to identify a rational set of clinical trial entry criteria and select outcome measures appropriate to that specific subpopulation
    - It will be important to exclude other diseases, recognizing that in clinical practice some conditions may coexist, but clinical trial population needs to be pure, and must develop/evaluate potential outcome measures using this pure population
  - There are many subpopulations, for whom outcome measures might be different
    - Acute onset and gradual onset
    - Patients with orthostatic postural symptoms and those without
    - Adults and children (and others who may not be able to report for themselves)
    - Those with abnormal neurological findings and those without
    - Recent onset and those with long-time suffering
    - Severe forms and less severe forms
    - Patients with varying symptom experiences (e.g., general all-day fatigue vs. post-exertion fatigue)
    - Others?

SELECTION OF A CLINICAL OUTCOME ASSESSMENT

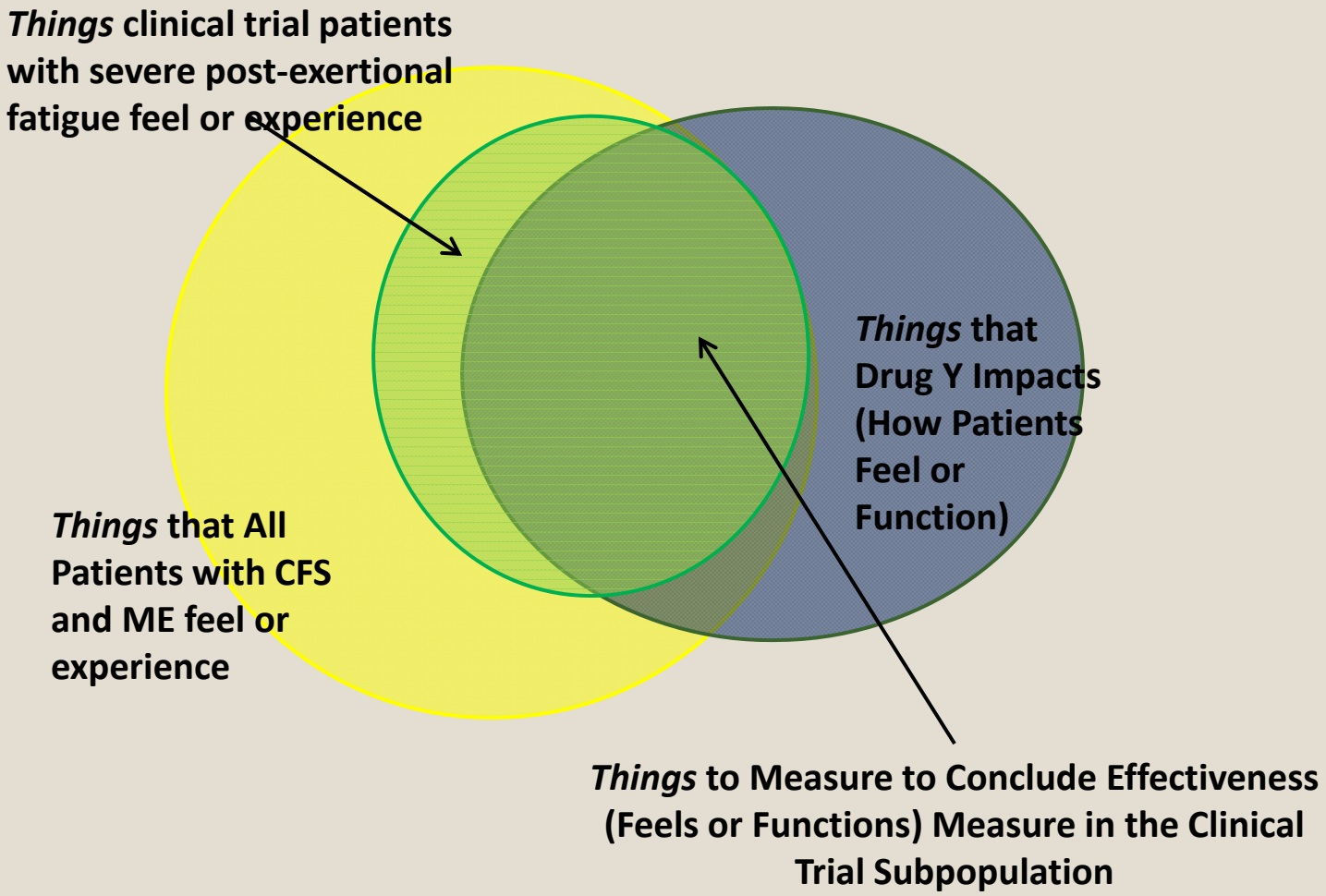
- Depends on what concepts are relevant and important to assess (i.e., the *things* we want to measure) in the particular context of use

CONCEPTS OF INTEREST (THE *THINGS* WE MAY WANT TO MEASURE)

- Fatigue (Multidimensional)
  - May be general / unchanging over the course of the day or related to exertion:
    - Physical tiredness
    - Mental tiredness/'brain fog'
    - Related to lack of sleep, sleepiness
    - Post-exertional
    - (wired fatigue, energy fatigue, flu-like fatigue[1])
    - Others ?
- Sleep problems
- Pain (body, joints, eye, chest, abdomen)
- Headache
- Muscle difficulties (twitching, weakness, stiffness, numbness
- Sensitivity to stimuli (lights, noises, smells)
- Cognitive difficulties (remembering, paying attention, finding words, focus, comprehension)
- Bladder of GI problems
- Feeling unsteady or dizzy
- Weight changes or appetite problems
- Sweating (hands; night sweats)
- Feeling hot or cold
- Cold or flu-like symptoms (sore throat, sore lymph nodes, fever, others?)
- Nausea/Vomiting
- Shortness of breath
- Irregular heartbeat
- Depth perception problems
- Alcohol intolerance
- Reduced Activity
- Assistance needed with activities
- Emotional concerns (nervousness, anxiety, depressed feelings)
- Visual problems
- Altered taste or smell
- Ringing in the ears
- Gait/walking problems

1 Jason et al., 2009. Examining Types of Fatigue Among Individuals with ME/CFS. Available online: http://dsq-sds.org/article/view/938/1113 . Disabil Stud Q. 2009 29(3).

Things Related to How Patients Feel or Function (Concepts) in CFS and ME Subpopulation of Patients with Severe Post-exertional Fatigue



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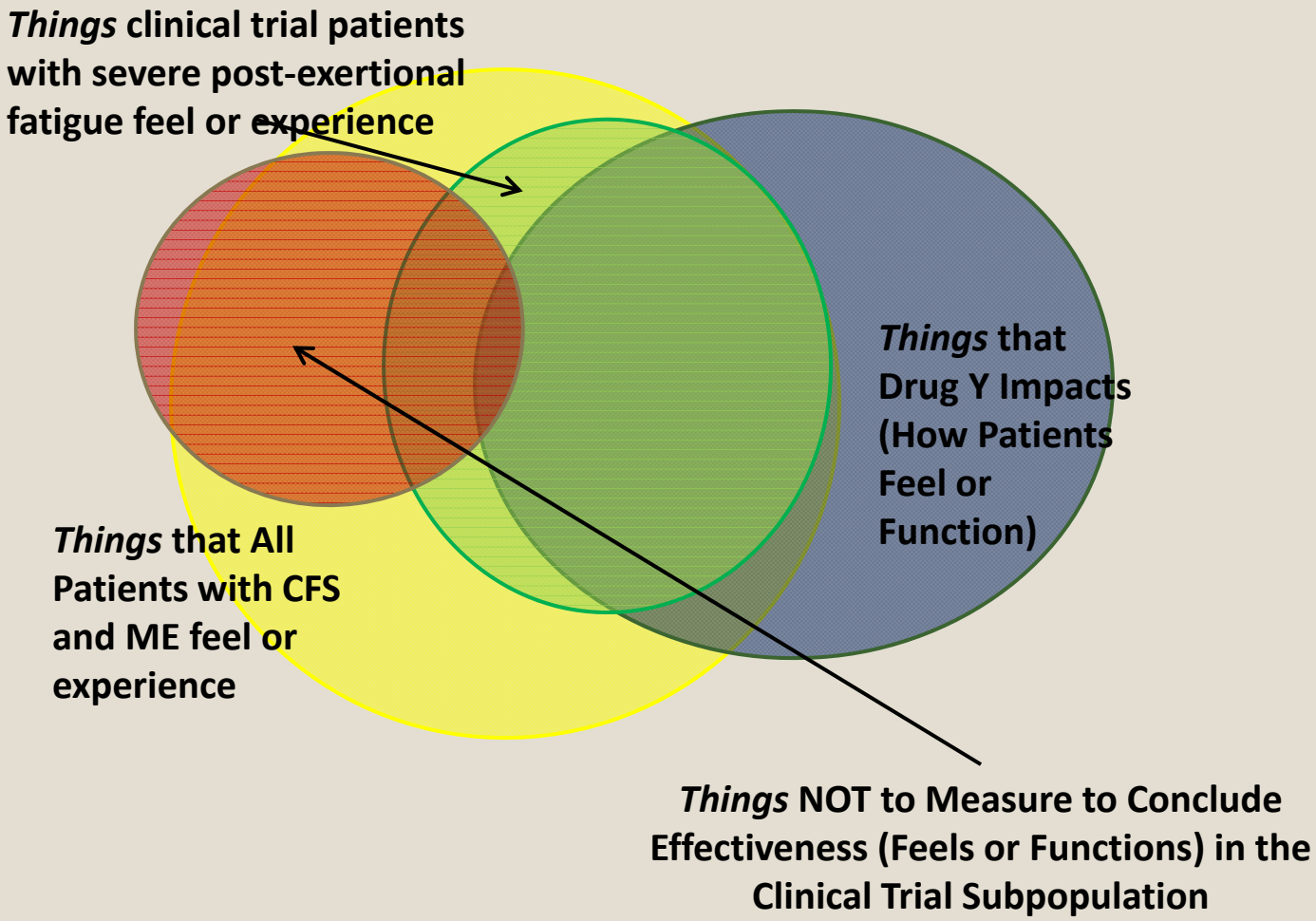
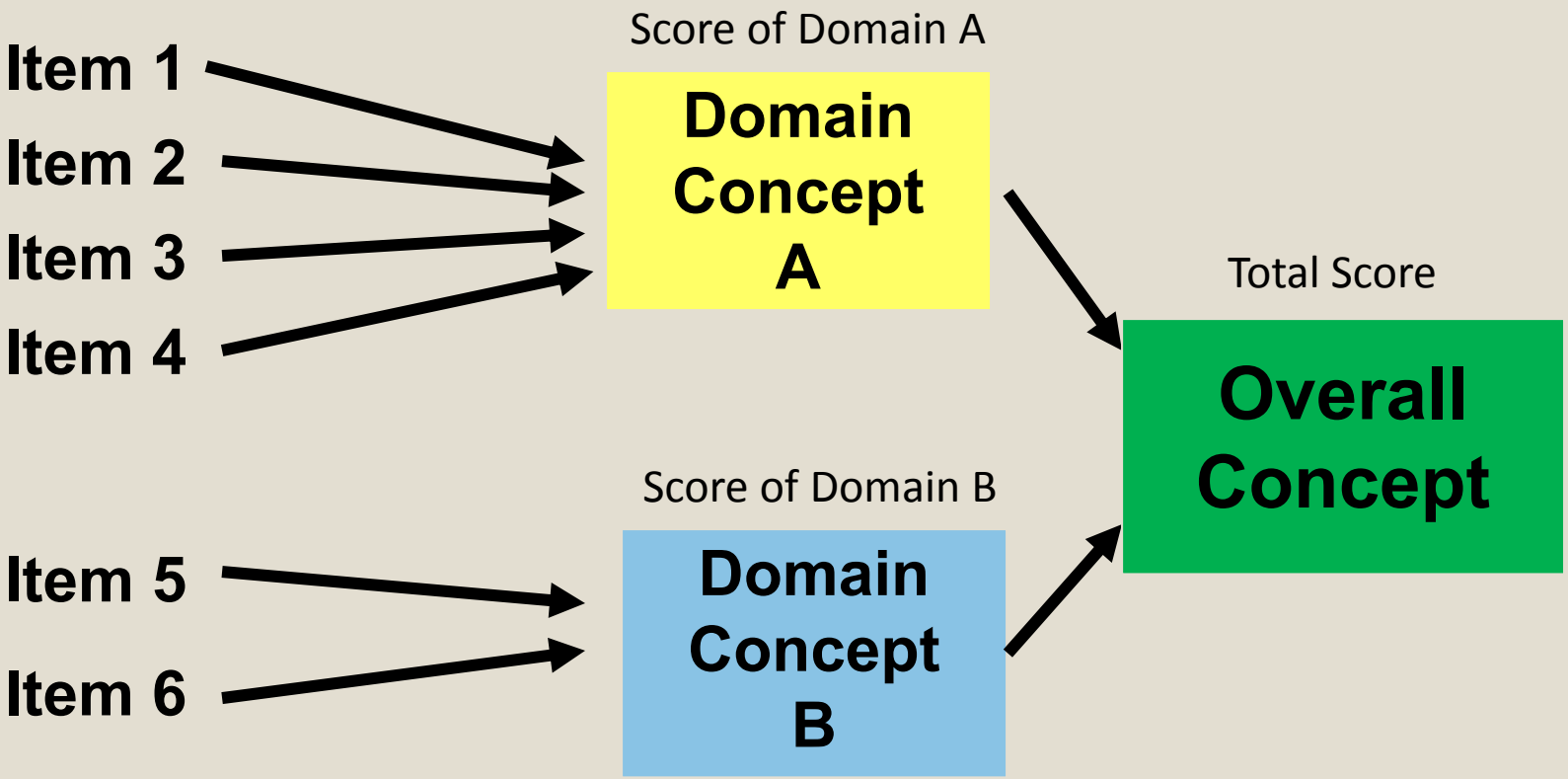


FOR EXAMPLE, CONCERNS ABOUT CONTENT VALIDITY…

- Study population = primarily bed-ridden, minimal physical activity (e.g., walking to the bathroom) very difficult
- Concept of interest to evaluate treatment benefit = physical functioning
- Clinical Outcome Assessment = patient-reported questionnaire to assess physical functioning
- One question in the assessment = "Do you have trouble running to the bus?"

CONCEPTUAL FRAMEWORK OF A CLINICAL OUTCOME ASSESSMENT



OTHER CONSIDERATIONS FOR SELECTING CLINICAL OUTCOME ASSESSMENTS FOR USE IN CLINICAL TRIALS

- Things to consider that impact content validity:
  - Recall period
  - Length (number of questions)
    - Long enough to capture all needed information, but not too long to overburden patients
      - Repeated administration: administered multiple times (e.g., daily) in clinical trials
  - Mode of administration
    - Electronic data capture helps limit missing data
  - Other measurement properties

EXAMPLES OF PATIENT-REPORTED OUTCOMES USED IN CFS AND ME

Measures of Multiple Concepts (Include Symptoms and Impacts)

DePaul Symptom Questionnaire (DSQ)
CDC Symptom Inventory
Patient Health Questionnaire (PHQ)
Functional Capacity Scale (FCS)

Measures of 'Fatigue'

ME/CFS Fatigue Types Questionnaire (MFTQ)
Multidimensional Fatigue Inventory (MFI)
PROMIS Fatigue short form
Brief Fatigue Inventory (BFI)
Fatigue Severity Scale (FSS)
Fatigue Impact Scale (FIS)
(CIS-20) Fatigue Scale

Physical Function / Abilities
Activities of Daily Living (ADLs)

Measures of Health Status
(SF-36): Health Status

Measures of Pain
Brief Pain Inventory (BPI)

Measures of Sleep
Epworth Sleepiness Scale (ESS)

EXAMPLES OF CLINRO AND OBSRO MEASURES USED IN CFS AND ME

Clinician-reported Assessment of Disability
Karnofsky Performance Scale

Clinician-reported Assessment of Exercise Capacity
Exercise Treadmill Testing

Observer-reported Outcome Assessments
None identified

EXAMPLES OF CHALLENGES IDENTIFIED WITH AVAILABLE CLINICAL OUTCOME ASSESSMENTS FOR USE IN CLINICAL TRIALS

- Developed as diagnostic or classification tool, not sensitive to treatment effects
- Developed as an epidemiological assessment, very comprehensive
- Generic measures, developed for a broad population, not specific to CFS and ME context of use
- Conceptual framework concerns
  - No conceptual framework and scoring algorithm available (e.g., checklists)
- Concerns with individual items
  - Items too general to determine what is being assessed (e.g., 'some signs or symptoms of disease ' are present)
  - Items use terms that are not clear or relevant to CFS and ME patients (e.g., "I feel fit"; "I feel peppy")
  - Items ask about 'fatigue', without defining
  - Item content is confusing (e.g., 'double-barreled' items: "trouble falling asleep or sleeping too much")

CURRENTLY IDENTIFIED CLINICAL OUTCOME ASSESSMENTS

- None of the reviewed instruments to date appear sufficiently well-defined and reliable to assess treatment benefit in clinical drug trials among CFS and ME patients

- Of course, no one wants the perfect to be the enemy of the good

WHAT ARE OUR CLINICAL OUTCOME ASSESSMENT OPTIONS IN CFS AND ME?

- Find an existing measure that is appropriate for use in clinical trials for a defined population(s) of CFS and ME patients
- Modify an existing assessment for use in clinical trials for a defined population(s) of CFS and ME patients
- Develop a new symptom assessment for use in clinical trials for a defined population(s) of CFS and ME patients

PARTNERING WITH THE FDA THROUGH THE DDT QUALIFICATION PROGRAM

- A novel and voluntary submission process for drug development tools (DDTs), intended for potential use, over time, in multiple drug development programs
- Goal: Publicly available drug development tools (e.g., clinical outcome assessments)
- Publication in the Federal Register and FDA DDT website
- Builds on developing public-private partnerships between FDA and consortia representing medical product industry, instrument developers, NIH, academia, and patients
- DDT Qualification Draft Guidance available: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf
- PRO Guidance describes good principles for measure development: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- DDT clinical outcome assessments qualification Liaison can discuss this in more detail/answer questions: SEALD.ENDPOINTS@fda.hhs.gov

Panel 3:
Audience Question and Answer Period

All Panelists

CHERRY BLOSSOMS ON THE TIDAL BASIN

Panel 4: Roundtable Discussion – Summary and Path Forward

Moderators:

Dennis Mangan, PhD

Badrul Chowdhury, MD

Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Panel 4:
Roundtable Discussion - Summary and Path Forward

- Lily Chu, MD, MSPH
- Jordan Dimitrakoff, MD, PhD
- Nancy Klimas, MD, FACP, FIDSA
- Nancy Lee, MD
  - Deputy Assistant Secretary for Health; Director, Office of Women's Health, Department of Health and Human Services
- Susan Maier, PhD
  - Deputy Director, Office of Research of Women's Health, National Institutes of Health
- Theresa Michele, MD
- Robert Miller
  - Patient
- Jody Roth, MS, RAC
  - Director Regulatory Affairs, Biomedicines, Eli Lilly and Company

Panel 4: Question 1

- What were the key messages on drug development you heard at this meeting?

Panel 4: Question 2

- What do you think are the most important factors in facilitating drug development in CFS and ME?

Panel 4: Question 3

- Based on the discussion from Panel 3, what clinical trial design elements are most important to ensure success of drug development programs for CFS and ME?

Panel 4: Question 4

- What do you think are the most important barriers to conducting research for CFS and ME and what can be done to overcome them?

Panel 4: Question 5

- How can we best leverage your individual experiences in order to facilitate drug development in CFS and ME? Please respond for your own group as identified below:
  - Other Health and Human Services (HHS) Agencies
  - FDA
  - Pharmaceutical and Biotech Companies
  - Academia
  - Patient/Advocacy community

Panel 4: Question 6

- What are possible next steps following this meeting? Please respond for your own group as identified below:
  - Other Health and Human Services (HHS) Agencies
  - FDA
  - Pharmaceutical and Biotech Companies
  - Academia
  - Patient/Advocacy community

Panel 4:
Audience Question and Answer Period

All Panelists

Closing Remarks

RADM Sandra Kweder, MD
Deputy Director, Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration