AUPN-VA Chiefs Workshop: Clinical Trials within the VA: Feasible and Necessary

Friday, October 20, 2023

AUPN
Association of University Professors of Neurology

Speakers

Vanessa Hinson, MD, PhD
Medical University of South Carolina
Ralph H. Johnson VA Medical Center

Moderator

John Duda, MD
Michael J. Crescenz VA Medical Center

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Michael J. Crescenz VA Medical Center

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Ralph H. Johnson VA Medical Center

Rebecca Walker
VA Puget Sound Health Care System

Course Description

- This virtual program will discuss feasibility of conducting clinical trials within the VA health care system.
- Overall goal: Encourage investigators to conduct research that includes Veterans.
- We will:
  - Discuss the role of VA affiliated non-for-profit research organizations
  - Introduce the VA Cooperative Studies Program introduced
  - Talk about ways to conduct industry sponsored research within VA
  - Learn how to best facilitate Veteran trial participation with an academic affiliate.

Learning Objectives

1. Define the role of non-for-profit research organizations in VA research
2. Restate the role of the VA Cooperative Studies Program
3. Identify ways to include Veterans in clinical trials through VA based programs or an academic affiliate

Save the Date!
AUPN In-Person Satellite Meeting

The VHA Workshop will be <u>in-person</u> starting in 2024!

Saturday, September 14, 2024 | 7:00am – 6pm ET
The Hilton Orlando Convention Hotel

- **Held <u>the day before</u> the ANA Annual Meeting**

The Satellite Meeting will offer <u>in-person educational sessions</u> for:

- Chairs – new & experienced
- Program Directors
- Clerkship Directors
- **VA Chiefs** *(VHA Workshop: 12:45pm – 2:15pm)*
- Women Leaders

The day will conclude with the **AUPN Business Meeting & Awards Ceremony** & a **Reception** hosted by the Past Presidents of AUPN

OVERVIEW OF THE VA COOPERATIVE STUDIES (CSP) PROGRAM and my experience with it

John Duda, MD
BLR&D Senior Career Research Scientist
National Director VA PADRECCS

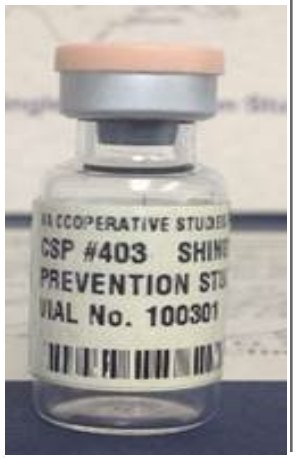
DISCOVERIES & BREAKTHROUGHS

Implantable pacemaker (1950s)

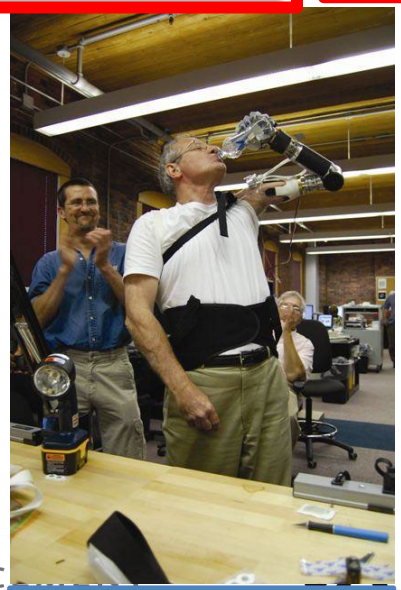
1st Liver transplant (1967)

Antihypertensive medication use (1970s)

Aspirin reduces heart attacks & death (1983)



ZostaVax Shingles Vaccine (2011)



VA-DEKA Arm (2014)

CSP study

VA funding organization

NIH	VA
R21, other	Local, regional, national pilots
K	CDA programs
R01	MERIT Review
Center (P, U)	COEs (‘RECCs), Center grants, CSP

Eligibility for VA Research Support

INTRAMURAL program: NO grants to colleges, universities, or any other non-VA entity:

PI/Co-Pis: demonstrate a **primary professional commitment to VA**:

VA Employment status – A current VA paid appointment of at least (5/8ths)

can be contingent

Physical presence at VA – VA research must be conducted, *principally*, in a VA facility.

VA Information Systems –use VA email for VA correspondence and VA business, and must comply will all VA privacy and information security requirements.

Commitment to VA –evidence of past and current roles and responsibilities within VA.

Merit Review Award Program

BLR&D: laboratory studies, *in vitro* and *in vivo,* including tissue culture, animal models and studies on human biological samples.

CSR&D: interventional, experimental, and observational studies involving human subjects.

RR&D: and to improve the health and rehabilitative care of veterans and our Nation

HSR&D: promote innovations in quality, effectiveness, efficiency, cost, and accessibility of health service to improve the health and care of Veterans.

Merit Review funding supports research by fully-trained independent investigators, analogous to NIH R01 grants.

Research Career Development Program

Mentored research time--advance awardees toward independence as funded VA scientists, *analogous to NIH K grants*.

Do not need to be VA employees AT THE TIME OF APPLICATION
FACILITY COMMITMENT to hire *if* funded

CDA-1 (limited): initial mentored research experience, up to two years of salary support.
no more than two years beyond completion of training

CDA-2: salary (75%) and/or project funds (not a lot). three to five year program of research career development and mentoring.
no more than five years beyond completion of training

CANNOT HAVE MORE THAN 25% ASSIGNED CLINICAL TIME

Research Career Development Program

-- **S**tarts with a Letter of intent (LOI)

-Short, basic, just to establish eligibility and get appropriate reviewers

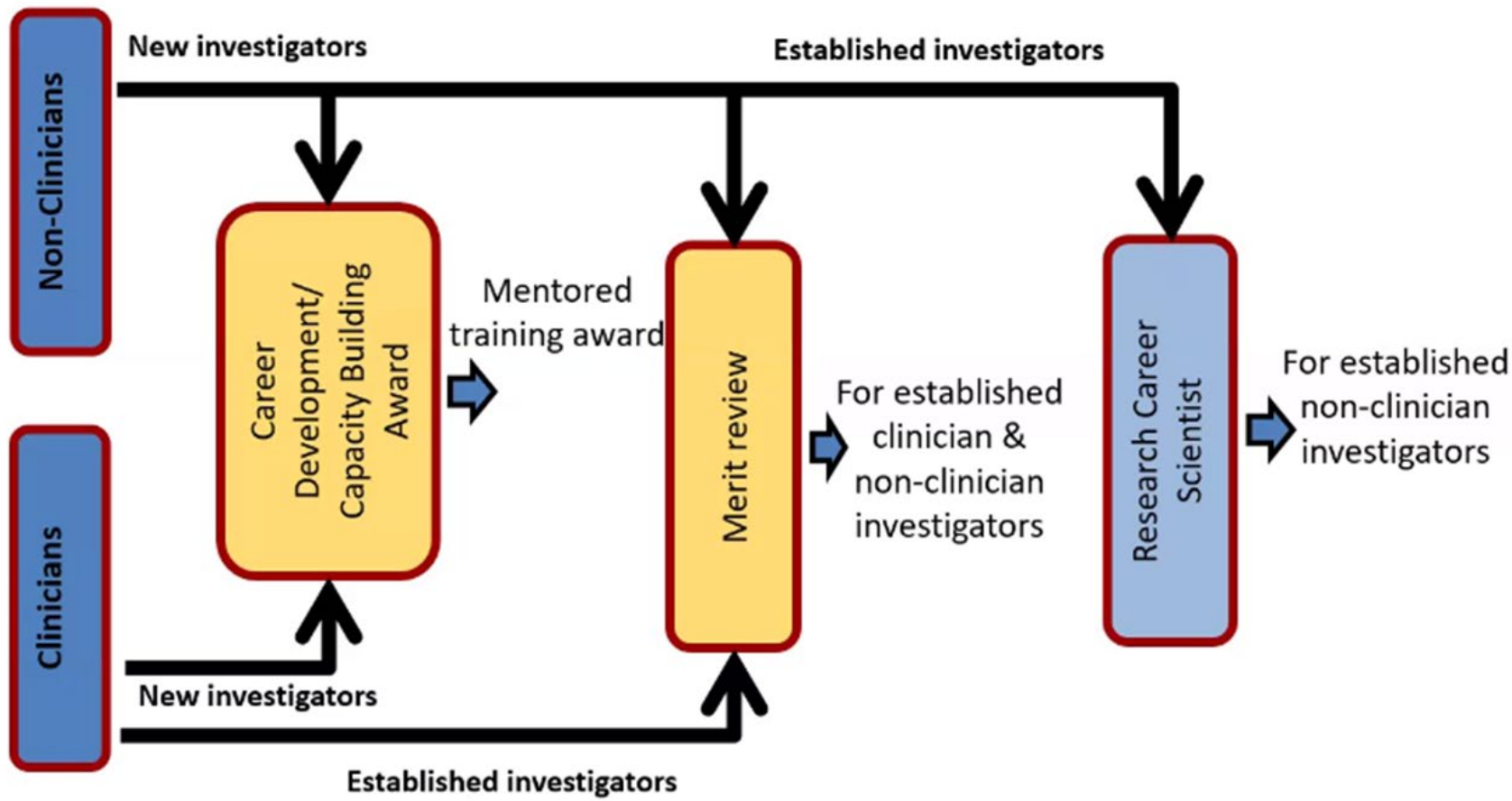
-usually 6-8 weeks before the full application

--Research project is important but:

-"The man (woman), the fan and the plan" are equal

- Don't just think about the "idea", build a mentoring team

Research Career Pathways



Cooperative Studies Program (CSP) OVERVIEW

- CSP is a national infrastructure for sponsoring, developing & executing:
  - Multi-site clinical trials
  - Epidemiological & population research
  - Innovative approaches in genomics, data science and informatics

- First Cooperative Study conducted in 1940s on streptomycin for treating tuberculosis in WWII veterans
  - Program formally established in 1972

- Nearly **200** clinical trials and observational studies completed including landmark studies in cardiovascular disease / cardiovascular surgery, infectious diseases, surgery, gastroenterology, mental health, oncology, and endocrinology.

CNN.com /health

MATTERS OF THE HEART

updated 5:16 p.m. EDT, Wed August 13, 2008

Drugs may be as good as stents for heart patients

USA TODAY

Health and Behavior

Posted 6/1/2005 7:06 PM Updated 6/1/2005 9:30 PM

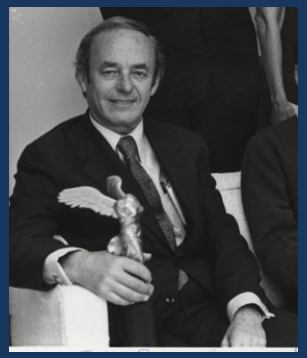
Shingles vaccine cuts cases by half

By Steve Sternberg, USA TODAY

U.S.News

By Serena Gordon
HealthDay Reporter
June 5, 2019, at 5:00 p.m.

Tight Diabetes Control Alone May Not Benefit the Heart Long-Term



WebMD
Better information. Better health.

New Look at Brain Stimulation for Parkinson's

Study Shows Good Results When Either of 2 Areas of Brain Are Targeted

By Katrina Woznicki
WebMD Health News
June 3, 2010

SCIENTIFIC AMERICAN

HEALTH

Veteran Genome Project Serves as an Early Test Bed for Customized Care

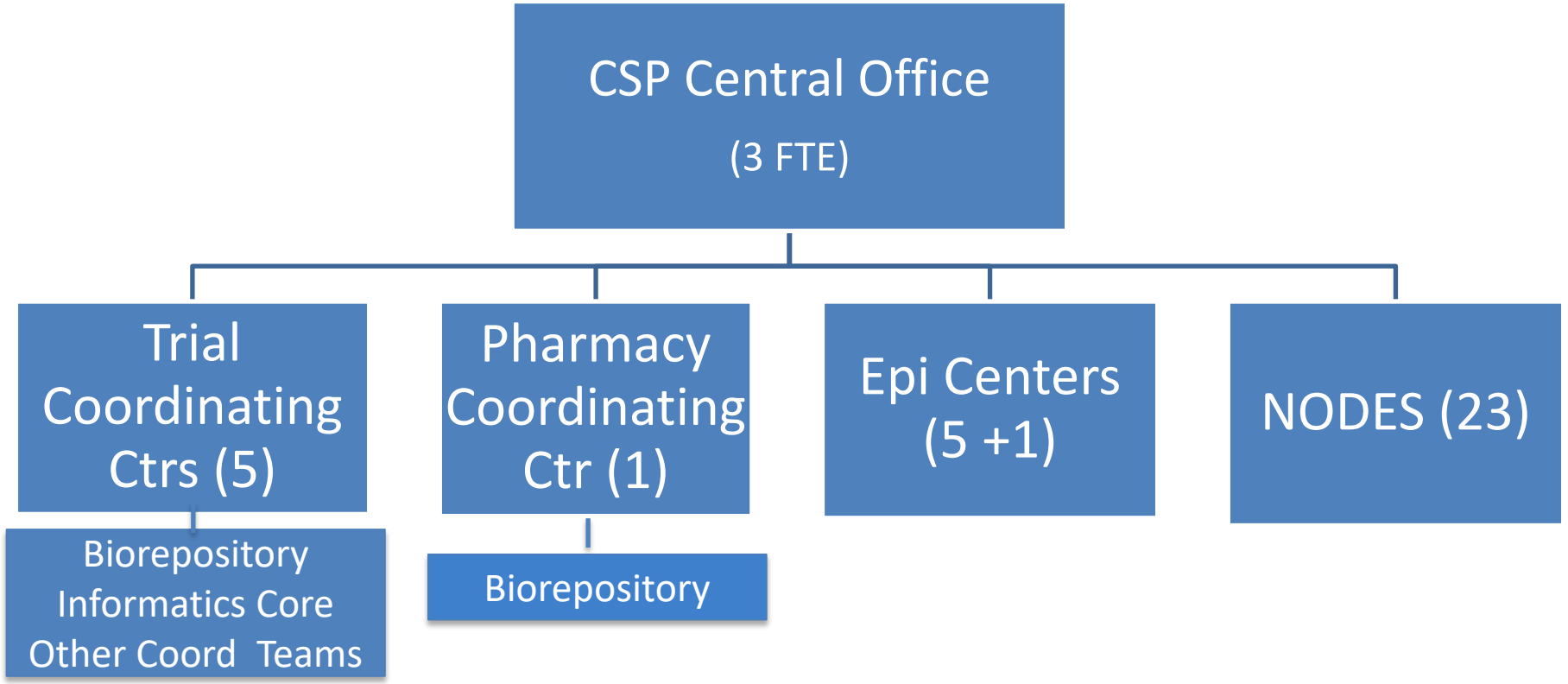
REUTERS

Bypass surgery safer using heart-lung pump - study

By Gene Emery

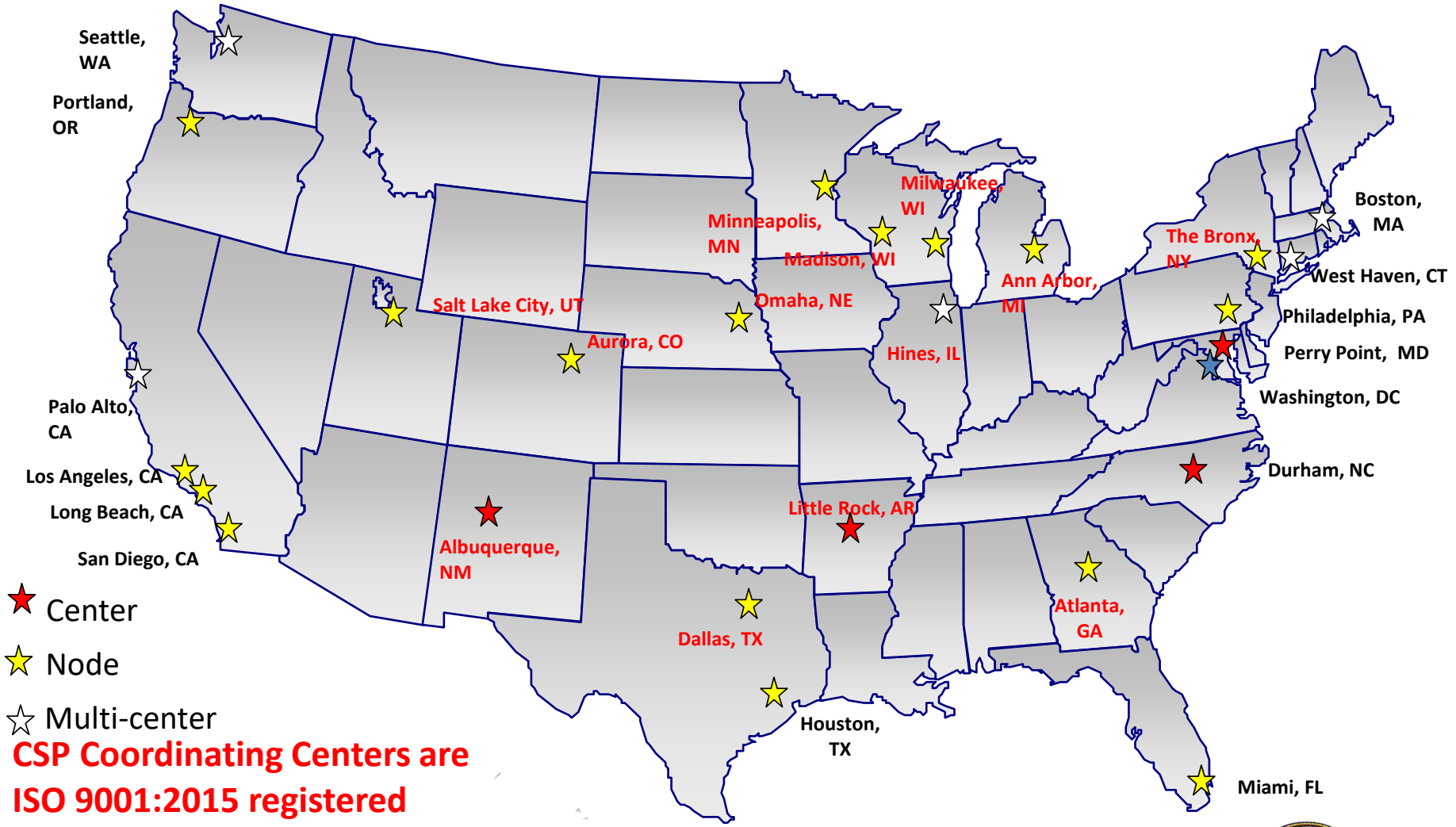
BOSTON, Nov 4 (Reuters)

CSP ORGANIZATION & PERSONNEL



- ~750 FTE (not including study personnel / sites)
- Centers primarily manage ~30 study protocols
- Staff also work in a matrix framework
- Range of professional expertise – scientific, administrative, clinical, quality, others

COOPERATIVE STUDIES PROGRAM:
VA NATIONAL CLINICAL RESEARCH ENTERPRISE



CSP Coordinating Centers are ISO 9001:2015 registered

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

DISCOVERY ★ INNOVATION ★ ADVANCEMENT

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
Office of Research and Development

CSP CLINCAL RESEARCH EXPERTISE

- Biostatistical / epidemiological (PhDs, ScDs)
- Clinical (MDs, PharmDs)
- Safety and regulatory oversight
- Data management
- Informatics / Data science
- Pharmaceutical management
- Project management
- Fiscal / budgetary
- Administrative (HR, Contracting)
- Quality & regulatory
- Genetics
- Site-level recruitment & operations

CSP COORDINATING CENTERS

- National network of centers that provide statistical and administrative leadership for designing and conducting CSP studies

- Responsible for central project management
  - Data collection / verification
  - Maintaining study records
  - Managing study budgets/finances
  - Monitoring site adherence to protocol
  - Communicating with key parties
  - Providing statistical analyses / reports

- Locations: Boston, Hines, Palo Alto, Perry Point/Baltimore, West Haven

CSP PHARMACY COORDINATING CENTER

- PCC services:
  - Pharmaceutical Project Management
  - Manufacturing (tablets, capsules, liquid filled capsules, liquids)
  - Dosage formulations and blinding
  - Packaging, labeling, and distribution
  - Biopharmaceutics/pharmcokinetics laboratory including quality control testing
  - Clinical chemistry central laboratory services
  - Regulatory submissions
  - Adverse event coding using MedDRA
  - Good Clinical Practice monitoring and auditing services
  - Information technology including drug assignments, randomization, and inventory tracking

- Location: Albuquerque

CSP EPIDEMIOLOGY CENTERS

- Supports epidemiologic research on Veterans' health and disease burden through
  - scientific expertise, human capital, data, research infrastructure

- Primary activities:
  - Designing and conducting large-scale observational epidemiologic studies
  - Providing scientific and administrative stewardship and sharing of epidemiologic resources
  - Enabling scientific collaborations and disseminating study findings

- Locations: Boston, Durham, Palo Alto, Seattle, West Haven

NETWORK OF DEDICATED ENROLLMENT SITES (NODES)

- Consortium of VA sites dedicated to conducting CSP studies to enhance the ***overall performance***, ***compliance*** and local ***management***
- A collaborative team that ***shares best practices*** and ***provides local insights*** on efficient and effective study design and execution

CSP INFORMATICS / DATA SCIENCE EXPERTISE

- Workflow modelling & design
- Data repository & database development
- User interface design & development
- System architecture design
- Development, integration & evaluation of software applications
- Reporting & advanced analytics
- Knowledge engineering & phenotyping
- NLP
- Data deidentification
- Medical image curation

CSP INFORMATICS / DATA SCIENCE ROLES

- Software developer
- Data scientist (AI/ML, NLP, image processing, phenotyping)
- Data engineer
- Software quality assurance engineer
- User experience (UX) designer
- Technical project manager
- Computer systems analyst
- Medical image curator

CSP SCIENTIFIC REVIEW PROCESS

Letter of Intent submitted to CSP Central Office

Central Office Administrative Review

External Review
External Review
External Review

Approved or Disapproved for Planning Support by DCRADO / Director

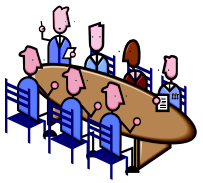
Planning Meetings Convened (2+)

Full Study Protocol Finalized

CSP partnered with study proponent and subject matters expertise

Ad hoc CSSEC Review
Biostat CSSEC Review
Clinical CSSEC Review

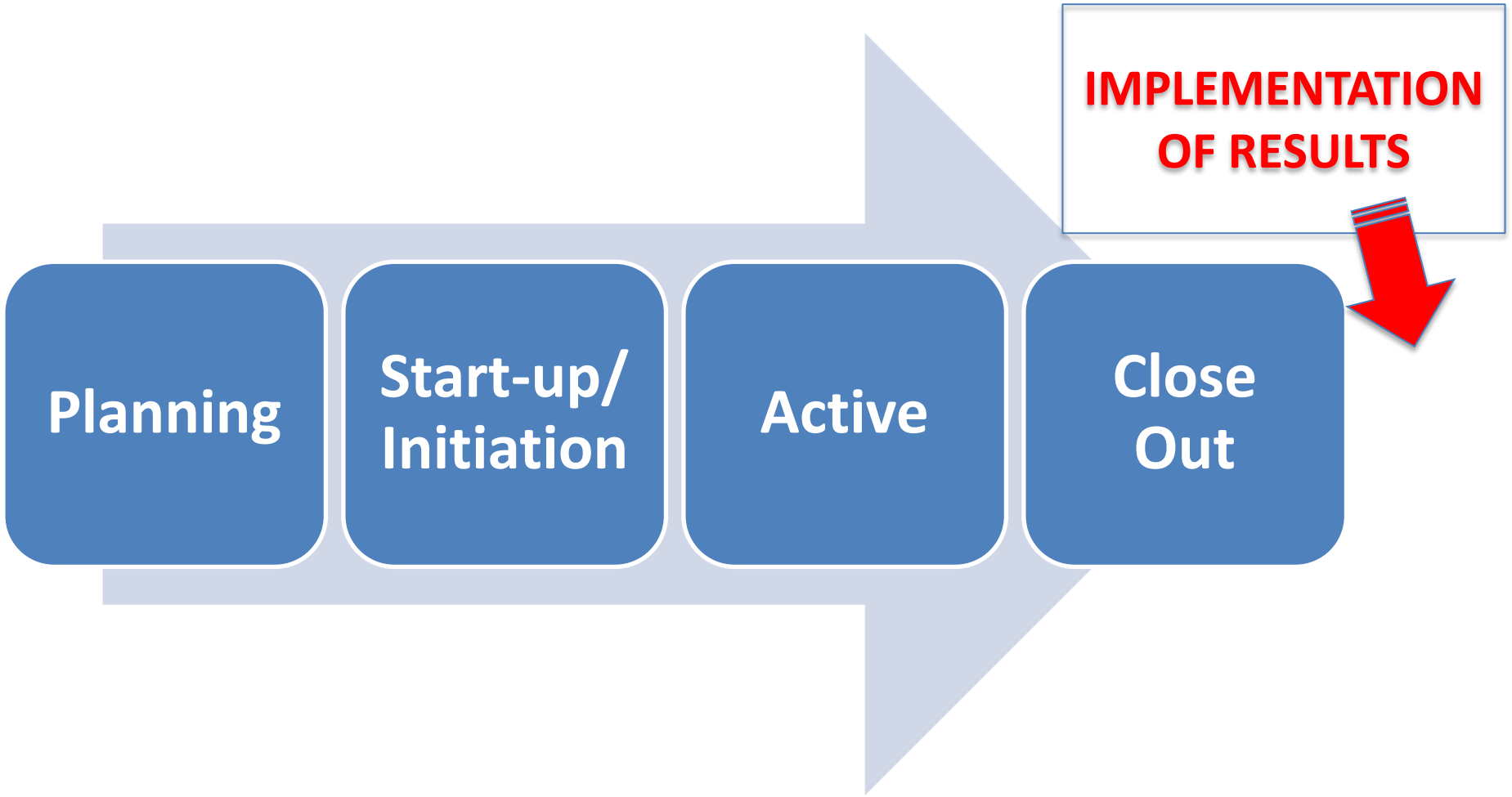
Cooperative Studies Scientific Evaluation Committee Review



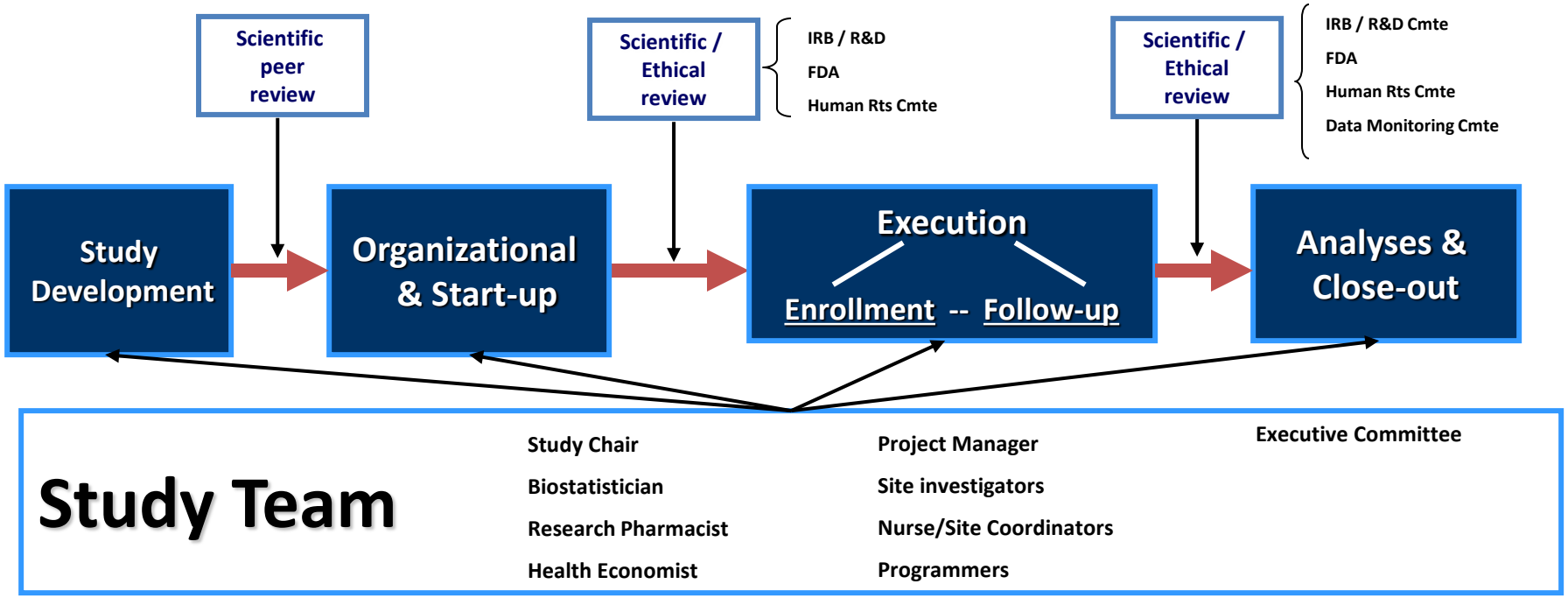
CSSEC Face-to-Face Study Review & Recommendation

Funding Decision by DCRADO / Director

CSP STUDY PHASES



CSP COLLABORATIVE APPROACH



ALL are key to the success of the study

CSP STUDY TOPICS in Neurology

- CSP #468, “A Comparison of Best Medical Therapy and Deep Brain Stimulation (DBS) of Subthalamic Nucleus and Globus Pallidus for the Treatment of Parkinson’s Disease”
  - The trial had two phases.
    - Phase I compared best medical therapy (medications and non-drug therapy) to deep brain stimulation (surgical intervention) for improving motor symptoms at six months; and
    - Phase II compared long-term (2 year) outcomes of surgical target for DBS [subthalamic nucleus (STN) vs. globus pallidus interna (GPi)] in improving motor function and reducing symptoms of PD.
  - Phase I found that time spent in the “on state” (good motor function and relief from PD symptoms) improved significantly for DBS patients compared to best medical therapy (BMT) patients.
  - Phase II found that both the GPi and STN groups improved significantly on motor function scores following DBS, with similar effects and quality of life improved in both groups after surgery.

CSP STUDY TOPICS in Neurology

- CSP #500, “Occurrence of amyotrophic lateral sclerosis (ALS) among Gulf War Veterans”
  - Chair: Ron Horner, PhD & Durham CSP Epidemiology Center
  - Found that military personnel who were deployed to the Gulf Region during the Gulf War period experienced a greater post-war risk of ALS than those who were not deployed to the Gulf.

- CSP #546, “A Randomized Clinical Trail of Vitamin E and Memantine in Alzheimer’s Disease”
  - Chair: Maurice Dysken, MD (Minneapolis VAMC)
  - Among patients with mild to moderate AD, 2000 IU/d of Vitamin E compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus Vitamin E. These findings suggest benefit of Vitamin E in mild to moderate AD by slowing functional decline and decreasing caregiver burden.

CSP STUDY TOPICS in Neurology

- CSP #558, "Robotic Assisted Upper-Limb Neurorehabilitation in Stroke Patients"
  - Chair: Albert Lo, MD, PhD (Providence VAMC)
  - Found that in chronic stroke survivors with moderate to severe upper-extremity impairment, 36 one-hour sessions of robot-assisted rehabilitative therapy resulted in modest improvements in motor function and quality of life 6 months after active therapy was completed compared to usual medical care following a stroke; at the end of robot-assisted active therapy (12 weeks), modest improvements were found for quality of life, compared to usual care; and over the 36 weeks of the entire study, there were also modest improvements for motor capacity and motor performance for robot-assisted therapy compared to usual care.

CSP STUDY TOPICS in Neurology

- CSP #567, "A Clinical Demonstration of an EEG Brain-Computer Interface (BCI) for ALS Patients"
  - Chairs: Robert Ruff, MD, PhD (Cleveland VAMC); Jonathan Wolpaw, MD (Albany VAMC); Richard Bedlack, MD, PhD (Durham VAMC); Patricia Banks, RN (Cleveland VAMC)
  - Found that the Wadsworth BCI home system is reliable and useful for patients in their homes; BCIs are most suitable for patients who are severely disabled but are otherwise healthy, such as those with severe cerebral palsy or high-level spinal cord injury; and improvements in convenience and performance should increase the number of patients who find BCIs useful and increase their usefulness.

CSP STUDY TOPICS in Neurology

- CSP #2003 - Exoskeleton Assisted-Walking for SCI
  - Study chairs: Ann Spungen, Ed.D. & William Bauman, M.D.
  - CSP Coordinating Center: Perry Point/Baltimore
  - Veterans with chronic SCI (> 6 months)
  - 2-armed RCT comparing home use exoskeletal-assisted walking device plus wheelchair standard of care (SOC) to SOC
  - 120 participants from 10 sites over 4 years
  - Primary outcomes:
    - Mental Health Component Scale of VR-36
    - Spinal Cord Injury – Quality of Life Scale for bladder, management difficulties, bowel management difficulties and pain interference

CSP STUDY TOPICS in Neurology

- CSP #2015, “Multicenter, Randomized, Double-blind Comparator Study of Antipsychotics Pimavanserin and Quetiapine for Parkinson’s Disease Psychosis (C-SAPP)"
  - Co-Chairs: Daniel Weintraub, MD and John Duda, MD (Philadelphia VAMC)
  - CSP Coordinating Center: Perry Point/Baltimore
  - A clinical trial comparing two antipsychotics for the treatment of Parkinson’s disease psychosis (PDP).
  - Most patients with PD experience significant non-motor symptoms, with psychosis occurring in 60% of PD patients long-term.
  - The most common PDP symptoms are visual hallucinations, followed by non-visual hallucinations and delusions.
  - This study seeks to enroll 358 participants from 24 VA medical centers.
  - Finding from this study will improve VA’s treatment options for PDP, an extremely debilitating disease for Veterans.

THANK YOU

Questions?

CONTACT

Grant D. Huang, MPH, PhD

Deputy Chief Research and Development Officer – Enterprise Optimization

Director, Cooperative Studies Program

VHA Office of Research and Development

810 Vermont Ave, NW

Email: grant.huang@va.gov

Experience from the VA ALS clinic: Trial collaborations with academic affiliates

COLIN QUINN, MD
DIRECTOR, CMJC VAMC INTERDISCIPLINARY ALS CLINIC
DIRECTOR, NEUROMUSCULAR CLINCIAL TRIALS
ASSOCIATE PROFESSOR OF CLINICAL NEUROLOGY
UNIVERSITY OF PENNSYLVANIA

Penn
University of Pennsylvania

U.S. Department of Veterans Affairs

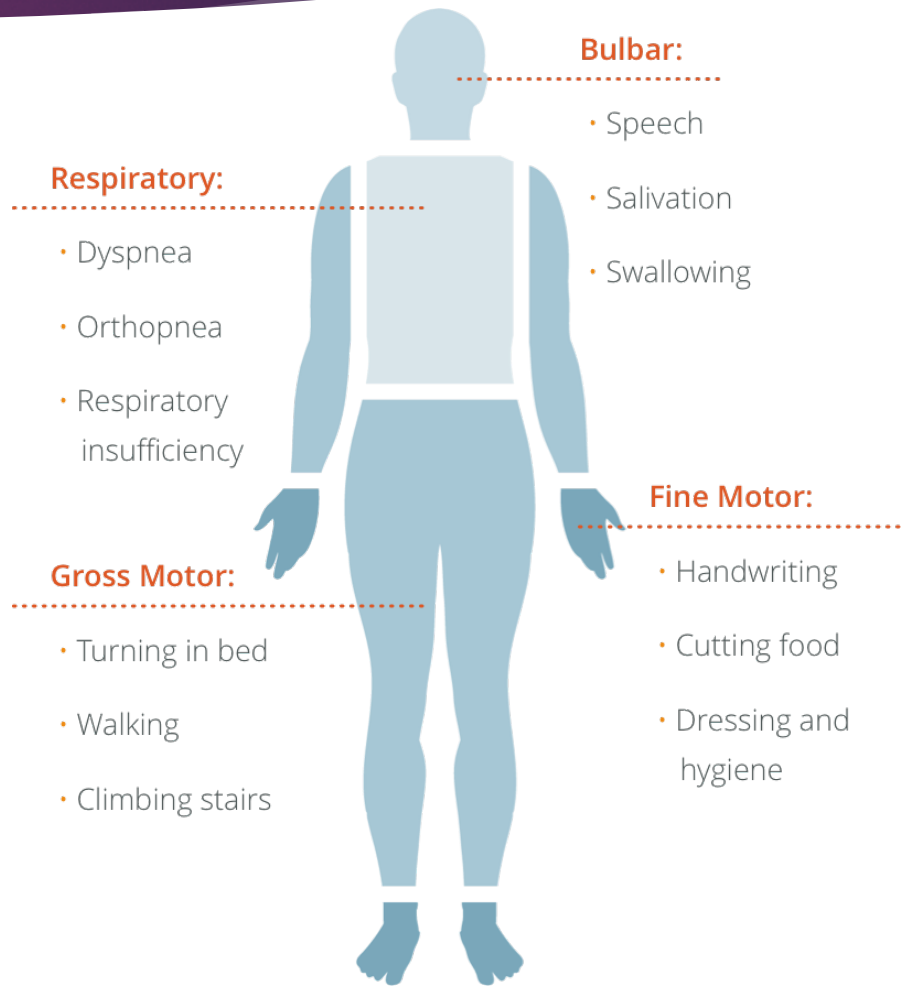
Objectives

- Introduction to ALS
- Why ALS is service connected
- Discussion of the VA directive
- Discussion of the growth of ALS clinical trials in the last 10 years
- Roadblocks to clinical trials at the VA
- Strategies to Improve Veteran Participation

ALS: Clinical Features

Heterogenous disease BUT all presentations include:

- Painless, **progressive**, nonfluctuating weakness and/or spasticity
  - Progression within an affected region and spread to nearby body regions (e.g. Left arm to right arm…)
- No equivalent sensory findings
- No alternative explanation



https://www.alspathways.com/hcp/monitoring-als/

ALS: Epidemiology

- Annual incidence 2-3/100K, prevalence 4-5/100K
- Lifetime risk 1:350 Men, 1:400 Women (lower in non-European populations)
- Risk Factors:
  - Age → Most significant risk factor for ALS:
    - Disease occurs throughout adult life
    - Peak occurring between 55 and 70 years of age

  - Genetics → Most cases are sporadic but ~ 10% are familial (Most AD)
    - Overall risk attributable to genetics 60% (environment 40%)

  - Environmental factors → Difficult to isolate and separate correlation and causation
    - Military service (1.5-2x), athleticism, concussions, toxic exposures (pesticides, organic solvents)

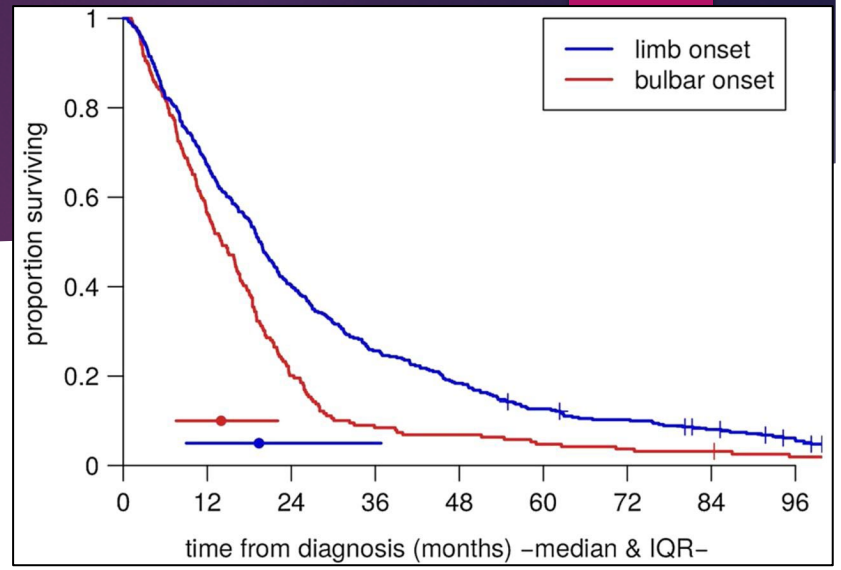
Quinn C, Elman L. Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases. Continuum. 2020

ALS: Prognosis

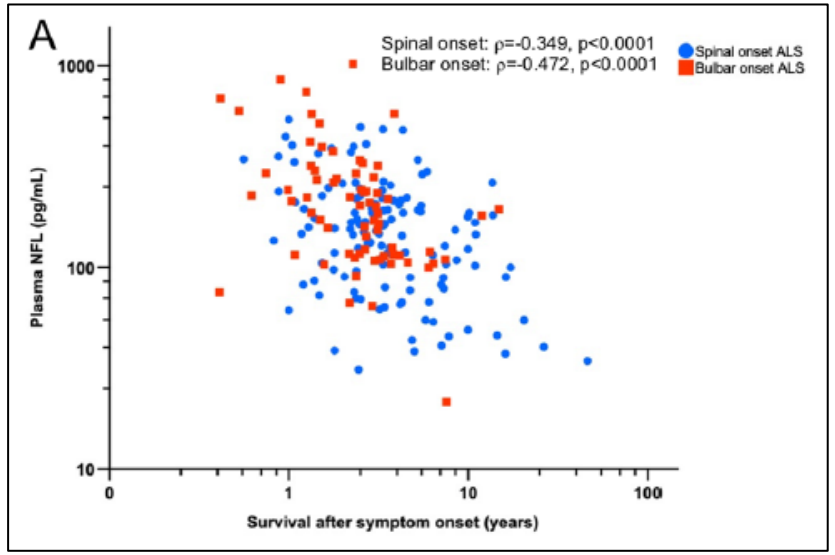
- Average survival: 3 years
  - HOWEVER 25% > 5 yr tracheostomy free survival, 10% >10 yrs

- Negative Clinical Prognostic indicators:
  - Bulbar-onset or respiratory-onset disease
  - Executive impairment or FTD
  - Weight loss
  - Lower respiratory strength correlated with shortened survival

- Biochemical Prognostic Indicators (not used clinically at this point)
  - Serum and CSF neurofilament levels
  - Serum urate, creatinine and chloride



Knibb JA. Journal of Neurology, Neurosurgery & Psychiatry 2016;87:1361-1367.



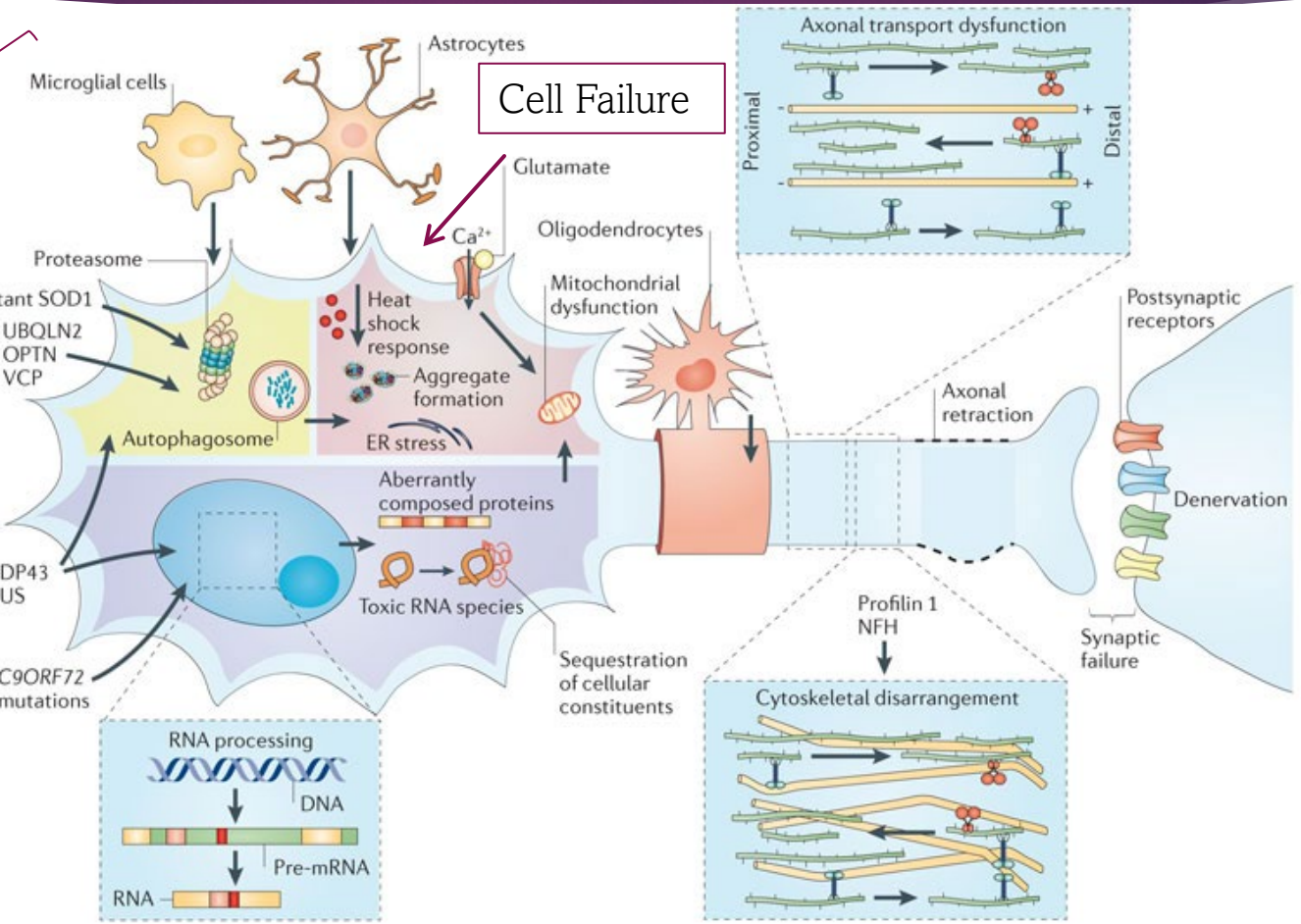
Behzadi, A. *Sci Rep* **11**, 22128 (2021).

What Causes ALS?
(Short version – Not sure.)

Inflammation

Impaired Protein degradation

Impaired RNA processing

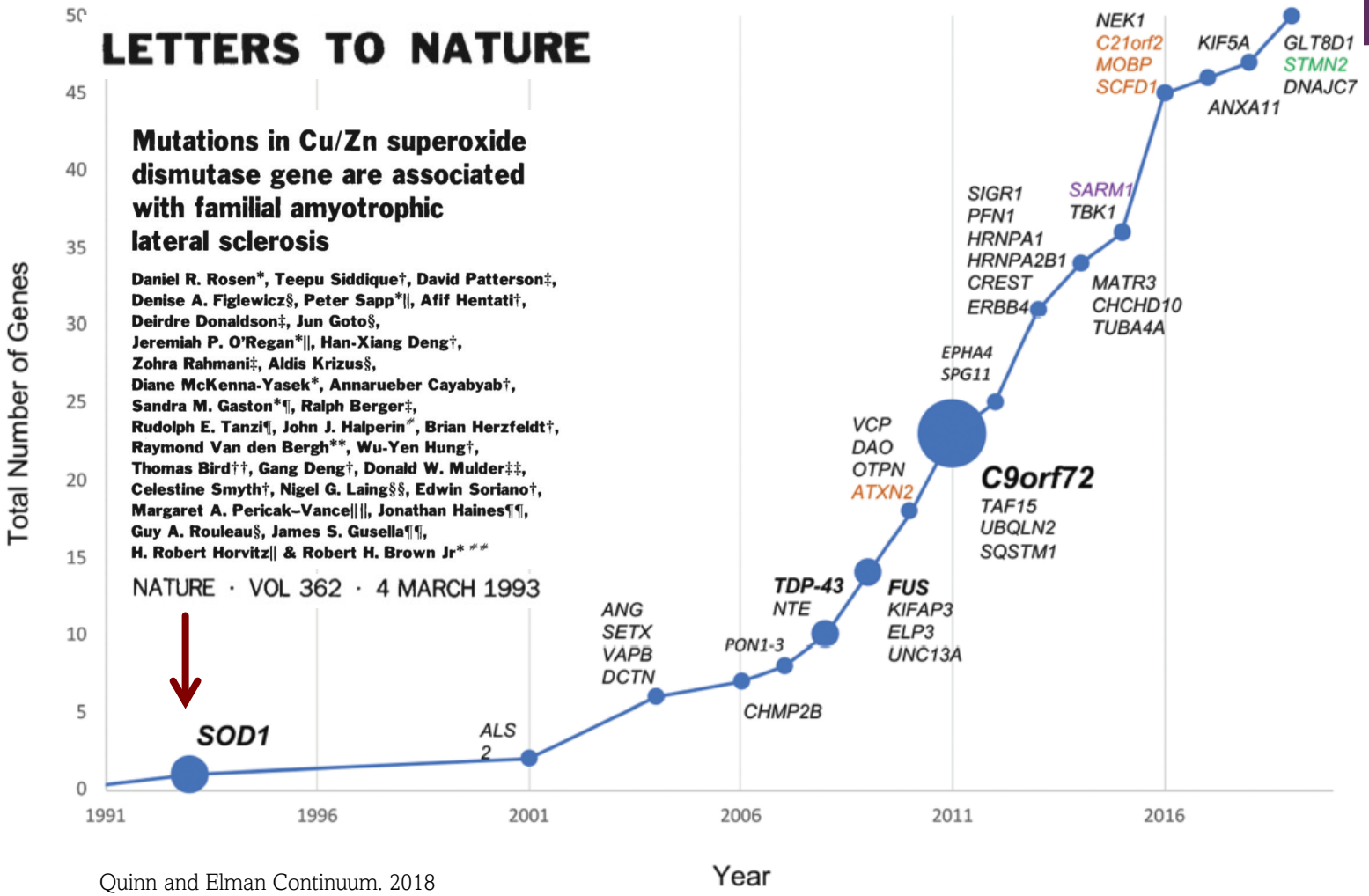


Robberecht Nat Rev Neurosci. 2013 Apr;14(4):248-64.

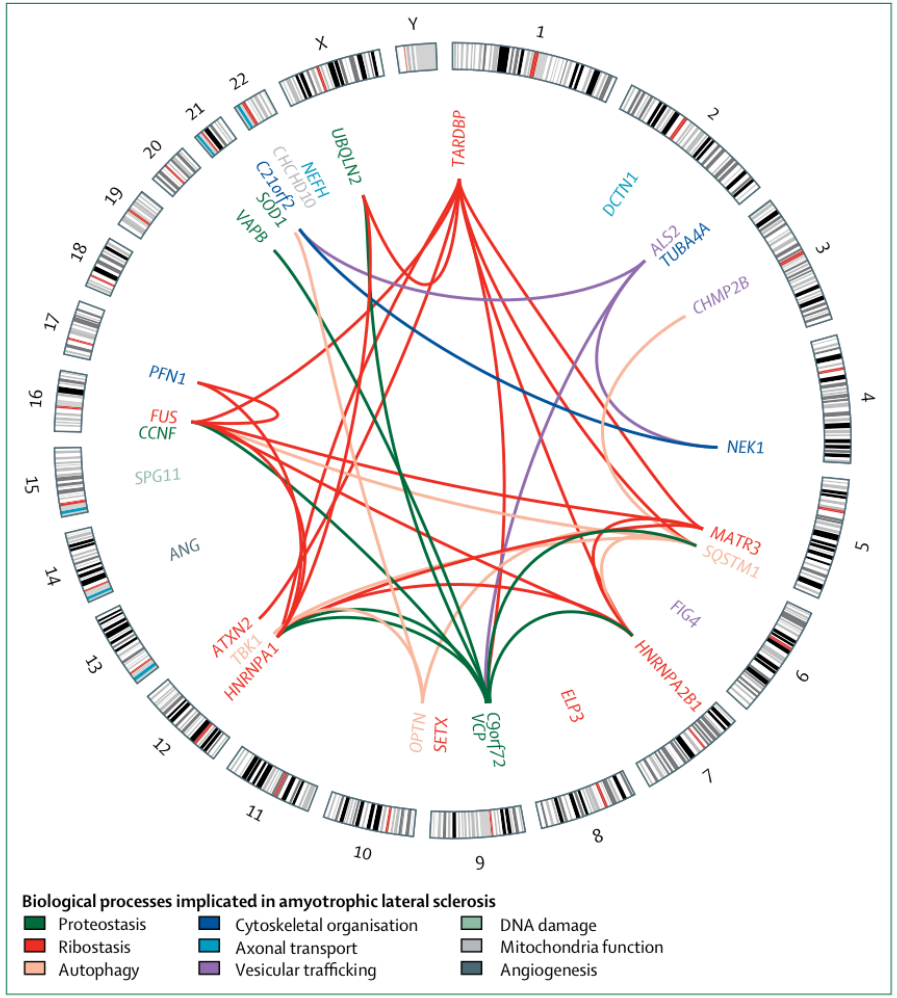
Penn
University of Pennsylvania

What Causes ALS?

...Leveraging our increased understanding of ALS genetics



Quinn and Elman Continuum. 2018



Chia R Lancet Neurol. 2018

ALS Disease-Modifying Agents

Four current FDA approved treatment options

- Riluzole
- Edaravone (Radicava)
- Sodium Phenybutyrate/Tursodiol (Relyvrio)
- Qalsody (Tofersen) (SOD1 fALS ONLY)

ALS: Non-Pharmacologic/Palliative Rx

- Non-Invasive Ventilation
- PEG
- Palliative Medications (Less invasive care ≠NO care)
- Multidisciplinary Clinic…

ALS: Multi Clinic

Multidisciplinary ALS care improves quality of life in patients with ALS

J.P. Van den Berg, MD; S. Kalmijn, MD, PhD; E. Lindeman, MD, PhD; J.H. Veldink, MD, PhD; M. de Visser, MD, PhD; M.M. Van der Graaff, MD; J.H.J. Wokke, MD, PhD; and L.H. Van den Berg, MD, PhD

NEUROLOGY 2005;65:1264–1267

Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities

A Chiò, E Bottacchi, C Buffa, R Mutani, G Mora, and the PARALS

J Neurol Neurosurg Psychiatry 2006;**77**:948–950.

A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland

James Rooney,[1] Susan Byrne,[1] Mark Heverin,[1] Katy Tobin,[1] Alison Dick,[2] Colette Donaghy,[2] Orla Hardiman[1]

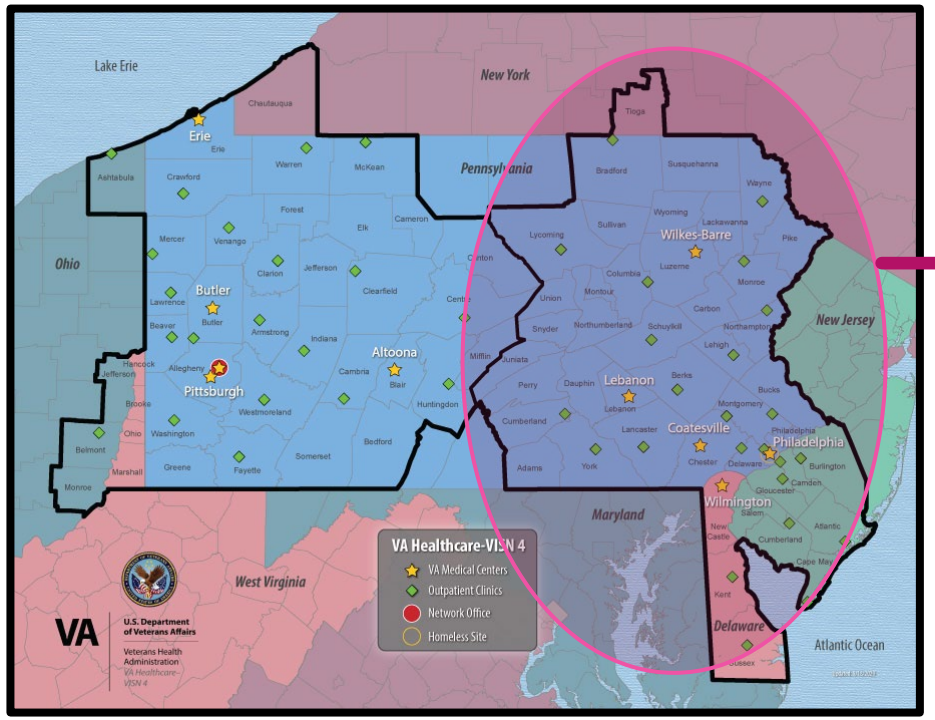
Rooney J, *et al*. *J Neurol Neurosurg Psychiatry* 2014;**0**:1–6.

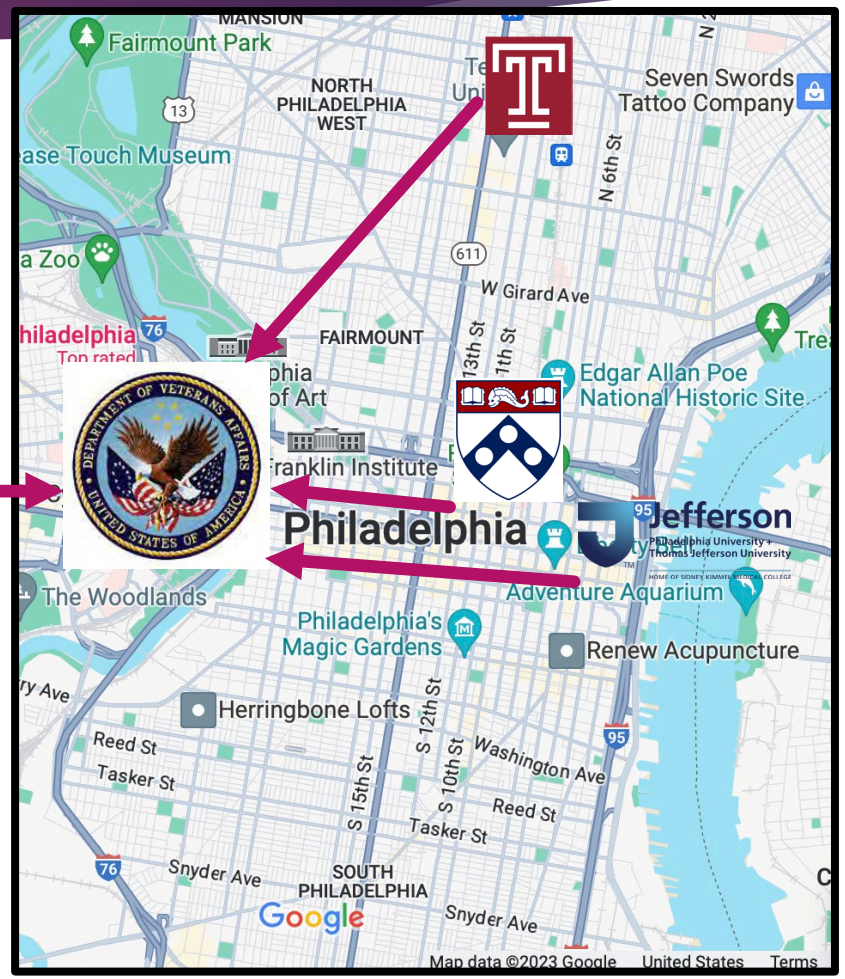
Benefits of ALS Multi-clinic

- Improved survival
- Increased utilization of Riluzole
- Increased PEG tube placement
- Increased utilization of NIPPV
- Fewer hospital admissions
- Higher QOL measures

ALS: CMJC VAMC (Philadelphia) Clinic

- Referrals from within VA (VISN4) and 3 academic centers
- Follow about 65 patients
- Services:
  - Neurologist
  - Neurology NP
  - Neurology nurse
  - SCI nurse
  - Speech
  - PT, OT
  - Resp Therapy
  - Psychologist
  - PVA rep
  - ALSA Rep





ALS: Veterans at Risk

Gulf War and risk of ALS

Is Systemic Lupus Erythematosus, Amyotrophic Lateral Sclerosis, or Fibromyalgia Associated with Persian Gulf War Service? An Examination of Department of Defense Hospitalization Data

Tyler C. Smith, Gregory C. Gray, and James D. Knoke — *Am J Epidemiol* Vol. 151, No. 11, 2000

- Deployed: 6 cases
- Non-deployed: 12 cases
- RR 1.65, (0.62 - 4.44)
- Not significant BUT underpowered

Excess incidence of ALS in young Gulf War veterans

Robert W. Haley, MD

NEUROLOGY 2003;61:750–756

- 1991-1998: 20 cases/700K GWV
- 17 were < 45 yo
- Actual vs. expected cases per age group in US population
- Max Risk 1998: 5 cases vs. 1.57 expected
- RR 3.19 (1.03 - 7.43)
- BUT did not control for sex (more males in military)

Occurrence of amyotrophic lateral sclerosis among Gulf War veterans

R.D. Horner, PhD; K.G. Kamins, PhD; J.R. Feussner, MD, MPH; S.C. Grambow, PhD; J. Hoff-Lindquist, MStat; Y. Harati, MD; H. Mitsumoto, MD, DSci; R. Pascuzzi, MD; P.S. Spencer, PhD; R. Tim, MD; D. Howard, MSPH; T.C. Smith, MS; M.A.K. Ryan, MD, MPH; C.J. Coffman, PhD; and E.J. Kasarskis, MD, PhD

NEUROLOGY 2003;61:742–749

- Deployed: 40 cases/700K
- Non-deployed: 67 cases/1.8 mil
- RR 1.92; (1.29 - 2.84)
- Concern for underreporting in nondeployed

ALS : Veterans at Risk?

Beyond the Gulf…

HIGH LIGHT CME

Prospective study of military service and mortality from ALS

M.G. Weisskopf, PhD; E.J. O'Reilly, MSc; M.L. McCullough, ScD; E.E. Calle, PhD; M.J. Thun, MD; M. Cudkowicz, MD; and A. Ascherio, MD

NEUROLOGY 2005;64:32–37

- Military vs. Nonmilitary using Cancer Prevention Study II Cohort
- Followed 400K men between 1989 – 1998. All older and therefore unlikely to be Gulf War Vets
- Did not distinguish deployed vs. nondeployed
- Military: 63 cases/1.1 Million person-years
- Non-Military: 217 cases/2.6 Million person-years
- RR 1.58 (1.14–2.19)
- Branch of service and duration of service did not appear to change risk

ALS: Veterans at Risk
VA Responds…

Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature

Committee on the Review of the Scientific Literature on Amyotrophic Lateral Sclerosis in Veterans

Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES

IOM Report, November 2006: *"Limited and suggestive evidence of association between military service and later development of ALS"*

DEPARTMENT OF VETERANS AFFAIRS

38 CFR Part 3

RIN 2900–AN05

Presumption of Service Connection for Amyotrophic Lateral Sclerosis

AGENCY: Department of Veterans Affairs.
ACTION: Final rule.

SUMMARY: This document adopts as a final rule the interim final rule amending the Department of Veterans Affairs (VA) adjudication regulations to establish a presumption of service connection for amyotrophic lateral sclerosis (ALS) for any veteran who develops the disease at any time after separation from service. This amendment implements the decision by the Secretary of Veterans Affairs to establish such a presumption based on a November 2006 report by the National Academy of Sciences Institute of Medicine on the association between active service and ALS.

2014: ALS Handbook

Department of Veterans Affairs
Veterans Health Administration
Washington, DC 20420

VHA HANDBOOK 1101.07
Transmittal Sheet
July 7, 2014

AMYOTROPIC LATERAL SCLEROSIS (ALS) SYSTEM OF CARE PROCEDURES

1. REASON FOR ISSUE: This Veterans Health Administration (VHA) Handbook establishes procedures for health care services to Veterans with Amyotrophic Lateral Sclerosis (ALS).

2. SUMMARY OF CONTENTS: This is a new VHA Handbook describing the essential components and procedures of the ALS System of Care that have been implemented by ALS care providers to ensure that all enrolled Veterans have access to ALS care. Necessary structural, procedural, and educational components for consistent ALS services are described.

Strengths

- Exceeded AAN Clinical Practice Guidelines
  - More INTERDISCIPLINARY team members
  - More COORDINATED care with primary care/home care
  - More emphasis on PALLIATIVE support
- Flexibility in structure

Weaknesses

- Guidelines, not requirements
- No funding

VHA Handbook 1101.07 ALS System of Care

Slide Courtesy Dr. Ileana Howard

2021: VHA Directive 1101.07

Purpose:

"describes the *essential components and requirements* of the ALS Program that have been implemented nationally to ensure that all eligible Veterans have *access* to ALS care"

Still no funding…

Department of Veterans Affairs
Veterans Health Administration
Washington, DC 20420

VHA DIRECTIVE 1101.07
Transmittal Sheet
August 30, 2021

AMYOTROPHIC LATERAL SCLEROSIS SYSTEM OF CARE

1. REASON FOR ISSUE: This Veterans Health Administration (VHA) directive states authority and policy for the development, implementation and sustainment of the Amyotrophic Lateral Sclerosis (ALS) System of Care.

2. SUMMARY OF MAJOR CHANGES: This directive updates information about ALS and includes the following major changes:

a. Updates and adds responsibilities in paragraph 4 to include Assistant Under Secretary for Health for Clinical Services; Assistant Under Secretary for Health for Operations; Chief Officer, Specialty Care Services; Department of Veterans Affairs (VA) medical facility Prosthetic and Sensory Aid Service Chief; VA medical facility Contract Officer's Representative; ALS Interdisciplinary Care Team; VA medical facility ALS Team physician; and VA medical facility ALS Coordinator.

b. Relocates previous Appendix A (ALS Interdisciplinary Team Clinics and Programs Identified) to the Neurology Program SharePoint.

3. RELATED ISSUES: VHA Directive 1094, Inter-Facility Transfer Policy, dated January 11, 2011; VHA Directive 1176(1), Spinal Cord Injuries and Disorders System of Care, dated September 30, 2019; and VHA Handbook 1101.10(1), Patient Aligned Care Team (PACT) Handbook, dated February 5, 2014; VHA Directive 1173.13, Home Oxygen Program, dated August 5, 2020.

4. RESPONSIBLE OFFICE: The Neurology Program Office within the National Office of Specialty Care Services (11SPEC15) is responsible for the content of this directive. Questions may be addressed to the Executive Director for Neurology at: VHA11SPEC15N2@va.gov.

5. RECISSIONS: VHA Handbook 1101.07, Amyotrophic Lateral Sclerosis (ALS) System of Care Procedures, dated July 7, 2014, and VHA Memorandum 2018-04-12, Amyotrophic Lateral Sclerosis (ALS), dated April 10, 2018, are rescinded.

6. RECERTIFICATION: This VHA directive is scheduled for recertification on or before the last working day of August 31, 2026. This VHA directive will continue to serve as national VHA policy until it is recertified or rescinded.

Slide Courtesy Dr. Ileana Howard

Changes with the Directive

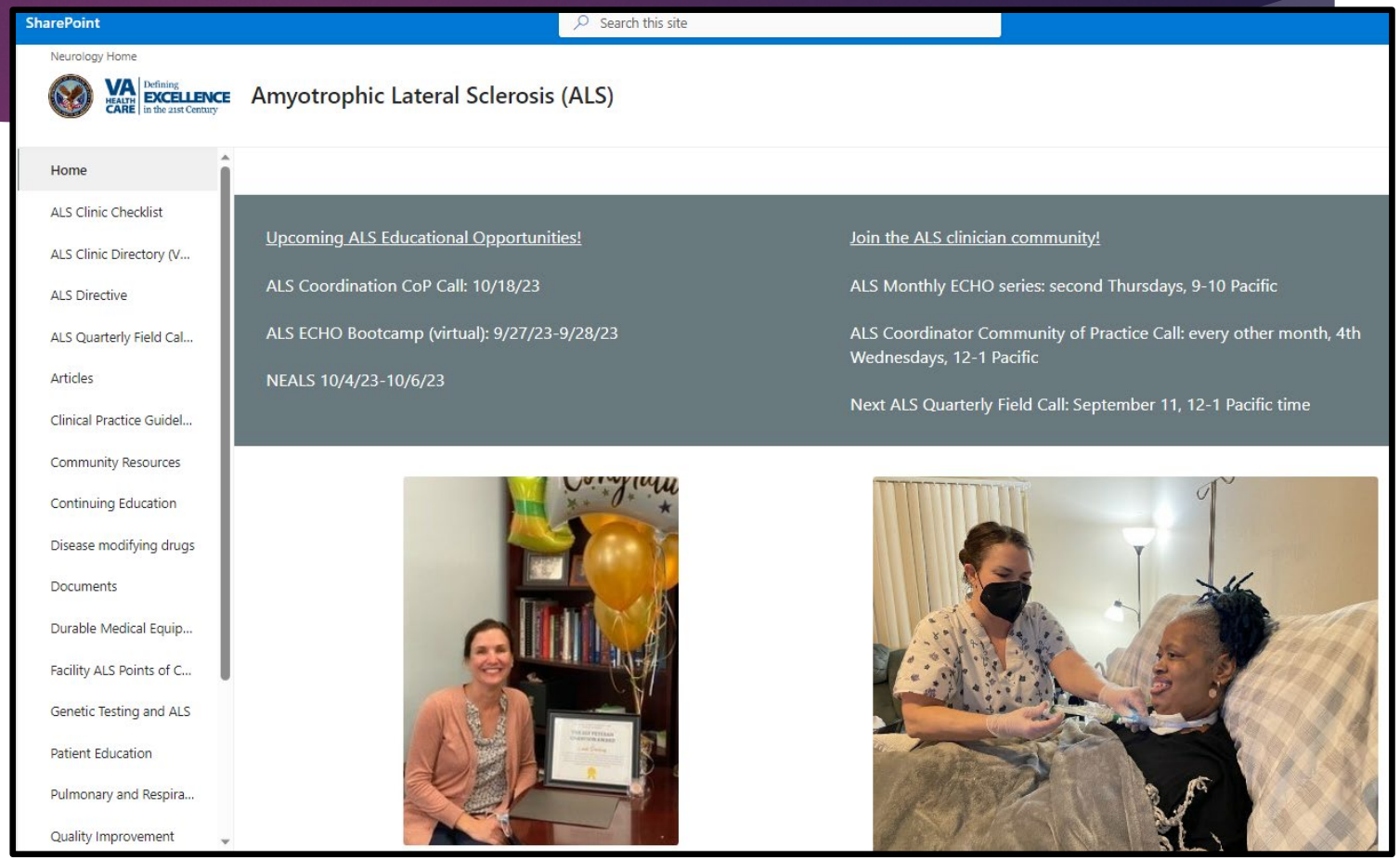
- ALS Coordinator in EACH VHA medical center (171)

	2014	2021
Recorded ALS Clinics	20	60
ALS Centers of Excellence	2	7 (5 pending)
ALS Recognized Treatment Centers	0	3 (2 pending)

Slide Courtesy Dr. Ileana Howard

ALS at VA: Towards a System of Care

- Monthly national ALS webinar
- Quarterly field call meetings
- Communication Groups
  - Email listservs
  - Internal Sharepoint page

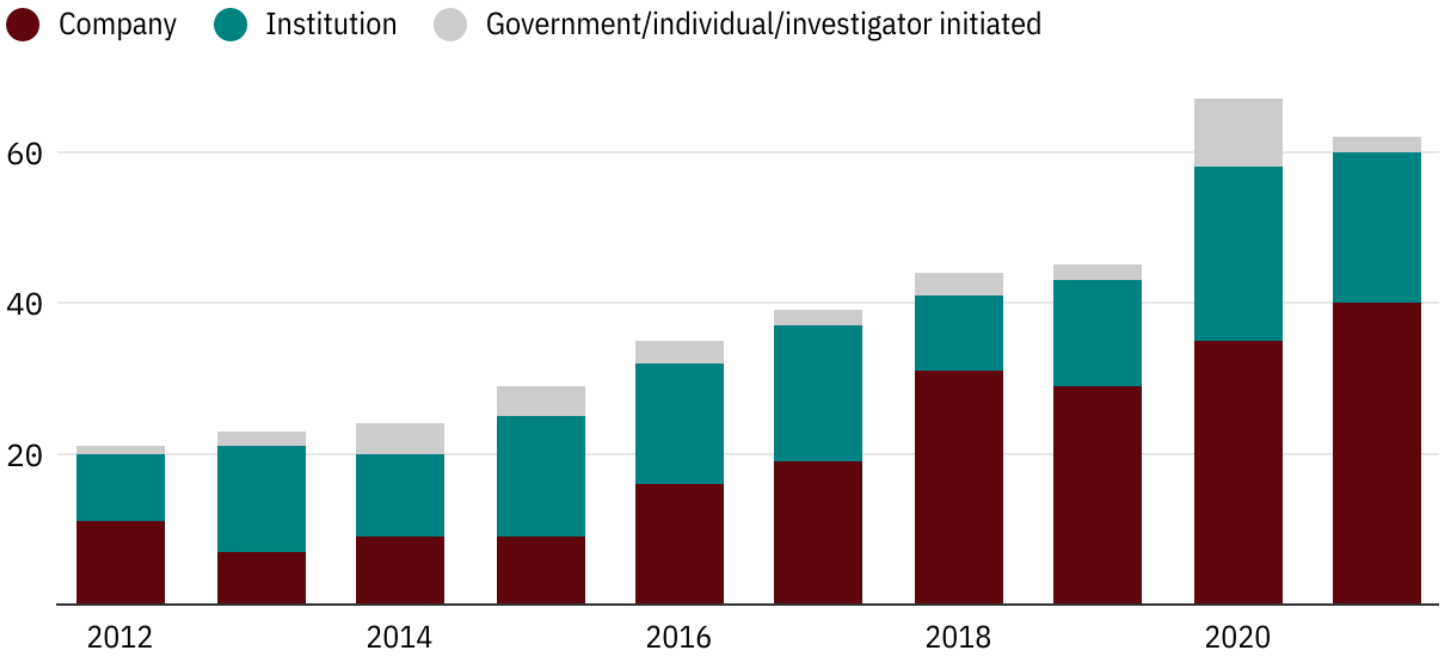


Slide Courtesy Dr. Ileana Howard

ALS Clinical Trials 2012-2022

Pharma companies have increased interest in ALS trials

Number of Phase I to Phase III drug trials in ALS, sorted by sponsor type and initiation year



Source: GlobalData

CLINICAL TRIALS ARENA

ALS Clinical Trials: Veteran Participation

- Unclear what percent of veterans participate in ALS trials (no resource for this) but
  - Only ~5-10% of PALS participate in CT*
  - ~60% excluded by I/E Criteria
- ALS Executive Committee discussion with I AM ALS
  - Veterans do not feel they have sufficient access to trials or a means to bridge the gap
- Why is this?

*Wong. Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective, *Brain Communications*, 2021

**an Eijk RPA. Refining eligibility criteria for amyotrophic lateral sclerosis clinical trials. Neurology. 2019

ALS Clinical Trials: Overall Opportunities and Challenges

Opportunities

- No highly effective therapies
- Generous population willing to volunteer their time
- Strong research network(s) developed over the last 10-20 years

Challenges

- Heterogenous disease
- Rapidly progressive (often rely on patients in the early stages)
- Insensitive outcome measures (ALS-FRS is usually primary)
- Approval of multiple modestly effective therapies

ALS Clinical Trials:
Specific Challenges to Veteran Participation

- VA sites unaware of clinical trial landscape
- VA sites unaware how to access information regarding clinical trials
- Lack of Clinical (Therapeutic) Trials within the VA
  - No current pharma trials using VA as trials sites
  - Related to complexity of IRB (no central IRB), contracting and staffing
  - VA focus on privacy over flexibility

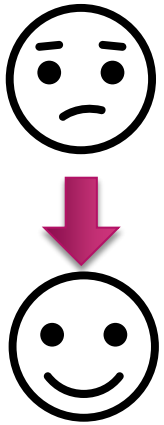
ALS Clinical Trials: Strategies to Improve Veteran Participation

- Education of VA Providers Regarding ongoing Clinical Trials
  - Use of the Quarterly field call meetings to discuss how to find ALS Clinical Trials
  - Use of Sharepoint for instructional document on accessing trials
- Educate VA Providers to empower independent trial searches and notifications

NIH National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov

- Search "ALS" → 834 Studies
- Filter: "Interventional", "Recruiting", "Within 50 miles" → 4 studies



CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

ACTIVE – ALS Research Notification for Clinical Trials and Studies

To receive automatic notifications about the latest clinical trials and studies, please join the Registry, click here.

ALS Clinical Trials:
Strategies to Improve Veteran Participation

- Enhancing Connections with Veterans Groups
  - Meeting with IAMALS Veterans group
  - Direct teaching of independent trial searches and notifications
- Prioritizing veteran enrollment within academic practices
  - Direct conversation within Penn group to prioritize veterans on our wait list for clinical trials

IAM ALS

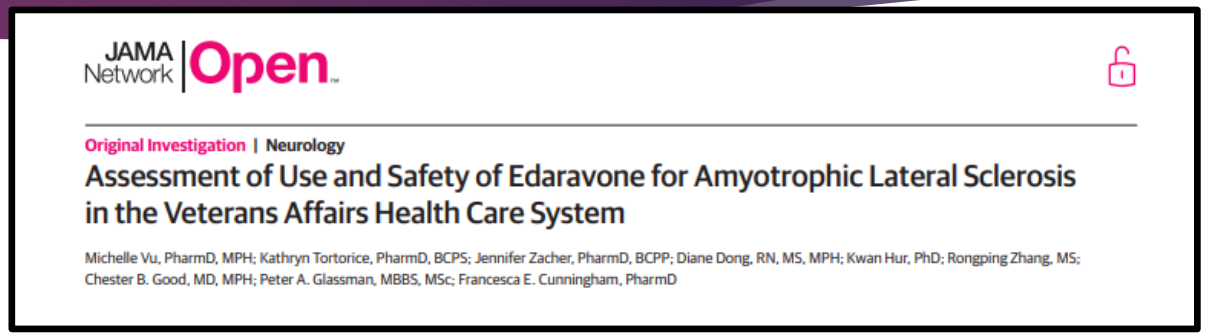
CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

ACTIVE – ALS Research Notification for Clinical Trials and Studies

To receive automatic notifications about the latest clinical trials and studies, please join the Registry, click here.

ALS Clinical Trials: Strategies to Improve Veteran Participation

- Focus on Observational Trials
  - Strength of the VA is common EMR
  - Post- Market Surveillance of DMTs
  - Common forms increase data granularity

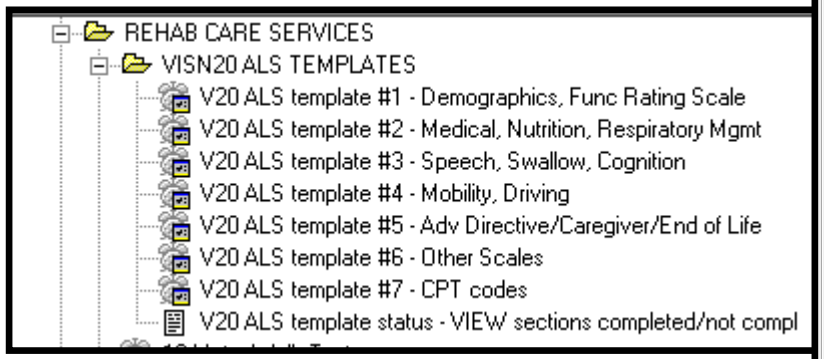


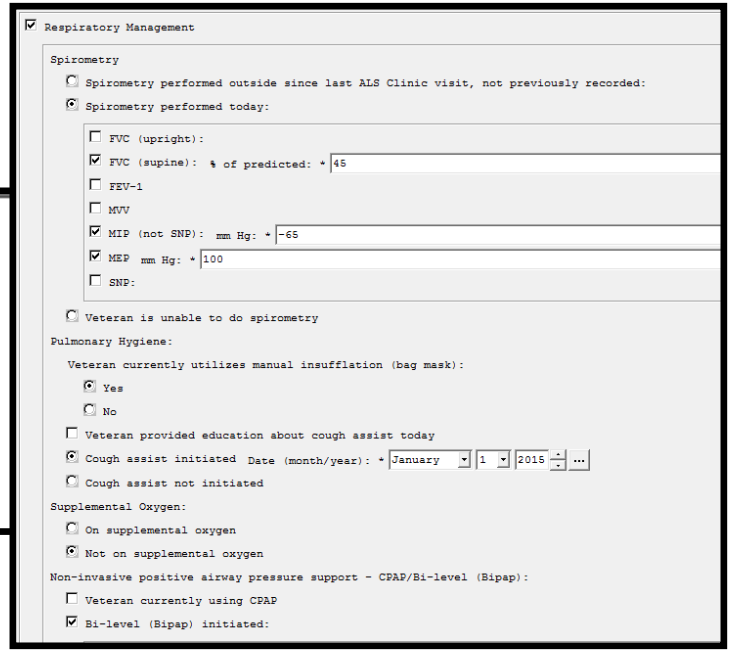
JAMA Network | Open

Original Investigation | Neurology

Assessment of Use and Safety of Edaravone for Amyotrophic Lateral Sclerosis in the Veterans Affairs Health Care System

Michelle Vu, PharmD, MPH; Kathryn Tortorice, PharmD, BCPS; Jennifer Zacher, PharmD, BCPP; Diane Dong, RN, MS, MPH; Kwan Hur, PhD; Rongping Zhang, MS; Chester B. Good, MD, MPH; Peter A. Glassman, MBBS, MSc; Francesca E. Cunningham, PharmD





Images courtesy Dr. Ileana Howard

ALS Clinical Trials: Strategies to Improve Veteran Participation

- Breakdown barriers to Pharma sponsored trials
  - Is this realistic? VA clinics are generally small. With a small number of qualifying patients, may not worth using VA clinic sites.
  - Allowance of commercial central IRB and common contracting?
  - Role of VA Associated Non-Profits
    - Looking forward to hearing more from Rebecca Walker from SIBCR

VA RESEARCH CURRENTS
Research News from the U.S. Department of Veterans Affairs

VA Research works with industry, other partners to launch COVID-19 clinical trials

Mary Kelleher and Mitch Mirkin
VA Office of Research and Development

May 7, 2020

NIAID had contracted with a commercial institutional review board (IRB) to oversee the study. VA had to jump through extra regulatory hoops to join in the arrangement, but Klote's dedicated team made it happen quickly—and made history in the process.

"This was the first time a VA research program was able to rely on a commercial IRB for the required ethical review," notes Klote. No small feat, considering VA started doing multisite clinical trials in the 1940s. Importantly, adds Klote, VA's ability to now use commercial IRBs when needed "positions us to be a much more viable research partner for industry."

Experience from the VA ALS clinic: Trial collaborations with academic affiliates

COLIN QUINN, MD
DIRECTOR, CMJC VAMC INTERDISCIPLINARY ALS CLINIC
DIRECTOR, NEUROMUSCULAR CLINCIAL TRIALS
ASSOCIATE PROFESSOR OF CLINICAL NEUROLOGY
UNIVERSITY OF PENNSYLVANIA

Penn
University of Pennsylvania

U.S. Department of Veterans Affairs

Clinical Trials with the VA: Feasible and Necessary

Industry and other Non-Federally Sponsored ADRD Research

Olga Brawman-Mintzer, MD
Professor of Psychiatry
Medical University of South Carolina
Staff Physician
Co-Director Low Country Institute for Brain Health
Ralph H. Johnson VA Healthcare System

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Necessary?

ADRD in the VA System

- The estimated number of US Veterans with Alzheimer's disease in FY2021 was approximately 457,000 with new cases of 131,000.
- Veterans are at a higher risk for developing dementia and other neurocognitive disorders than the general population[1-3]
- As is the case in state-of-the-art cancer treatment models, access to clinical trial participation is considered an integral part of clinical care.
- Although there are number of initiatives (e.g., MIRECC & GRECC) geared to improve research access for Veterans with dementia and other neurocognitive disorders, these initiatives have been fragmented, difficult to implement and are not integrated into a cohesive research and care program. *Therefore, generating a limited increase in dementia research, particularly in new therapeutics trials*

1. Zhu CW, Sano M. Demographic, Health, and Exposure Risks Associated With Cognitive Loss, Alzheimer's Disease and Other Dementias in US Military Veterans. Front Psychiatry. 2021 Feb 25;12:610334. doi: 10.3389/fpsyt.2021.610334. PMID: 33716816; PMCID: PMC7947283.
2. Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, Kluse M, Marmar C. Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry. 2010 Jun;67(6):608-13. doi: 10.1001/archgenpsychiatry.2010.61. PMID: 20530010; PMCID: PMC2933793.
3. Van Den Heuvel C, Thornton E, Vink R. Traumatic brain injury and Alzheimer's disease: a review. Prog Brain Res. 2007;161:303-16. doi: 10.1016/S0079-6123(06)61021-2. PMID: 17618986.

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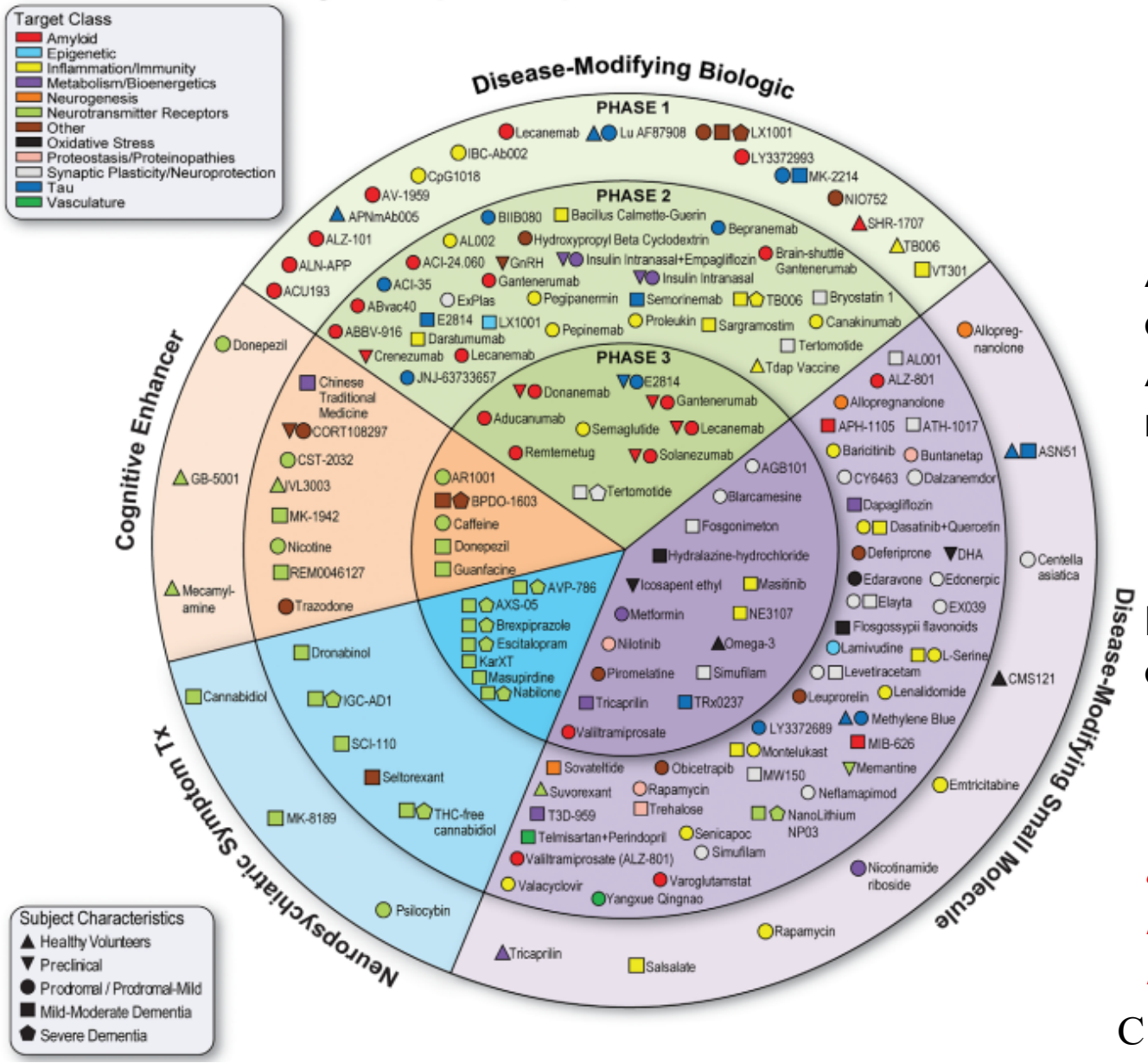
2023 Alzheimer's Drug Development Pipeline



As of January 2023, there were 187 trials, evaluating 141 unique treatments for Alzheimer's disease (not including no-medication treatments, such as TMS etc.)

- Phase 3: 55 trials
- Phase 2: 99 trials
- Phase 1: 33 trials

Disease modifying therapies are the most common (79% of drugs).

Unless, captured differently in IRBNet, only 16 trials (including non-pharmacological) are listed in clinicaltrials.gov as recruiting/recruited/completed in VAMCs, if a Veteran was to search for trials.

ClinicalTrials.gov as of the index date of 1.1.23

Cummings J et al., Alzheimer's disease drug development pipeline: 2023. *Alzheimer's Dement.*

Feasible?

Critical Elements Needed to Conduct Clinical Trials

- Availability of study subjects
- Availability of an appropriate team
- Availability of protocols
- Administrative capabilities to process contracts and to meet regulatory requirements

Availability of Subjects

- Significant percentage of Veterans currently suffer from or are at risk of developing ADRD
- Numerous barriers have contributed to the limited identification of Veterans eligible for dementia clinical trials
- To identify those barriers, we performed:
  - 88 interviews with primary clinical providers
  - Four interviews with specialty providers, such as Neurology and Geriatric Psychiatry

Availability of Subjects

- The interviews unveiled several common themes among providers:
  - PCPs provide care for:
    - Veterans at high risk of developing cognitive impairment
    - Veterans with subjective and/or objective complaints about memory loss
    - Veterans with clear symptoms of dementia.
  - Most PCPs were not familiar with the available research protocols
  - Even if PCPs were aware of various research protocols, they did not have the time nor the ability to perform specific/initial evaluations needed to assess individuals for clinical trial eligibility
- Memory disorder clinics are often booked months in advance
- Therefore, PCPs would refer to specialty clinics only the most complex patients with multiple comorbidities who, in principle, were unlikely to be eligible for clinical trials.
- Discussions with specialists showed similar limitations.

Availability of Subjects

- To address these issues:
  - We created a one-click, generic, self-populating referral note
  - We instructed PCPs and specialists to refer every individual at risk with subjective complaints or with a clinical diagnosis of dementia who agrees to be included in a patient registry using this referral note
- Thus, we eliminated the burden of a complex referral process and the need for extensive knowledge of specific protocols
- Both PCPs and specialists responded positively, generating approximately 10 referrals per month
- Each referral was automatically forwarded to the registry coordinator who subsequently scheduled a phone screening

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Availability of Subjects

- The Alzheimer's Disease Registry Study (ADRS)
  - Supported by the National Alzheimer's Association
  - No cost evaluation of memory and thinking conducted in the context of research parameters, giving patients direct access to current and future clinical trial opportunities for which they may qualify
  - Allows for a collaborative relationship between the research clinic and referring providers offering providers valuable information to help with treatment decisions
- The total number of Veteran referrals to ADRS was 130
- 23% of those initial referrals were ultimately not appropriate for ADRS/research for the following reasons:
  - Subjects changing their mind
  - Special circumstances
  - The presence of concomitant conditions that would not allow them to participate or made them ineligible to participate
    - An example of such a circumstance would be a Veteran with no decision capacity who is living alone and does not have a potential study partner or someone who could function as an authorized representative.

Availability of an Appropriate Team

We have successfully recruited and retained:

- An experienced Principal Investigator(s)
- Leading coordinator(s)
- Recruitment coordinator
- A neuropsychologist
- An experienced clinician

Availability of Protocols

There are three critical elements that facilitate our goal to assure an appropriate flow of scientifically important protocols:

1) The type of population that can be recruited in the VA (ethnically diverse population)

2) The development and cultivation of relationships with non-for-profit and for-profit stakeholders

3) Ability to develop investigator-initiated protocols

The Diverse Population of the VA

- The Veteran population is expected to become increasingly racially and ethnically more diverse.
- Between 2021 and 2046:
  - The share of Veterans who are non-Hispanic white is expected to drop from 74% to 62%.
  - The share of Veterans who are Hispanic is expected to double from 8% to 16%
  - The share of Veterans who are Black is expected to increase slightly from 13% to 15%.

Veteran Population in ADRS

- Of the Veterans included in the ADRS:
  - 22% are Black/African American
  - 1% are from other ethnic/racial minority groups
  - 29% have 12 years of education or less

The Development and Cultivation of Relationships with Non-Profit Institutions

- Alzheimer's Association
- AARP/Global Council on Brain Health
- Our team serves on the steering committees of all leading national NIH-supported research networks:
  - Alzheimer's Clinical Trials Consortium (ACTC)
  - Alzheimer's Disease Cooperative Study (ADCS)
  - Alzheimer's Disease Neuroimaging Initiative (ADNI)
  - Alzheimer's Therapeutic Research Institute (ATRI)
  - Johns Hopkins Center fo and Evidence Synthesis

Global Council on Brain Health
A COLLABORATIVE FROM AARP

ACTC
ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

ADCS
Alzheimer's Disease Cooperative Study

Keck School of Medicine of USC
Alzheimer's Therapeutic Research Institute

ADNI
ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

ALZHEIMER'S ASSOCIATION

JOHNS HOPKINS
BLOOMBERG SCHOOL of PUBLIC HEALTH

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The Development and Cultivation of Relationships with for-profit Institutions

- Our corporate sponsors include:
  - Cerevel Therapeutics, LLC
  - Eisai Inc.
  - Suven Life Sciences Ltd.
  - Vivoryon Therapeutics
  - Lilly
  - Otsuka/Avanir
  - GSK

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Ability to develop investigator-initiated protocols

- The Life's End Benefits of Cannabidiol and Tetrahydrocannabinol (LiBBY) Study (NIA R01AG068324)
  - Multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of an oral combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) compared to placebo over 12 weeks
  - Designed to test the hypothesis that treatment with an oral combination of THC ation hospice care-eligible patients wit itia

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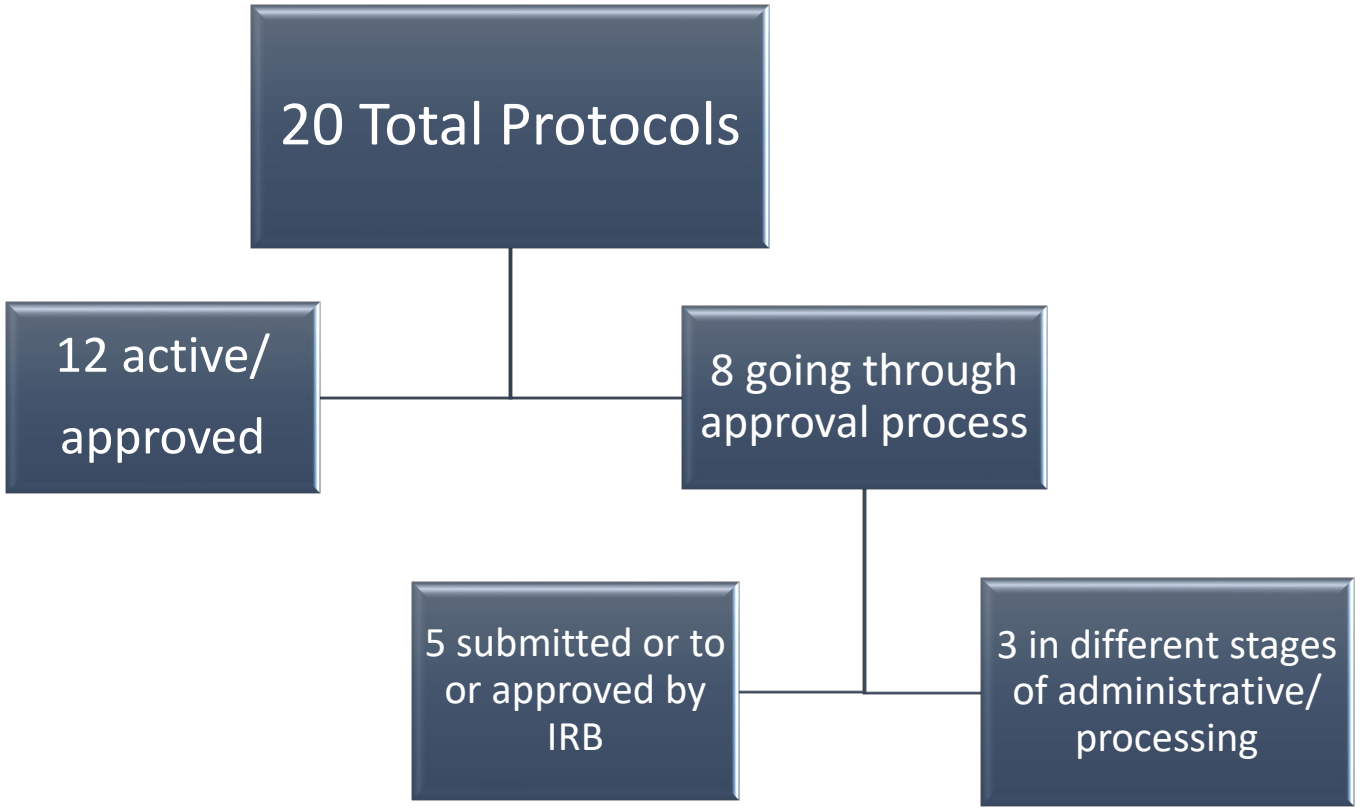
Administrative Capabilities to Process/Manage Contracts and to Meet Regulatory Requirements

- All grants except internal VA grants (CSPs, Merits) are processed through the VA non-for-profit 501c3(s): National Association of Veterans' Research and Education Foundations (NAVREF)
- Our local non-profit, the Lowcountry Center for Veterans Research (LCVR)
  - Has the capability to successfully manage the research portfolio:
    - Pre-contract management (including executing Cooperative Research & Development Agreements (CRADA)
    - Contract management
    - Post-contract management
    - Billing management

Regulatory Requirements

- Sponsored trials can utilize independent IRBs, such as Advarra
- VA system requires submission and approval by the local Research and Development (R&D) Committee
- R&D submission includes approvals by privacy officer, safety officer, research biosafety committee, information system security officer
- This process is time-consuming and laborious
- The average time from initiation to first subject enrolled may range from 4-10 months

Current Non-VA Research Portfolio



VA HEALTH CARE Defining EXCELLENCE in the 21st Century

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Summary

- We have discussed the four key elements of clinical trial conduct:
  - Availability of subjects
  - Availability of an appropriate team
  - Availability of protocols
  - Administrative capabilities to process contracts and to meet regulatory requirements
- It is challenging and resource and time consuming
- VETERANS DESERVE IT!

VA Non-Profits and Clinical Trials

AUPN VHA Workshop
October 20, 2023

Rebecca E. Walker
Director of Sponsored Programs
Seattle Institute for Biomedical and Clinical Research

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Relevant Jargon

- NPC: Non-profit corporation
- VA NPC: A non-profit corporation facilitating VA research and education functions.
- Extramural Research: Research funding outside of an organization
  - Non-VA funded research performed by VA
  - E.g. NIH/DoD, other federal agencies, private foundations, industry collaborations on clinical trials

Background

Before statutory authorization for VA NPCs (pre-1988):

- VA administered VA-funded research
- Extramural research (non-VA) funding was difficult for VA to leverage
  - General Post Funds (ill-suited VA mechanism)
  - Academic affiliate medical schools/universities
  - Foundations without official authorization to support VA

VA NPCs

- VA NPCs are established and operate under their respective state nonprofit corporation laws
- 38 U.S.C. §§7361-7366 authorizes VA medical centers to establish nonprofit research corporations to serve as “flexible funding mechanisms for the conduct of approved research and education”
- VA NPCs are also subject to VA oversight and regulation
- VHA Handbook 1200.17, "VA Nonprofit Research and Education Corporations Authorized by Title 38 U.S.C. Sections 7361 through 7366"
  - VA NPC research must be approved by the VA R&D Committee
  - Operate in VA facilities following the VA rules
  - PIs and staff are VA employees/WOCs/IPA assignees

Existence and Nature of VA NPCs

https://www.research.va.gov/programs/nppo/default.cfm

Flexible Funding Mechanism

- VA NPCs receive funds for VA extramural research
- Administer the funds within the funder's terms
- Spend the money to facilitate VA research (without giving the money to the VA)
  - Can reimburse or pay for VA services to support research

Clinical Trials

- Federal grant-supported clinical trial administration depends on local practices (university affiliate vs. VA NPC)
- Industry-funded clinical trials:
  - Cooperative Research and Development Agreement (CRADAs)

CRADA

- Cooperative Research and Development Agreement
  - The form of clinical trial agreement available to VA
  - 3-way agreement between funder/sponsor, VA, and VA NPC
    - VA to perform research, provide data to Funder/Sponsor if needed
    - Funder/Sponsor to support performance, may provide protocol or test articles or funding
    - VA NPC official role is only the receipt and disbursement of funds
- VA NPC cannot agree to CRADA terms on behalf of VA or sign a CRADA without VA approval

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Financial Operations

- VA NPC must invoice for invoiceable items in your budget and receive the auto-payments
- VA NPC manages purchasing within their standard purchasing policy
- VA NPC needs study team input for this:
  - Did we get paid for everything that has happened?
  - Did the vendor billing us complete this work satisfactorily?
- Provide regular budget/account balance reports
- Close out of financial obligations when the project ends

VA NPCs *MIGHT*

- Facilitate CDA/NDA then CRADA negotiations between the funder/sponsor and the VA OGC's Specialty Team Advising Research ("STAR Attorneys")
- Assist with costing and budget negotiation, with study team input on:
  - Research vs. standard care
  - How long will this take?
  - Who will do this work?
  - What procedures will be involved?
- Choose not to pursue clinical trials where the budgets will not cover the projected costs
- Have resources or assistance with regulatory committee paperwork
- Other activities in support of research

Questions

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