ALS Patients Demand

Richard J. Barohn MD, Jeffrey M. Statland MD,
University of Kansas Medical Center
Kansas City, KS

Keywords: *ALS, Drug cocktails, Bayesian adaptive design*

RFA/PRA: PAR 15-172

Type of Grant: U01. National Center for Advancing Translational Sciences Special Emphasis
Panel CTSA Collaborative Innovation Award Application (U01) Special Emphasis Panel
Date Submitted: early 2016. (We need to ask robin or spa date this was submitted)

Date of Review: May 10, 2016

Grant was: Not funded

Contact information:
Richard J. Barohn, MD
University of Kansas Medical Center
3901 Rainbow Blvd.
Kansas City, KS 66160
rbarohn@kumc.edu
(913) 945-9943

Sources of support: This work was supported by a CTSA grant from NCATS awarded to the
University of Kansas for Frontiers: University of Kansas Clinical and Translational Science
Institute (# UL1 TR002366). The contents are solely the responsibility of the authors and do not
necessarily represent the official views of the NIH or NCATS.

Explanation Regarding the Proposed Grant: Patients and health care providers were discussing the possibility of doing a multiple drug "cocktail" trial for amyotrophic lateral sclerosis (ALS). When this U01 PRA/RFA grant opportunity was released in 2015 we thought it might be a good vehicle to attempt to get this funded. The goal was to leverage multiple sites funded by NIH Clinical and Translational Science Awards (CTSA sites) and also include other sites (total 25 sites). After a great deal of discussion, we decided on a three-arm study and the drug cocktail was designed to potentially attack the pathophysiologic processes of neuroinflammation, motor neuron hyperexcitability and glutamate excitotoxicity. In all three study arms patients were to receive standard of care which included access to riluzole, PEG, BIPAP and then they would be randomly assigned to one of three arms:

1) tamoxifen (20mg: 2 times/day) and ranolazine (500 mg: 2 times a day
2) tamoxifen (20mg: 2 times/day) and mexiletine (200 mg: three times/day
3) tamoxifen (20 mg: 2 times a day) and memantine (20 mg: 2 times/day)

Subjects were to be randomly assigned using a Bayesian adaptive design process that we used successfully in the PCORI funded comparative effectiveness drug study for neuropathic pain.

We called the project ALS PATIENTs DEMAND which stood for the ALS Patient-Driven Electronic-based Multidrug Adaptive Network Design clinical trial

Because the grant was to NCATS and the goal was to introduce novel trial designs that could be extrapolated to other diseases, we also had an aim to utilize a number of new initiatives to streamline regulatory oversight, ensure meaningful patient -engagement, enhance recruitment and decrease the burden of outcome collection.

We divided the sites into three regions and proposed to use IRB reliance models at U California -Irvine on the west coast (Dr. Tahseen Mozaffar as Irvine sites PI and leader of the west coast group), at Univ. Kansas as the lead in the Greater Plains Collaborative PCORnet network, (Dr. Jeffrey Statland as site PI) and in the NIH Create consortium based in Miami (Dr. Michael Benatar site PI and leader of the CReATe group).

We proposed to use the then recently created EPIC downloadable ALS clinic templates to collect the data.

We proposed two-way video web-based interactions with patients so they would not have to come in for as many visits.

We believed the study could create a model for multicenter research studies seeking to more efficiently maximize network-level collaborations to study any rare disease.

This was an ambitious proposal that did get scored (41) but this was not in a fundable range.

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At the time these U01 grants allowed for direct costs of nearly 1 million dollars a year for 5 years.

We had to apply via an XO2 preproposal mechanism to apply for the large study. The XO2 was submitted in the summer of 2015 and was accepted in the fall of 2015. We submitted the full proposal in early 2016.

We have attached PDFs of the Specific Aims page, the Research plan, and the Critiques.

The reviewers were very critical of our attempt to use three IRBs to control the study and in retrospect this was a valid criticism. They stated this could potentially jeopardize the safety of the study. This is why they concluded the protection of human subjects "was unacceptable" along with some toxicology concerns. Even with the three central IRB approaches we still had intended for Univ Kansas to be the primary CCC/DCC, but this did not come across in the proposal. They thought we were saying the three CTSA hubs (Kansas, Miami, Irvine) each were responsible for all the DCC/CCC activities of the sites using their IRBs. That was not our intention.

Regarding the cocktail approach, some of the reviewers thought this was not novel as it had been used in cancer and HIV studies. We felt these reviewers did not appreciate the difficulties in doing this for ALS.

Only one reviewer addressed the drugs in the cocktail. They stated tamoxifen was not well justified and that each drug had side effect profiles and that the side effects of each drug "could be viewed as exacerbating the ALS disease process"!

They really liked the Bayesian adaptive design.

In talking to leaders at NCATS after we received the critiques, they encouraged us not to do a cocktail study.

When we resubmitted the proposal, we engaged the new NIH funded Trial Innovation Network resources. Johns Hopkins is one of the TINS and we applied for a consultation on how to improve our proposal and we were accepted into the TIN program. We worked for nearly a year to improve the application and resubmitted with more simplified trial design comparing mexiletine and ranolazine and also randomizing sites to enrolling subjects as traditional urban research centers (TURCs) or mobile innovation research centers (MIRCs) to also test the hypothesis that we can just as easily do research remotely. This application did not do much better with a score of 40. We continued to work with the TIN and now we believe we have further improved the trial which was resubmitted in March 2020.

1. Specific Aims

New translational science tools and approaches for more rapidly advancing health research to the common goal of improved cures and treatments are especially needed for studies of rare diseases. The goals of this application are 1) to create a model for leveraging existing national research initiatives and new translational science tools to build the infrastructure to run multi-site studies in rare diseases; and 2) for proof of concept, to use this CTSA-based national research infrastructure to test the hypothesis that drug combination therapy in amyotrophic lateral sclerosis (ALS) will be more effective than standard of care alone. ALS is a rare progressive neurodegenerative disease which is uniformly fatal. Traditional approaches to developing therapies have failed in ALS, yielding only a single FDA approved therapy with a modest benefit on survival. Thus, there is a pressing need for new therapeutic approaches in ALS. One such approach used to treat cancer and HIV has been drug combinations targeting different pathological pathways. We convened an ALS patient and caregiver focus group who expressed overwhelming interest in using a drug 'cocktail' approach to ALS therapy. Patients also frequently state they feel left out or abandoned once their disease progresses beyond the earliest stages, the most common focus of most ALS clinical trials. Therefore, we designed a patient-driven clinical trial to assess which of three drug cocktails targeting different pathological pathways are the most effective in slowing disease progression in ALS: the **ALS Patient**-**D**riven **E**lectronic-based **M**ultidrug **A**daptive **N**etwork **D**esign clinical trial (**ALS PATIENTs DEMAND**). For **ALS PATIENTs DEMAND** we will leverage existing major initiatives to simplify the regulatory process, to connect electronic health records (EHRs) of large academic ALS centers, and to roll out common data elements through the EHR and via CTSA funded REDCap databases to build a large national ALS clinical trial network—providing the bandwidth to study large numbers of ALS patients, and importantly, to broaden study inclusion criteria to include ALS patients often excluded from traditional clinical trials.

Aim 1: To leverage existing research initiatives and introduce new innovations to streamline regulatory oversight, ensure meaningful patient-engagement, enhance recruitment, decrease the burden of outcome collection, and hasten results dissemination using 3 CTSA Coordinating Centers and 25 sites (19 CTSAs). Specifically:

a. We will compare the regulatory efficiencies across 3 different networks: two IRB reliance models (Greater Plains Collaborative: a PCORNet CDRN; and the University of California Regulatory System); and one central IRB (the ALS Rare Disease Clinical Research Network). We will compare the time to regulatory approval, time from regulatory approval to first patient enrollment, and rates of accrual.

b. We will create a patient engagement plan which incorporates the patient voice into all aspects of the clinical trial: protocol development, recruitment, retention, study conduct, and dissemination of results.

c. We will use EHR-defined computable phenotypes for patient screening, and compare this approach to traditional recruitment strategies in the clinic or via patient advocacy groups.

d. We will leverage the availability of EPIC downloadable ALS clinic templates for the primary set of outcomes to compare outcomes collected by this EHR-i2b2 interface with those collected by using REDCap database links within the local clinic work-flow. We also will explore whether this approach reduces the burden on patients, caregivers, and health care providers.

e. We will implement a patient visit and adverse event monitoring system via a two way web-based video system already in production to reduce the burden of participation and ensure retention.

Aim 2: To determine which of three drug regimens added to standard of care has the greatest efficacy for slowing ALS disease progression. For this aim we will conduct a prospective 12 month three-arm Bayesian response adaptive randomization clinical trial. Drug combinations will repurpose FDA approved drugs for other indications which act on potential ALS pathological pathways (neuroinflammation, motor neuron hyperexcitability, and glutamate excitotoxicity). Informative priors and stopping criteria will be derived from the PROACT data base of 8500 patients. The diverse ALS population in our national ALS network (over 4700 patients) and the informative priors derived from PROACT will allow us to broaden our inclusion criteria to include patients often excluded from current clinical trials.

Our proposed collaboration among CTSA coordinating centers to create a model for assembling study-specific infrastructure for rare diseases will <u>not only serve as a blueprint for future clinical trials in ALS, but also will inform any multi-center clinical trials seeking to more efficiently maximize network-level collaboration to study any disease.</u>

2. Research Strategy

A. Statement of the Problem and its Significance to Translational Science

The goal of this application is to create a model whereby we will leverage existing national research initiatives and translational science tools to create the infrastructure needed to run multi-site studies in rare diseases. We intend to show that deploying innovative translational science approaches can accelerate testing of putative therapeutics for rare diseases. By definition a rare disease in the US is one where < 200,000 people are affected; however, taken together there are approximately 7000 rare diseases(1). This represents a significant burden to the US health care system. Barriers to developing new therapies for rare diseases include: 1) the need to use multiple sites to recruit sufficient numbers of patients to obtain statistical rigor; 2) difficulties with regulatory oversight for large multicenter studies causing delays in start-up and increasing study costs; 3) difficulties with assembling efficient networks for data collection, while minimizing patient burden; 4) ensuring patient and caregiver voices are heard throughout the therapeutic development process; 5) using technology to overcome barriers in distance or medical infirmity to allow all eligible patients to participate in the research enterprise. The national CTSA system gives us an unprecedented opportunity to use our existing infrastructure to build on the models for IRB reliance, use the national REDCap database infrastructure, use CTSA based patient engagement initiatives, leverage new health care technology development, and formalize existing multi-institution relationships to address a large unmet medical need. We propose to leverage the broad CTSA-based national research infrastructure and the regulatory structure of 3 established clinical research networks to conduct a clinical trial in amyotrophic lateral sclerosis (ALS).

ALS is a progressive uniformly fatal neurodegenerative disease. The median age of onset is between 50 and 60 years, where individuals are at the peak of earning, which places a tremendous financial and emotional burden on patients, family members, and their communities(2). ALS is characterized by spasticity and hyperreflexia from the loss of upper motor neurons in corticospinal tracts and from muscle weakness, fasciculations, and atrophy due to lower motor neuron degeneration and death in the anterior horns of the spinal cord(3). Disease progression leads to limb paralysis, loss of speech, swallowing, and respiratory functions, and ultimately death. While ALS is regarded as a rare disease, affecting only ~21,000 people in the US at any point in time, the incidence (at 2 per 100,000) matches that of common neurological diseases such as multiple sclerosis(4-6). Moreover the lifetime risk of dying from ALS is about 1 in 400(7). ALS therefor appears rare only because we have no effective therapies and because the disease is fatal.

Traditional approaches to therapy development have so far failed in ALS, yielding only one FDA approved drug, Riluzole, which prolongs life by 2-3 months(8, 9). The current standard of care for ALS patients is primarily supportive with the goal of maximizing quality of life(10). The 2009 American Academy of Neurology recommendations for the management of ALS patients state that in addition to Riluzole, enteral nutrition via percutaneous endoscopic gastrostomy (PEG) should be considered to stabilize body weight in patients with impaired oral intake, and noninvasive ventilation (NIV) should be offered in order to prolong survival and slow the impact of declining forced vital capacity (FVC). PEG or NIV can extend life by approximately 6 months if the treatments are adhered to and applied early(10, 11).

Since traditional approaches to therapy development have failed, we urgently need to apply innovative translational science approaches to ignite a paradigm shift in the way we approach therapy development for this fatal neurodegenerative disease(12). Thus, as a first test of our proposed approach, we will establish the ALS Patient-**D**riven **E**lectronic-based **M**ultidrug **A**daptive **N**etwork **D**esign (**ALS PATIENTs DEMAND**) infrastructure needed specifically for studying ALS treatment options and determining which of three drug combination regimens has the greatest effect on slowing ALS disease progression.

The significance of this project is: 1) it will present a model for leveraging existing national infrastructure and translational science innovations for clinical trials in rare diseases; and 2) it will answer the question of whether drug combinations work better than standard of care in ALS, which would have an impact on patient care.

B. Rationale

Establishing an innovative CTSA-based national research infrastructure will allow us to contribute to advancing translational science by critically assessing innovations such as patient-engagement, streamlining regulatory oversight, and using other new initiatives (e.g., IRB reliance agreements) and translational science tools (e.g.,

EHR-i2b2 interface capabilities for downloadable clinic templates). Our project also is innovative in being the first to rigorously test the efficacy of drug combination regimens for ALS.

Accumulating evidence points to multiple pathological processes being active in ALS – this raises concerns that the disease cannot be halted or slowed by simply targeting one of these mechanisms. Important lessons for approaching ALS can be learned from other diseases: in HIV they found that only by targeting multiple steps in the pathological cascade could they affect a significant health impact on controlling HIV; and in cancer the use of combination therapies which target multiple pathological pathways has essentially become standard of care for many malignancies (3, 13, 14). The exact underlying cause of ALS motor neuron degeneration may remain uncertain; however, convincing evidence, supports the role of a number of pathological pathways—including glutamate excitotoxicity, neuroinflammation, and motor nerve hyperexcitability (15-17). Each of these pathways has FDA approved drugs for other indications than ALS currently available on the market. Many of these drugs have shown promise in ALS studies *in vitro*, in animal models, or in small often underpowered clinical trials(18). This is frustrating to both patients and clinical researchers, as many currently available and potentially effective drugs are not being tried or are being discarded in ALS due to lack of money or initiative. We have convened two patient and caregiver focus groups who have expressed overwhelming interest in using a drug 'cocktail' approach to ALS therapy. By creating drug combination regimens which target multiple pathological pathways we may be able to slow progression in a more profound and lasting fashion than any one drug alone.

The ability to obtain statistical rigor to test drug combination regimens in ALS requires large number of patients and multiple sites participating across the country. ALS patients are seen in either an Amyotrophic Lateral Sclerosis Association (ALSA) or Muscular Dystrophy Association (MDA) sponsored clinics, usually at tertiary care centers. While the vast majority of our ALS patients are seen in ALS specialty clinics, most of which are affiliated with CTSA academic centers, our ability to pool resources and recruit large populations of ALS patients for studies has been limited. This is not due to lack of interest from patients. The existing CTSA national infrastructure, combined with three large existing network initiatives, provide an unprecedented opportunity to consolidate resources and build on these existing initiatives to advance translational science.

With respect to the specific proposed trial, if any of the tested drug combinations prove effective in ALS; this will have a dramatic and immediate impact on patients, their family members, and communities. All of the proposed drug combinations repurpose FDA approved medications currently used for other indications *which should all be available in generic preparations by completion of this trial*. Thus, most ALS patients could obtain immediate access to and benefit from these proposed treatments.

Equally important, if the study design innovations proposed here prove feasible this may not only transform the way we approach clinical trials in ALS and rare diseases, but also will inform any multi-center clinical trials seeking to more efficiently maximize network-level collaboration to develop new therapeutics for any disease.

C. Strategy and Methodology

Aim 1a. *We will compare the regulatory efficiencies across 3 different networks: two IRB reliance models and one central IRB.*

Collaboration: In order to maximize efficiency and streamline design of the **ALS PATIENTs DEMAND** infrastructure we will leverage three existing research networks (Figure 1):

- We will designate three CTSA Coordinating Centers (CTSA CC), each of which plays a key role in an established research network.
- The CTSA CCs will share the workload of reviewing the 25 sites, thus gaining efficiencies in the start-up process.
- There are 5 sites not affiliated with a CTSA CC. These unaffiliated sites will be added to a CTSA CC.
- All sites are ALS specialty centers with long histories of working together in smaller existing research consortia: i.e. the Western ALS Study Group, the Northeast ALS Consortium, the ALS Research Group, or in prior investigator-initiated ALS studies.

The three research networks included in this study are: **1) the Patient Centered Outcomes Research Network (PCORnet) Greater Plains Consortium (GPC) (19), 2) The University of California Biomedical Research Acceleration, Integration, and Development (UC BRAID)(20), and 3) The Clinical Research in**

ALS and Related Disorders for Therapeutic Development (CReATe), a Rare Diseases Clinical Research Consortium that forms part of the NIH's Rare Diseases Clinical research Network. Within the GPC there are ALS specialty clinics that already have demonstrated the ability to combine resources to perform ALS research by conducting a survey of ALS patients using a single IRB of record. UC BRAID also has mature reliance architecture in place which will be used for this study. CReATe has an ongoing natural history study to better understand the phenotypic variability in ALS (that will not compete with the current proposed study), and a central IRB model in place. Part of CReATe is the ALS patient registry (**CReATe Connect)**, with hundreds of ALS patients registered, who have agreed to be contacted for future studies.

Our organizational structure will include one CTSA CC site representing each of the above networks, and 25 ALS specialty centers spread across the country (20 CTSAs, Figure 1). These CTSA CCs will be: 1) the University of Kansas Medical Center (KUMC) which serves as the data coordinating site for the GPC and the overall lead site for this study; 2) The University of California Davis (UC-Davis), which will coordinate with the UC BRAID system; and 3) The University of Miami, which serves as the main coordinating site for CReATe.

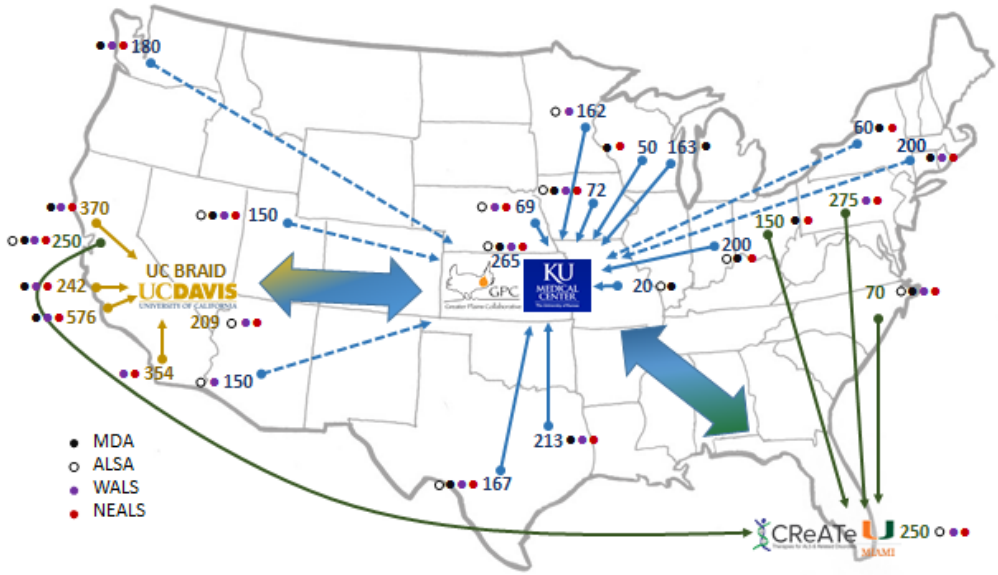


Figure 1. The three CTSA CCs and their existing research networks include 25 academic centers. The numbers represent estimated ALS clinic populations. Yellow=UC BRAID, Blue=GPC, Green = CReATe, *MDA = Muscular Dystrophy Association Clinic, ALSA = Amyotrophic Lateral Sclerosis Association Clinic, WALS = the Western ALS Study Group, NEALS = the Northeast ALS Consortium. Dotted lines represent sites not currently in GPC, UC BRAID, or CReATe.*

The organization structure will stem from the 3 CTSA CCs. We will compare the existing IRB regulatory models of these networks on key study timelines.

The GPC, UC BRAID and CReATe will be responsible for providing regulatory oversight of institutions in their existing networks. The workflow will include: Each of the CTSA CC ALS physicians will interact the with an **ALS PATIENTs DEMAND** steering committee (see below) to produce the final study protocol; and then the 3 CTSA CC regulatory members will create a common informed consent form. The KUMC IRB will coordinate with the other two CTSA CCs to facilitate communication and administration of regulatory tasks necessary for a successful start-up. The KUMC IRB is well situated to lead this cooperative model, and:

- Has experience in serving as the coordinating center for 3 PCORI funded trials,
- Has a dedicated reliance coordinator,
- Will lead development of the universal consent form to be used at all sites and customized only in limited areas relevant to local information (this important step will speed the approval of consent and other patient-facing materials by the 3 IRBs),
- Will centralize version control for all materials submitted to the three reviewing IRBs, and
- Will disseminate any updates to protocol or patient materials, safety monitoring updates (adverse events, DSMB reports, etc.)

A study steering committee was established for the design phase of this study and included: each of the CTSA CC PIs and ALS doctors, a patient representative, the study informatics officer, statistician, a PhD pharmacist, and representatives from patient advocacy groups. In addition the steering committee sought specific input

from patients who had participated in prior focus groups who agreed to be contacted for this study.

Innovation: Our innovation is creating a nation-wide **ALS PATIENTs DEMAND** infrastructure not only to perform a large multi-center ALS clinical trial that uses established research networks with IRB reliance agreements in place, but also to test comparative efficiencies of different IRB reliance agreements and to serve as a model for assembling similar infrastructure to run multicenter clinical trials for any rare disease.

Translation: Comparatively testing existing IRB reliance models and will inform translation by determining which is the most efficient on key factors that often delay or slow clinical trials. *Statistical considerations:* We will investigate the relative efficiency of each network by comparing their sites using outcomes: number of days to IRB approval and number of days from regulatory approval until the first patient is enrolled. Our first key metric will be **IRB Duration** (as defined in the proposed CTSA Common Metrics): "the time in days between the date that the application for IRB review is received by the IRB office and the date of final approval granted by the IRB with no IRB-related contingencies remaining." Our second metric is time from IRB approval to first enrollment—will track efficient study start-up processes once IRB approval has been granted. Since these are time-to-event outcomes we will use Bayesian Weibull models, including a censoring indicator for sites that may not have achieved an event within the study time, to assess this metric. We will follow rates of accrual across the different networks, and determine demographic features which could affect accrual rates. We will compare regulatory efficiency to KUMC's (GPC), and UC BRAID past values on these metrics. Identifying mechanisms to improve these metrics address an intermediate barrier to getting trial results into practice for ultimate patient health benefit.

This model of assembling research networks using existing infrastructure in a study-specific fashion can directly benefit patients with rare diseases, by allowing the assembly of the large multi-institute trials which will be necessary to bring scientific rigor to testing new therapeutics, but also pragmatic questions of patient care.

Partnership: Dr. Richard Barohn is the overall study PI and KUMC CTSA PI and is responsible for coordinating all members of the study team. He will work with his collaborating CTSA PIs Drs. Lars Berglund (UC Davis) and Ralph Sacco (Miami) to ensure smooth operation of the informatics and regulatory conduct of the study. The lead ALS doctors, Michael Benatar (Miami), Bjorn Oskarsson (UC Davis), and Jeffrey Statland (KUMC) will coordinate within their respective CTSA CC to ensure smooth recruitment and retention of ALS patients across all 25 sites. Dr. Barohn, an experienced ALS multicenter trial investigator, is the PI on two FDA-OPD R01 ALS studies (for rasagiline and memantine). He has led the Western ALS (WALS) Consortium, participates in the Northeast ALS (NEALS) Consortium, and been on the executive committee of the ALS Research Group (ALSRG). He was instrumental in developing the ALS Common Data Element Forms (ALSCDE). Dr. Sacco, CTSA PI at the University of Miami, is Chairman of Neurology and was the PI of the Northern Manhattan Study which described the greater incidence of stroke in the Hispanic population. Dr. Berglund has been the PI of the UC Davis CTSA since 2006 and is the Senior Associate Dean for Research at the UC Davis School of Medicine. He has extensive experience with both basic and clinical research, serving as PI for several NIH R01 grants. Michael Benatar, MD, PhD is a Professor of Neurology at the University of Miami, Chief of the Neuromuscular Division, Executive Director of the Kessenich Family ALS Center, and holds the Walter Bradley Chair in ALS Research. He is the PI for CReATe (U54), an FDA funded trial of arimoclomol in SOD+ familial ALS (R01), the ongoing MDA and ALSA funded Pre-symptomatic familial ALS (Pre-fALS) study, and the University of Miami NeuroNEXT hub (U10). Björn Oskarsson, MD is an Associate Professor at the University of California – Davis and directs their Multidisciplinary ALS clinic. He has been in numerous clinical treatment trials and epidemiological studies in ALS. Jeffrey Statland, MD is an Assistant Professor of Neurology at KUMC, helps run both MDA and ALSA clinics, is a current CReATe ALS research fellow, and co-investigator on the GPC ALS projects.

Barriers: 1) *IRB Reliance, and IRB coordination between CTSA CC sites* – by building on existing consortia that use IRB reliance agreements and selecting sites with a history of working together, we expect to accelerate the timeline for study approval. The three CTSA CCs are committed to working together to solve issues in a timely fashion that may come up in start-up (see Letters of Support).

Defining Success: We have already developed 3 research networks involving 20 CTSA sites. We are going to demonstrate cooperation among the 3 networks, with regard to recruitment and trial innovation. We will determine if any network has superior efficiency and why. We will then disseminate our experience to the entire CTSA community via the CTSA leadership channels.

Aim 1b. *We will create a patient engagement plan which incorporates the patient voice into all aspects of the clinical trial.*

Collaboration: Increasingly, collaboration with patients has become critical for translational research. True **patient engagement** reflects commitment to transparency, the practice of open, bidirectional communication, and an appreciation for the lived experience that only patients can provide as members of the research team. Investigators at the 3 lead CTSA sites have decades of community-engaged and community-based participatory research experience in frontier, rural, minority, disease-specific, and underserved communities in diverse geographic settings (FL, CA, KS) and are skilled at meshing investigators' concerns with those of participating patients, communities and stakeholders. Our investigators have a history of maintaining ongoing personal relationships with ALS patients and other stakeholders relevant to this application. These trusted relationships have and will continue to provide the project with established connections to further engage patients in and with this study. The community/patient engagement faculty from the 20 CTSA sites will serve as models to assist the non-CTSA participating sites that may not have established engagement programs.

Our comprehensive framework for patient engagement is the "ALS engagement ecosystem" (Figure 2), developed and refined with patient input. Each engagement element informs the other, and each makes a unique contribution. The model is a visual tool that ensures investigators understand the complex and unique contributions the non-academic members make to the team. It also is a useful reference point for addressing organizational and representational issues for decisions at all levels and for the design of the study.

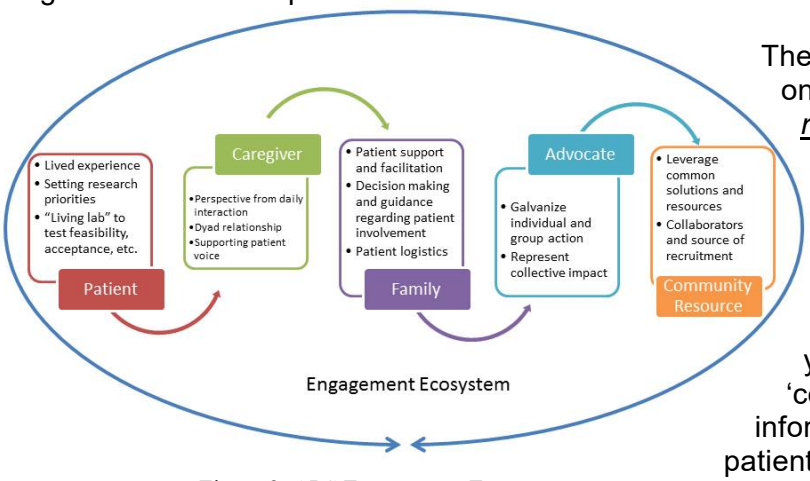


Figure 2. ALS Engagement Ecosystem

The approach for this project stemmed from ongoing dialogue with patients and families – *many of whom knew they would not likely benefit from participation given their advancing ALS.* Using facilitated discussion groups, these individuals asked the investigators to operationalize the "cocktail" design they discussed. Our ALS physicians discussed this issue with their patients and conversations yielded overwhelming support for a drug 'cocktail' approach to therapy. Using this information, we then convened a patient and patient/caregiver dyad focus group by phone (to reduce transportation and cost burden to participants).

Four key findings from this focus group helped shape the approach for this study:

1. First, patients shared enthusiastic support for a multidrug study and agreed that better understanding the specific treatments proposed in **ALS PATIENTs DEMAND** would benefit patients.
2. Second, the patients and caregivers were passionate about ensuring that the study would be available to as many patients as possible. They discussed this topic at length. They understood that opening inclusion criteria would require more patients, and they suggested using functional criteria for inclusion, rather than disease duration.
3. Third, the participants said they preferred to use their personal computers or tablets to input their own patient-reported outcomes. Patients, as well as caregivers, were unanimous in sharing how stressful and energy-draining additional study visits are for both of them, so they want to provide as much information from home as possible.
4. Finally, the group overwhelming wants to stay involved throughout the study and to continue to advise and help in any way possible—especially in dissemination strategies that will assist the ALS community to learn about the study's findings.

They called on the investigators to be bold, to "think big," and to do all they could to remove barriers in order for more patients to become involved in research that could lead to better treatments. We look forward to continuing to work with our patient and caregiver partners.

Innovation: In addition to patient and caregiver input already obtained for the study design we will keep patients and caregivers involved throughout the running of the clinical trial.

- We will designate patient engagement leaders at each of the CTSA CCs

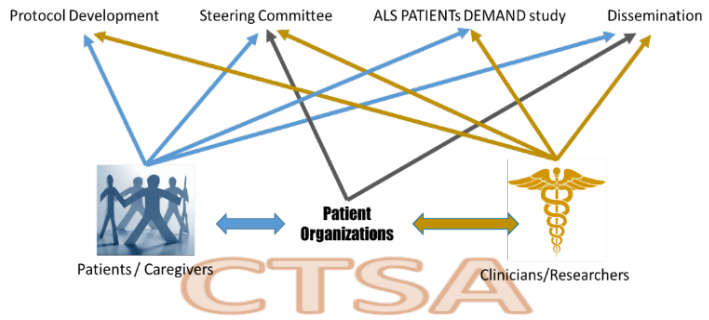
- We will create patient engagement circles and identify a pool of patients and their caregivers who can be called upon on an as-needed basis for focus groups to address specific study concerns regarding conduct, recruitment, and retention
- We will designate patient/caregiver representatives to formally participate in the **ALS PATIENTs DEMAND** study Steering Committee
- We will use both patient-representatives and our patient engagement circles to help disseminate study findings, as well as leverage existing patient outreach technologies from the MDA and ALSA clinics, and **CReATe Connect** ALS patient registry

Each of the 3 CTSA CCs will have engagement facilitator to ensure efficient and effective engagement activities at the network level. A lesson learned from our early work is that designated patient engagement leaders who can reach out and communicate with the entire engagement ecosystem need to be in place at the earliest possible point of the project. This ensures a consistent liaison function between the various engagement stakeholders and ensures maintaining fidelity so that no aspect of the study moves forward without the input or review from relevant stakeholders. For most participating sites, these trained site engagement facilitators will be the staff of their CTSA award community engagement programs. In addition to engaging patients as collaborators and full members of research teams, our patient engagement activities will address effective mechanisms for encouraging patients to become participants in research.

Translation: Comprehensive engagement, necessary for translation, must include active stakeholder involvement in project oversight, monitoring and leadership functions, not just for recruitment. We include stakeholders on all project committees and at all stages of the research, from early concept development through dissemination of findings. We will hold monthly team meetings (using GoToMeeting, or phone conferencing) to discuss study status. Patient representatives, site investigators, and data and safety monitoring board members will be on these calls. The specific composition of these groups will be established to ensure perspectives and input from patients, caregivers, MDA and ALSA clinics, and the CTSA CC engagement officers. We are sensitive to not burdening patient/caregiver/family stakeholders and overtaxing individuals willing to participate in this work. For example, participation at in-person team meetings can be exhausting, so use of online meeting resources like GoToMeeting.com and telephone conference calls that can be done from home always will be offered. Likewise, meeting times will be variable to be as convenient as possible for everyone.

We also will adopt a novel online platform developed at the Mid America Chapter of the ALSA. This innovation introduces a strategy to encourage camaraderie and increase knowledge penetration about the study. Co-developed with a private health IT firm, (HeartToHeart Network, LLC), the **ALS Care Portal** provides a way to communicate effectively and on an ongoing basis with ALS patients and facilitating the translation of our findings.

Upon completion of this study, we will establish a study communication committee composed of volunteers from our patient and caregiver collaborators and from registry and advocacy partners (MDA, ALSA, Prize4Life, and the **CReATe Connect** Registry). Results will be communicated through the broad network of ALS specialty centers from all 3 networks (GPC, UC BRAID, and CReATe). *The ability to mobilize patient and caregivers and engage them at each stage of the **ALS PATIENTs DEMAND** study, and to partner them with investigators and patient advocates will create an environment where all major stakeholders are directly involved, thus maximizing the impact of potential study findings, and accelerating their implementation into ALS clinical practice.*



Ultimately the success of **ALS PATIENTs DEMAND** is a collaborative effort (Figure 3). By combining three large existing networks, using ALS specialty centers, many which operate ASLA and MDA clinics, and bringing the patient voice into trial planning and conduct, we will create a flexible, highly leveraged ALS trial infrastructure, responsive to individual site level concerns and individual patient concerns, and will use this network to test combination therapies to halt disease progression in ALS.

Figure 3. Effective research into rare diseases is a collaborative effort – from the patient, to patient organizations, to ALS physicians. **ALS PATIENTs DEMAND** is built on CTSA infrastructure.

Barriers: *Maintaining patient engagement throughout the complete study process* is one major barrier for this aim. We have a track record of maintaining patient engagement through our PCORI sponsored projects. We already have a strong commitment from patients and caregivers to serve on our Steering Committee. As any study is a fluid process, and success requires adapting to unforeseen circumstances, we have identified CTSA CC engagement leaders who will adapt our engagement efforts throughout study conduct.

Defining Success: We will develop a broad engagement plan, demonstrate which engagement initiatives are the most successful, and disseminate the lessons across the CTSA consortium, and ALS research networks. We will define success for this aim as 1) established patient engagement circles and use of topic-specific focus groups to help with conduct, recruitment, and retention; 2) engaged patient representatives; and 3) a dynamic communication committee for study result dissemination.

Aims 1c-e. *We will use EHR-defined computable phenotypes for patient screening, and compare this approach to traditional recruitment strategies in the clinic or via patient advocacy groups. We will leverage the availability of EPIC downloadable ALS clinic templates for the primary set of outcomes to compare outcomes collected by this EHR-i2b2 interface with those collected by using REDCap database links within the local clinic work-flow. We will implement a patient visit and adverse event monitoring system via a two way web-based video system already in production to reduce the burden of participation and ensure retention.*

Collaboration: **ALS PATIENTs DEMAND** includes 25 sites with varying capabilities for EHR-i2b2 (Informatics for Integrating Biology and the Bedside)(21) interface and different EHR systems (e.g. Epic/Cerner). Despite the diversity many features unite the study sites—including membership in broad research networks (GPC, UC BRAID, and CReATe), and most importantly, the underlying CTSA infrastructure resources (e.g., REDCap) at 20 of the proposed sites. We will build on the informatics infrastructure set up by the CTSA CCs to implement broad data 'packages' that will be within the technical operating capabilities at each site. Russ Waitman, PhD, PI of the GPC and head of informatics for the KUMC site, will take an overall coordinating role for this project. KUMC Informatics has integrated and augmented two widely used CTSA technologies (REDCap(22) and i2b2(21)) to CReATe HERON (Healthcare Enterprise Repository for Ontological Narration)—an i2b2-based data repository of EHR data from the KU Hospital and clinics integrated with biospecimen, a research participant registry, and national data—and have used REDCap as a low cost method for data capture and secure data delivery from HERON.(23) KUMC Informatics also has extensive experience through its leadership of the GPC, a PCORnet Clinical Data Research Network (CDRN) of 12 sites associated with 8 CTSAs and geographically dispersed over 1300 miles.(19) We have invested a major effort to develop and publish open source rich Extract/Transform/Load (ETL) software methods to facilitate data and methods sharing and are solidly positioned to tackle and contribute to new informatics advances in support of translational science. Dr. Waitman will work collaboratively with his counterparts at UC-Davis (Nick Anderson) and the University of Miami (Nick Tsinoremas). The ability to leverage existing PCORnet initiatives like an EHR-i2B2 interface and computable EHR phenotypes (GPC and at UC BRAID sites), and the ability to build on the common CTSA REDCap infrastructure, will maximize the roll out of existing technologies. *While logistically challenging the data innovations proposed here are feasible within the time frame of the grant.*

Innovation: For the **ALS PATIENTs DEMAND** we will implement the following innovations: 1) we will use EHR computable phenotypes to assist with patient recruitment; 2) we will collect outcomes during the clinic work flow using an EHR-i2b2 interface, or customized REDCap link built into standard work-flow; and 3) we will use two way video to follow AEs or perform study visits for patients not able to travel into clinic.

Recruitment: At sites which have the capability (GPC, UC BRAID), we will use EHR computable phenotypes defined by diagnosis, standard diagnosis codes (e.g. ICD10), number of visits, and status as living. We will compare this recruitment approach to a standard approach of recruiting patients through clinics, use of advocacy groups (MDA and ALSA), and use of the **CReATe Connect** ALS registry.

- KUMC will define study cohort computable phenotype and study recruitment strategy using i2b2 queries developed for the PCORnet ALS cohort characterization. Recruitment will use a.) Manual

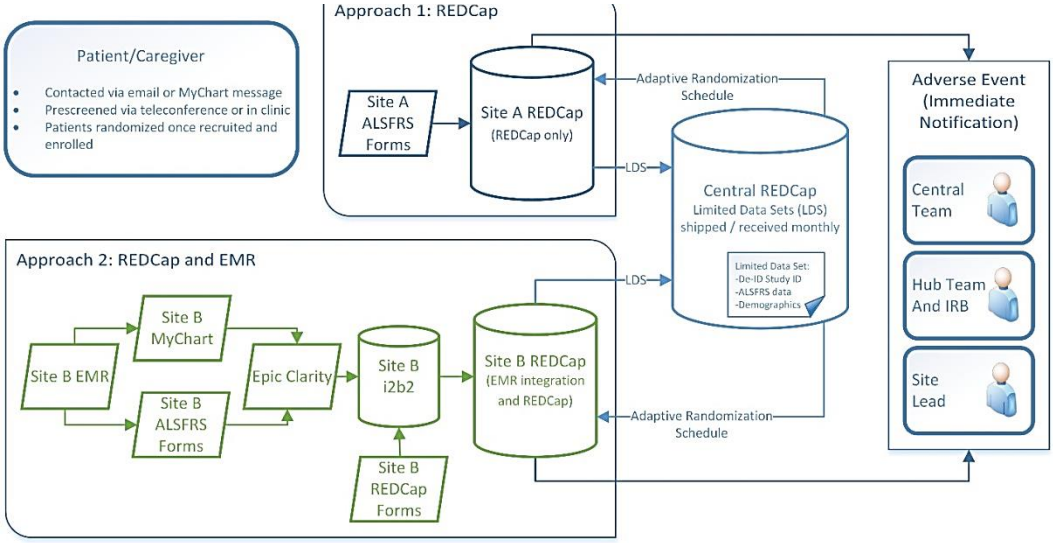
screening model (where coordinators enter prescreening info in REDcap), b.) Direct email to REDCap workflow for sites for prescreening of patients, and, (c.) MyChart to REDCap for the advanced sites.

- UC BRAID has the University of California Research eXchange (UC-ReX) Data Explorer which enables UC investigators to identify potential research study participants at the five UC medical centers. That system can be searched in a similar fashion to the HERON system in the GPC.

As proof of concept for this approach, the GPC used direct patient input to develop a revised version of the ALS Functional Rating Scale (ALSFRS-DEMAND) which patients complete from home. They then used the existing IRB reliance model to approve a protocol to conduct a survey of GPC ALS patients, using EHR computable phenotypes to identify patients, and combining survey response data with existing EHR demographic data as proof of concept for the approach. In that study we identified > 2000 ALS patients and greater than 50% of those who returned the survey stated they would be interested in participating in a clinical trial of combination therapy.

Outcome collection: We have designed two pathways for data collection. *Both approaches keep protected health information (PHI) local, and transmit de-identified data to the KUMC central REDCap architecture*. As shown in Figure 4 below, each site in **ALS PATIENTs DEMAND** will implement one of the two proposed data collection approaches. For Approach 1 (REDCap-only), data will be collected in a site level REDCap survey. For Approach 2 (EHR and REDCap), several sites will pilot this proposed advanced approach to data collection that leverages site level Epic-EHRs and REDCap.

***Figure 4**. Informatics Architecture for ALS Patient DEMAND*



For Approach 1, KUMC Medical Informatics (KUMC MI) will design and develop REDCap data dictionaries to be used to deploy the primary data collection instruments in REDCap installations at each site. Deployment at each site will be done via webinars with KUMC Informatics team members providing hands on support. KUMC MI team also will help the REDCap site teams deploy KUMC MI-developed REDCap plugins to use for notifying both site level and KUMC study team members of an occurrence of a Serious Adverse Event. A limited dataset version of the REDCap study data shared by the site with KUMC will inform the interim analyses for the Bayesian Adaptive Design. KUMC MI will coordinate with the site REDCap administrators to extract/upload the data and to deploy new randomization schedules derived from the interim analysis.

For Approach 2, sites will leverage EHR data collection and patient portal (MyChart) features in addition to the REDCap features of Approach 1. In this approach, patients will complete pre-screening via the site's Epic EHR patient portal, MyChart. Post-enrollment outcome measures, including ALSFRS, will be documented in the EHR along with REDCap. Initial work will involve implementing the EPIC forms and integrating them into test and development environments at each site. After validation the forms will be deployed in a production environment for use in the study. KUMC Medical Informatics also will develop additional ETL methods to integrate the measures collected at each site through their EHR and REDCap into a site-level i2b2 in order to enable sharing limited dataset versions of study data with the central study team for interim and final analysis. Data extraction will leverage the R Data Builder module developed by KUMC MI. The ETL code and R data builder will be tested at KUMC before distribution to all the sites. KUMC will host substantive, individual webinars with each site during installation of the shared code. In addition to these technical webinars, KUMC MI will provide training for study coordinators involved at sites implementing either approach.

Two-way web based video: KUMC also will leverage its experience deploying secure two way video communications through its https://telehousecalls.org application. Telehousecalls was developed for secure in-home patient/caregiver/provider communication with funding from the National Science Foundation and has been used to support both pediatric behavioral health and pediatric primary care consults for vulnerable populations through a grant from the REACH Healthcare Foundation.(24) For **ALS PATIENTs DEMAND**, Telehousecalls will be available for patients and caregivers as a platform for communication and assessments with providers. It will be modified to best support this trial with patients who may be affected by mobility issues. The ALSFRS-R can be collected via video interview and this two-way video can be used for adverse event (AE) reporting. The latter enables personal interaction and assures participants that their symptom is understood investigators that more serious AEs are not missed. This two-way video technology is adaptable to a variety of platforms (both PC and Mac, Android and iPhone) and enables patients who can no longer physically travel to the clinic for study visits to continue to participate in the study.

***Translation*:** The ability to assemble flexible clinical trial networks using existing CTSA, regional network, and NIH funded network infrastructure is transformative for patients with rare diseases like ALS. Our approach to such 'assembled' study-specific networks needs to be flexible, and **ALS PATIENTs DEMAND** will be a model for future studies. Key concepts such as: keeping PHI local; using EHR for both recruitment and data collection; using modern communication modalities to facilitate including patients who may not physically be able to travel to study centers; and creating work-throughs for assembling networks across multiple institutions all are addressed by **ALS PATIENTs DEMAND,** providing proof of concept that such a study can practically be assembled and conducted.

***Partnership*:** The key partnerships for Aim 1c-e will include the informatics officers at KUMC and the other two CTSA CCs, data personnel at each of the 25 participating sites, the local investigators, and the patients and caregivers participating in the study. The CTSA framework of sites with informatics people already familiar with REDCap makes the informatics portion of this study possible.

***Barriers*:** *Creating a universal REDCap data base with links to local EHRs* can be challenging, but we have already successfully used the proposed model in a current GPC ALS survey. For sites where we cannot provide live links via the EHR, patients will be provided web browser bookmarks for their tablet or computer. *Patient selection and recruitment via EHR* also can be challenging, but we also already have used computable phenotypes to identify ALS patients at the GPC and UC BRAID sites. That most ALS patients are seen in ALS specialty clinics allows us to recruit in clinic, from clinic rosters, or from regional ALSA or MDA patient lists as well.

***Defining Success*:** We will compare the frequency of recruitment via the EHR computable phenotype to traditional clinic / advocacy based recruitment. We will survey both patients and providers regarding data capture techniques, to determine if the current model reduces the overall study burden. We will disseminate the successful translational science approaches developed here to the CTSA consortium, and use this as a model for future ALS studies.

Aim 2. *To determine which of three drug regimens added to standard of care has the greatest efficacy for slowing ALS disease progression.*

***Collaboration*: ALS PATIENTs DEMAND** will be a three-arm, 12 month open label, response adaptive response randomized study involving 25 sites (and 20 CTSAs) associated with one of three cooperating regulatory networks (Figure 1). We will enroll 300 ALS participants. The sites included all have ALS specialty clinics, and include: 11 MDA certified ALS clinics; 5 ALSA certified clinics; and 9 clinics which run both MDA and ALSA certified clinics. Many of these sites have considerable experience participating in ALS clinical trials, and include: 16 sites who are members of the Western ALS Study Group (WALS) and the Northeast ALS Consortium (NEALS), 6 sites who are members of NEALS, and 2 sites who are members of WALS. Together WALS and NEALS have conducted over 21 interventional or observational ALS studies. Together the **ALS PATIENTs DEMAND** national ALS cohort is over 4700 patients. ALS patients seen in these clinics represent the full spectrum of disease, both genders, all races, and diverse socioeconomic status. Study visits will be designed to coincide with routine clinic visits, and will use the EHR patient portal, telephone calls, and video conferencing to collect information on patient functional status and adverse events between study visits. We will allow study personnel to report outcomes using the EPIC standardized forms via the EHR or via REDCap links during clinic visits.

***Innovation*:** The key innovations for Aim 2 are: 1) opening up of the entry criteria for the study, 2) the use of targeted combinations therapies, 3) the use of a Bayesian Adaptive trial design and the PROACT data set for informative priors; 4) entry of study data directly into EHR at the time of clinic visits, and by patients in the patient portal between visits; and 5) use of EPIC/EHR downloadable ALS clinic templates.

1) Patient characteristics: clinical trials of experimental interventions in ALS use narrow inclusion criteria which exclude most ALS patients by limiting studies to patients with symptom onset within 2 years, and FVC >75% predicted. This excludes more than half of patients who will have FVC < 75% predicted at diagnosis(25). In focus groups patients and their family members made it clear they find this approach makes them feel *left out* of studies of new or promising therapies. They suggested a more reasonable approach for inclusion would be by baseline functional status. Therefore, our inclusion criteria will be: a) A clinical diagnosis by a study investigator of ALS; and b) ALSFRS-R $\geqslant$ 20 (moderately affected); and our exclusion criteria will be: a) Any medication contra-indications for the particular drugs being studied; b) inability to provide informed consent; and c) current pregnancy or lactation.

2) Interventions: Considering the seriousness of the disease, the lack of robust efficacy of Riluzole (the only approved treatment for ALS), and limited options for further treatment, there remains a pressing unmet medical need for effective treatments for ALS. Three of the more promising pathological mechanisms with existing FDA registered drugs which could be repurposed for ALS are neuroinflammation, glutamate excitotoxicity, and nerve hyperexcitability. By creating drug combination therapies which target multiple pathological pathways we may be able to slow progression in a more profound and lasting fashion than any one drug alone.

Inflammation*:* Inflammatory monocytes and macrophages in the CNS have been shown to be involved both pathologically and in the rate of progression in ALS.(26-28) The importance of inflammation has been seen in both preclinical and animal model data.(27) The inflammation is associated not only with locally acting microglia, but also circulating inflammatory cells, which release cytokines believed to play a role in neurodegenerative processes, and to be harmful to motor neurons.(29, 30) Inflammation also is found in post mortem tissue from ALS patients.(29) The synthetic nonsteroidal drug tamoxifen is widely used in chemotherapy for breast cancer. A phase 2 randomized, dose ranging, selection trial of tamoxifen in ALS showed significant improvement in survival (P= 0.04) in those randomized to a 20 mg, 30 mg, or 40 mg daily tamoxifen treatment cohorts combined together.(31) For each dosage, survival was better at the higher dosage.(32, 33) Tamoxifen also may be neuroprotective – as metabolites have antioxidant actions since they are strong intramembranous scavengers of peroxyl radicals.

Nerve Hyperexcitability: Recent studies suggest that neuronal hyperexcitability may play a pathogenic role in ALS. Whole cell recordings from both embryonic and early postnatal SOD1G93A spinal motor neurons demonstrate increased persistent sodium current.(34, 35) Increased repetitive firing of cortical motor neurons following injection of current using current clamp conditions in SOD1G93A mice relative to age-matched controls has been shown to correlate with cortical hyperexcitability in the mutant mice.(36) Cell culture models for ALS have shown direct toxic effects of motor nerve hyperexcitability.(37, 38) Mexiletine and ranolazine are both FDA approved agents which act to reduce motor neuron hyperexcitability.(39-42). Ranolazine has been shown to block persistent sodium currents believed to play a key role in axonal neuro-degeneration and to block brain sodium channel excitability, suggesting both central and peripheral actions on axonal excitability. Two small human trials of mexiletine in ALS showed promising early results.(41, 43) Both studies were small, and in the only controlled study they did not see any change in the ALS Functional Rating Scale; however a slowing of the decline in respiratory function was seen in the lower-dose mexiletine group, and researchers did find a dose-dependent reduction in muscle cramps with mexiletine compared to placebo(44).

Glutamate excitotoxicity: Increased activation of N-methyl-D-aspartate (NMDA)-type glutamate receptors accounts, at least in part, for excitotoxic neuronal damage—potentially contributing to a wide range of acute and chronic neurologic disorders(45). Memantine is a non-competitive NMDA receptor antagonist that may reduce the effects of glutamate mediated excitotoxicity(46). Inhibition of excessive NMDA receptor activity by memantine, via a mechanism of noncompetitive open-channel blockade, can ameliorate excessive production of NO, protein misfolding, and neurodegeneration(47). Memantine has been shown to prolong survival in a mutant SOD1 transgenic mouse model of ALS. The data demonstrated that mutant SOD1 transgenic mice

survived longer when treated with memantine than placebo controls (p=0.03)(48). A small open label study of memantine suggested a possible slowing in the rate of progression (p=0.10), which persisted in 8 patients taking memantine for > 2 years compared to historical controls(49). A second small randomized controlled study showed memantine to be safe but did not demonstrate slowing of progression(50). This study, however, was powered to detect a large (50%) reduction in rates of progression, so was likely underpowered for a meaningful clinical effect.

Each arm of the study will consist of standard of care (SOC) as detailed in the AAN Guidelines (access to Riluzole, PEG for nutrition, and BIPAP as indicated) plus one of three drug combinations:(10)
1) tamoxifen (20 mg: 2 times/day) and ranolazine (500 mg: 2 times/day);
2) tamoxifen (20 mg: 2 times/day) and mexiletine (200 mg: 3 times/day); and
3) tamoxifen (20 mg: 2 times/day) and memantine (20 mg: 2 times/day).

The drug interactions for the proposed study arms were reviewed by a consulting pharmacist PhD.

3) Bayesian Adaptive Design: We can vastly improve the efficiency of our study by using an adaptive Bayesian study design, informative priors and interval analyses to adapt randomization during the study to favor drug combinations which interval analyses suggest are beneficial. Informative priors can be drawn from The Pooled Resource Open-Access ALS Clinical Trials data base (PRO-ACT), the largest database ever created of clinical data on ALS patients. PRO-ACT contains over 8500 fully de-identified clinical patient records, and more than 8 million longitudinally collected data points. Patients will be randomized to one of three treatment arms (groups) with a maximum number of patient's nmax= 300 (see Protocol Synopsis for specific power calculations and modeling). The primary endpoint used to drive adaptive randomization and stopping criteria is: the average disease progression (monthly measures of ALSFRS-R) from enrollment to 52 weeks. A longitudinal model using early estimates from 26 weeks will allow early adaptive randomization to promote a smaller, faster, but more powerful trial. Interim analysis will occur after 100 patients have 52 week data and every 8 weeks thereafter. These data will inform an updated adaptive randomization schedule. We will "stop for success" if the probability a treatment is best is > .965. For interim analyses, all data are used on all enrolled patients with at least 26 weeks of data. For the final analysis: (1) a treatment is best if pr(it is best) > .95 or (2) a treatment is loser if pr(it is best) < .01. It was deemed the most likely effect size will be a disease progression of 1 point/month for usual care, but only 0.75 point/month for the best drug combination (an effect size greater than current SOC)(8) . For example, in the "One Best" case, the study design has 94% power to find the best treatment with an estimated 238 subjects, trial duration of 135 weeks, and 47% of the subjects in the winning group. Type I error rate is 5%. A pre-specified subgroup analysis, suggested by our patient group, will use a Bayesian ANOVA to estimate the interaction of gender and site of onset with drug.

Translation: By leveraging existing CTSA and PCORnet programs we can accelerate the **ALS PATIENTs DEMAND** milestones (Table 1). We already have used the EHR to computer phenotype ALS patients, and can use this to accelerate recruitment. The two-way video system is already in production. We have used REDCap surveys embedded in an EHR link, or through web interface, in our PCORnet ALS patient survey.

Table 1. ALS PATIENTs DEMAND 5 year timeline

		Study Year				
Aim	**Milestone**	**1**	**2**	**3**	**4**	**5**
Aim 1	**IRB**					
	Patient Engagement					
	Screening EHR-defined phenotypes					
	Two way video / AE					
	EHR-i2b2 data package / REDCap					
	PRO Outcomes via Web/Tablet					
Aim 2	**Recruitment**					
	Clinical Trial					
	Analysis / Dissemination					

The ALS clinical and research community have agreed on standard clinical measurement tools to assess outcomes, and the **ALS PATIENTs DEMAND** study will use these tools. Standard functional and symptom scales include: the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), forced vital capacity, and the ALS Global Impression of Change scale.(51) These scales have

largely been adopted by the **ALS PATIENTs DEMAND** clinics at this time, and because of the simplicity of these forms, the ease of creating REDCap surveys for the forms, and a commitment from Electronic Privacy Information Center (EPIC) to make them available to clinics using EPIC EHRs, it is feasible to collect them in **ALS PATIENTs DEMAND**.

Primary outcome: Functional status is the primary outcome. The ALS Functional Rating Scale (ALSFRS) was designed to assess the ability of ALS patients to perform activities of daily living and to detect functional changes during clinical trials(52). Precedent for using this scale in clinical trials stems from the only positive treatment trial of riluzole in ALS, which showed slower decline in treated patients relative to placebo(53, 54). The ALSFRS-R, a revised version of the ALSFRS, is a quickly administered, by research personnel or study staff, (five minutes) ordinal rating scale that assesses capability and independence in 12 functional activities. These include six bulbar-respiratory functions, three upper extremity functions (writing, cutting food, and dressing), and three gross motor functions (walking, climbing, and turning in bed). Each activity is recorded to the closest approximation from a list of five choices, scored 0-4, with the total score ranging from 48 (normal function) to 0 (no function). The ALSFRS-R has been used extensively in previous clinical trials and validity has been established by correlating ALSFRS-R scores with quantitative strength testing and changes in strength over time (55-63).

For this project we further revised the ALSFRS-R and created the ALSFRS-DEMAND. We modified the ALSFRS-R so that it would be patient user friendly and so patients could fill it out themselves. The ALSFRS- R was sent to approximately 20 ALS patients throughout the GPC region and their caregivers. They were asked if the scale was difficult to understand; if there were items they felt should be dropped from the ALSFRS-R; or if new items should be included. We held two focus group conference calls where the patients discussed and commented on the scale. Patient focus group recommendations included a need for clarification in meanings of some of the words in the ALSFRS-R, but overall the impression was that this instrument reflected the types of functional limitations they experienced on a daily basis. However, there also were several items patients believed should be added to the ALSFRS-R: a question about pain; a question about emotional liability; and a general non-denominational question about faith. These were added and our new ALSFRS-DEMAND survey is designed to be completed by patients between clinic visits and can be completed via the EHR patient portal or an individualized email link to a REDCap database.

Currently Riluzole is the only approved medication for patients with ALS, which extends life by only 2-3 months. If any of the drug combination proposed here proves effective in ALS, this will have a dramatic and immediate impact on patients, their family members, and communities. All of the proposed drug combinations are readily accessible registered FDA medications used for other indications, and should be available in generic formulations by the end of the study. It would be expected most ALS patients interested could obtain access to the proposed treatments, and so benefit. In addition if the study design innovations proposed here prove feasible this also may transform the way we approach therapies in ALS by:

***Partnership*: ALS PATIENTs DEMAND** is fundamentally a partnership between the patient and caregivers who will have an active role in study design, conduct, and dissemination of results; the engagement officers; the patient advocacy groups who will have role in recruitment and dissemination; the GPC, UC BRAID, and CReATe who will provide regulatory oversight; and the 25 participating ALS specialty clinics across the country.

***Barriers*:** *Rolling out a Bayesian adaptive design across multiple CTSAs across the country* will be challenging. However, we have used this approach to randomization in a current PCORI sponsored study evaluating pain medications in patients with small fiber neuropathies. The current model of using the EHR-i2b2 interface *or* REDCap links embedded in the clinic workflow allows a backup mechanism built into the study design to ensure we will be able to perform interim analysis and adjust randomization. *Difficulty with recruitment* is another challenge. We believe our combined networks, which cover approximately 4700 ALS patients, and the broadening of our inclusion criteria, will lessen this challenge for our goal of recruiting 300 participants. However, if we do encounter difficulty we will add additional sites and assign them to their closest regional CTSA CC.

Defining Success: The ultimate success of this study would be to identify a treatment arm which slows down ALS progression. In addition we will consider ALS PATIENTs DEMAND successful if we: 1) meet our

enrollment and study completion timeline; 2) if at least half of the sites can enter data directly into the EHR at the time of clinic visits (the remainder using REDCap links), and this can be successfully abstracted; 3) if patients can use the patient portal to enter data between study visits; and 4) use of two way video for adverse event monitoring.

Ultimately developing the infrastructure proposed for **ALS PATIENTs DEMAND**, demonstrating the feasibility of conducting a large national multi-site study, and disseminating the innovations in efficiency back across the CTSA consortium will provide a viable model for repurposing drugs for use in ALS, and for testing new therapeutics for rare diseases, and potentially any disease.

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1U01TR001815-01 BAROHN, RICHARD

RESUME AND SUMMARY OF DISCUSSION: This is a new application for the Collaborative Innovation Award, Clinical and Translational Science Award (CTSA) Program (U01) from the University of Kansas Medical Center entitled “ALS Patients Demand.”

The purpose of this application is to create a model for building infrastructure to run multisite-studies in rare diseases by leveraging existing resources, and the applicants plan to use the CTSA-based national research infrastructure to test the hypothesis that drug combination therapy in amyotrophic lateral sclerosis (ALS) will be more effective than standard of care alone. Strengths of the application include the urgent need for drug combination therapy studies to target ALS as single drug therapies failed to stop the disease progression; the well-experienced Principal Investigator (PI); the plans to integrate existing coordinating centers from Clinical and Translational Science Institutes (CTSIs) and rare disease networks; the plans to use Bayesian adaptive designs in the proposed three arm clinical trial of three drug combinations in ALS patients; and the excellent resources at the partnering institutions. The plans to use electronic health records (EHRs) in addition to RedCap to identify subjects and transmit data and video conferencing for study follow-up visits are additional strengths. The proposed patient engagement plan to involve stakeholders from early stages of study design and the plans for patient-driven clinical trial to assess ALS combination therapies are innovative. Weaknesses include the lack of clear information on how interim metrics will be obtained from three institutional review boards and the three CTSA hubs to improve the regulatory submissions or recruitment efforts and the inadequate information on the expected side effects of the proposed combination drug therapy. Although there are plans to conduct trial visits of patients by video conferencing, there are no alternate plans described to visit them if they cannot participate by video. The lack of systematic pharmacovigilance during the clinical trial and of a real time, study-wide, centralized live database are major weaknesses that will have an impact on the ability to implement adaptive randomization and interim analyses, and also increase the risk for human subjects. This resulted in a rating of unacceptable for protection of human subjects.

Overall, the application received an Impact/Priority Score of 41; the committee recommended the budget as requested.

DESCRIPTION (provided by applicant): New translational science tools and approaches for more rapidly advancing health research to the common goal of improved cures and treatments are especially needed for studies of rare diseases. Amyotrophic lateral sclerosis (ALS) is a rare progressive neurodegenerative disorder caused by loss of motor neurons in the brain and spinal cord which is invariably fatal. Traditional approaches to developing therapies have failed in ALS, yielding only a single FDA approved therapy with a modest benefit on survival. Thus, there is a pressing need for new therapeutic approaches in ALS. Accumulating evidence points to multiple pathological processes being active in ALS – this raises concerns that the disease cannot be halted or slowed by simply targeting one of these mechanisms. One approach used to treat cancer and HIV has been to use drug combinations targeting different pathological pathways. The goals of this application are 1) to create a model for leveraging existing national research initiatives and new translational science tools to build the infrastructure to run multi-site studies in rare diseases; and 2) as proof of concept, to use this CTSA-based national research infrastructure to test the hypothesis that drug combination therapy will slow disease progression in ALS. Several institution level innovations will make such a study feasible. We will leverage IRB reliance agreements across 3 large networks (comprised of 25 sites and 20

CTSAs) to increase the efficiency of regulatory oversight. We will build on principles of patient engagement we utilized in focus groups to involve patients and caregivers in the design, conduct and dissemination of results for our study. We will maximize the use of the electronic health records (EHR) to identify eligible participants using automated systems based on diagnosis codes and clinic visits. We will build a large REDCap data infrastructure based on the common underlying CTSA infrastructure, and compare data collection using REDCap to data capture using EPIC downloadable ALS clinic templates and the EHR-i2b2 interface. We will implement a two way web-based video system for adverse event reporting, and to enable ALS patients no longer physically able to come to clinic to remain in the trial. All of the institutional level innovations will complement innovations at the level of the clinical trial. We will utilize a Bayesian response adaptive design to test which of 3 drug combinations is most effective in slowing disease progression in ALS. If any of the drug combinations proposed here prove to be effective in ALS, this will have an immediate impact on patients, the family members, and communities. All of the proposed drug combinations are readily accessible medications currently prescribed for other indications which could be repurposed for ALS, and all should be available in generic preparations by completion of this trial. Our proposed collaboration among CTSA Coordinating Centers and model for assembling study-specific infrastructure will not only serve as a blueprint for future clinical trials in ALS and other rare diseases, but also will inform all multi-center clinical trials seeking to more efficiently maximize network-level collaboration to study any disease.

PUBLIC HEALTH RELEVANCE (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease affecting the voluntary motor system which is invariably fatal. Patient focus groups expressed overwhelming interest in using a drug `cocktail' approach to ALS therapy, with drugs targeting different pathological pathways. We will create a national network of CTSA sites and implement novel innovations in patient engagement, regulatory oversight, patient recruitment, and outcome collection to conduct a patient-driven clinical trial to assess which of 3 drug cocktails are the most effective in slowing disease progression in ALS: the ALS Patient-Driven Electronic- based Multidrug Adaptive Network Design clinical trial (ALS PATIENTs DEMAND).

CRITIQUE

Critique 1

Significance: 1

Investigator(s): 1

Innovation: 5

Approach: 4

Environment: 1

Overall Impact

Therapeutic development in rare disorders is severely limited by the number of available subjects and their possibility to participate in trials. In fast aggressive diseases like ALS, the time it takes to initiate trials directly and negatively impacts the number of available subjects. Despite the availability of national networks and CTSAs, there is still a need for better coordination of efforts to increase recruitment and accelerate trial initiation. New technology offers the possibility of remote patient participation in trials, minimalizing the site visits, very burdensome in this disease. A separate problem

that has been plaguing ALS and other rare disorders, is the failed attempts to halt or stop the disease progression by targeting one abnormal pathway at the time (one trial-one target), in diseases where multiple pathways combine to cause a rapid, irreversible pathology. This ambitious application sets up to both, create a supra structure to efficiently run large, multicenter clinical trials in ALS (Aim 1) and to test this structure while investigating the first combination therapy approach (Aim 2) to ALS. Both aims, if successful, can have a great impact in the field of ALS therapeutics, as well as set up the bases to similar approaches for other rare disorders. If successful, this project has the potential to highly impact the field. The impact of this application is diminished by the lack of tight pharmacovigilance. Though the drugs proposed for combination are FDA approved, with the subsequent large amount of available safety information, their systematic long term combination is unique to this study and has not undergone rigorous toxicology evaluation. Though adverse events (AEs) reporting is clearly delineated, there is a lack of systematic and centralized laboratory and AEs pharmacovigilance, which could identify safety signals before they become an issue. Since these combination trials are most likely to be conducted by academic networks such as this one, the investigators need to establish industry-standard safety and data monitoring.

Significance

Strengths

- This application addresses a critical barrier to therapeutic studies in ALS: time to study initiation and patient recruitment and multi-target therapeutic approach. Despite large advances in ALS pathophysiology and genetics, ALS clinical trials, one after another, have been disappointing, failing to translate encouraging pre-clinical (and small clinical) study results. The reasons might lay on the study design, but also on the fact that in very rapid and aggressive diseases like ALS a single target approach is likely to provide very small benefit, and thus result in negative trials. Combination therapy, however, introduces another challenge, requiring much larger number of subjects to adequately power the studies. This application addresses these issues by providing a plan to create a supra-structure including three CTSA hubs and 25 centers across North America, including all the well-established ALS networks, to increase efficiencies in regulatory approval and patient recruitment.
- The application also includes utilizing clinical EHR in addition to RedCap to identify subjects, collect and transmit data. They are making a tremendous effort to include patient's input in all aspects of the trial, which is the mandate in rare disorders. It is also bringing telemedicine into the trial design, which will facilitate patient's participation and follow up. Even if partially successful, this application will provide valuable information on how to conduct these large multi-center trials in an academic setting, and what kind of efficiencies (or deficiencies) might result from such efforts. It has the potential to change how the field is moving forward and as such it is highly significant.

Weaknesses

- Lack of systematic pharmacovigilance during the clinical trial and of a study-wide centralized live database increases the risk for human subjects and adds unnecessary risk to the overall conduct of the study.

Investigator(s)

Strengths

- Excellent, experienced investigators, all leaders in the field of ALS therapeutic research.
- Investigators have history of collaborating and participating in multi-center ALS trials.

- Three CTSA hubs are involved in the project, with the central hub being at University of Kansas Medical Center.

Weaknesses

- None.

Innovation

Strengths

- Though none of the proposed methodologies or concepts are novel, these are novel in the field of ALS.
- Video conferencing for study follow up visits and patient portal and involvement in trial design and data dissemination are clear strengths.

Weaknesses

- Large supra-structures to conduct clinical trials and combination trials have been established for decades in the field of oncology and HIV, and are thus not novel.

Approach

Strengths

- Aim 1 will provide metrics on different institutional review boards (IRBs) reliance and central IRB approval methods, which could result in more efficient, unified regulatory submissions in future trials.
- Three different coordinating centers will be used to accelerate regulatory approvals and launching trial at the 25 centers by dividing efforts, increasing trial initiation efficiencies.
- Patient engagement and input is sought from the conceptualization of the clinical trial to the data monitoring and dissemination.
- Clinical databases (Electronic Health Records (EHR)) will be used to identify patients for trials. The investigator shows feasibility, successfully identifying more than 2000 ALS patients through EHR phenotyping, fifty percent of which returned a survey positively backing up combination therapy trials.
- It could be efficient to integrate the clinical EHR and Epic databases and RedCap for data collection and for patient recruitment, though this also could be a very time-consuming effort and very error prone.
- Combination therapies are needed for ALS. The drugs chosen for this trial have a clear rationale and target important pathological pathways, and proof of activity has been shown in animal models or small trials. The investigators have thought about the pharmacodynamics interactions that could affect data results and consideration to these are included in the data analysis plan.
- Primary outcome for the trial is ALS progression as measured by one well-established, validated, clinical relevant functional scale. This makes the study simple, cheaper, and relevant. Though the lack of biomarkers could result in a type 2 error, the bar is set high for disease modification and that is reasonable.
- A Bayesian adaptive design will help to delineate wining combinations and potentially decrease the needed number of subjects.
- The PIs have addressed barriers and proposed alternative plans.
- There are clear plans to disseminate results and to measure success of the projects.

Weaknesses

- Although Aim 1 is strong on its conceptualization, it becomes weaker on the outcome front. It is not clear how the metrics to be obtained from the three types of IRBs and the three CTSA hubs' recruitment efforts will be translated into improving the mid-way regulatory submissions or recruitment efforts. Since the study is large and will last at least five years, it would have been stronger to have interim data analysis of Aim 1 metrics, and use this information to correct or improve ongoing regulatory submissions and recruitment efforts based on what is being learned from the first years.
- The main weakness of this application is having three different CTSA hubs acting as separate coordinating centers, including the collection and management of interim data. A lack of centralized live database hinders the clinical trial pharmacovigilance. They propose a risk-based review, randomly performed by each CTSA hub. Though AEs are clearly being collected and transferred monthly to a central database, laboratory analysis are said to be reviewed only by PIs, and data not entered and transferred on electronic case report forms. Monitoring of AEs will be done at each one of three CTSA hubs and then every four months reviewed by a Data and Safety Monitoring Board (DSMB). That means that there is no continuous, centralized pharmacovigilance, where one person or team will be looking at trends in labs and AEs study wide. This could result in safety signals being missed until a significant AE is reported.
- The DSMB will review data every four months, and it is not clear that this includes labs (not mentioned). Though these are FDA approved drugs, they all have a significant side effect profiles and their combination has not been systematically studied in humans or toxicological studies.
- The lack of a central data system also introduces several potential complications, which will make the study implementation and conduct inefficient and error prone. There are no centralized data quality check tools and no data monitoring plan. Since they will be using a Bayesian adaptive design, they would rely on clean, real time data, arriving to some central location, and it is not clear how they will smoothly achieve this with once a month limited data transfers and no ongoing data management and cleaning.
- They have plans to conduct trial visits by video if patient cannot come to the site, but no systematic efforts to have a home nurse visit the patient to collect vitals and blood work. The latter should be part of any missed visit to assure patient is safe.
- Inclusion criteria are broad, which is good, but there is no statistical language on how the heterogeneous population will be taken into account in the data analysis.

Environment

Strengths

- The central coordinating centers, and all participating institutions, are ALS centers of excellence and well established research networks.
- There are letters of support from all three IRBs.
- The project builds on the existing strengths and resources of the CTSA program, and at the individual investigators Institutions and CTSA hubs.

Weaknesses

- None.

Protections for Human Subjects

Unacceptable. Though the drugs proposed for combination are FDA approved, with the subsequent large amount of available safety information, their systematic long term combination is unique to this study and has not undergone rigorous toxicology evaluation. Though AEs reporting is clearly delineated, there is a lack of systematic and centralized laboratory and AEs pharmacovigilance, which could identify safety signals before they become an issue. This is an unacceptable risk to humans.

Inclusion of Women, Minorities and Children

Acceptable. Study will recruit both sexes and adults. Children are not included, as ALS is very rare in children.

Vertebrate Animals

Not Applicable.

Biohazards

Not Applicable.

Select Agent Research

Not Applicable.

Resource Sharing Plans

Acceptable. The investigators propose clear ways of sharing and disseminating study results.

Budget and Period of Support

The budget for a centralized, systematic pharmacovigilance monitoring and reporting is not included. The safety monitoring budget is at 0.12 calendar months per year. This is a very low effort for pharmacovigilance in a 300 patient trial. The data management relies on one person with an effort of 4.8 calendar months per year. It appears low for the type of decentralized database and potential issues that could be found from different sources.

Critique 2

Significance: 2

Investigator(s): 1

Innovation: 1

Approach: 4

Environment: 3

Overall Impact

ALS is a devastating progressive disease, where few therapeutic options exist. Translation from pre-clinical efficacy studies in mouse models to efficacious approaches in human patients has largely failed, leaving patients few options for treatment. This application plans to establish a trans-CTSA clinical trial

network for ALS clinical studies, leveraging key domain expertise at participating institutions. A key goal is to begin combination therapy clinical trials; an approach that patients are requesting. The application is highly innovative in many ways. There is extensive patient engagement in trial content, focus and design, and an ongoing elaborate means of soliciting patient feedback. This is extended to encouraging contact between patients through established infrastructures. The application takes the important strides made in different coordinating centers, both within Clinical and Translational Science Institutes (CTSIs), and outside (e.g. Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe)), and works very hard at integrating these. The combination drug trial, requested by patients, is also highly innovative, particularly the use of the Bayesian adaptive design, the ALS Patient-Driven Electronic-based Multidrug Adaptive Network Design (ALS PATIENTs DEMAND) clinical trial patient recruitment and phenotyping tools, and broad inclusion criteria. The weaknesses centered on feasibility. The applicants have chosen to tackle a large number of problems such as integration of networks, multiple coordinating centers, broadening of inclusion criteria with new outcome measures, three drug combinations (where there is scant evidence that each shows efficacy in ALS individually), and large-scale patient involvement simultaneously. Any one of these is important, with significant innovation if successful. But with such a large (n=300 patients) and complicated study, there is a relatively high risk that the data once (and if) obtained may be difficult to interpret. There are also significant side effect profiles for each drug individually, and concerns about combined side effects (over and above drug metabolic interaction).

Significance

Strengths

- ALS is a relatively common neurological disorder with no effective treatment. Efforts to develop therapeutic approaches are highly significant.
- Efforts to leverage and integrate multiple existing networks are highly significant.

Investigator(s)

Strengths

- The proposed investigative team is outstanding. The PI brings extensive clinical trial and clinical experience in ALS to the collaborative network. The participating CREATE network and CTSA hubs all have extensive resident experience to carry out the proposed roles.

Innovation

Strengths

- The model of integrating different existing coordinating centers both from the CTSIs and rare disease networks under the umbrella of broader CTSI infrastructure is innovative. There are clear strengths to the participating institutions and great strides that have been made in data collection and access, and trans-center data queries.
- The patient engagement aim is innovative. There is increasing recognition that stake holders should be involved from early stages of study design, and the EU seems to be ahead of US in this. The proposed (relative elaborate) effort to include stake holders is impressive, and innovative.
- The patient-driven desire to undertake a clinical trial of combination therapies is innovative.
- The use of Bayesian adaptive designs in the proposed three arm clinical trial of three drug combinations in approximately 300 ALS patients is innovative.

- By focusing on repurposed drugs, there is no need for the complication of an IND. A letter from FDA confirmed this.

Approach

Strengths

- The proposed ALS DEMAND network describes an interesting structure, where there are three sub-hubs managing a total of 25 recruitment sites. The major hub is the Kansas CTSI (parent institution of the ALS DEMAND network) managing 14 sites, a University of Miami site managing an existing network of four ALS recruitment sites (CREATE network), and the UC system UC BRAID network servicing four recruitment sites via UC Davis. The rationale provided is that this will share the workload, thus gaining efficiencies. In fact Aim 1 will test this rationale by providing metrics during the trial (Aim 2) startup phase, comparing each site in terms of IRB approvals, contracts, initial enrollment, and subject accrual metrics.
- Aim 1b describes a patient engagement plan. This is very well described and impressive in scope and depth. This is a major strength.
- The application builds on existing network strengths, including the CREATE ALS network.
- Patients' phenotypes will be collected using a computed method via an integrated EHR between the 25 sites. The applicants acknowledge that there is significant heterogeneity between sites regarding i2b2, EHR systems, and computing infrastructure. Integrating the EHRs to the point of computable phenotypes sounds intimidating. However, the applicants provide a good example of receiving data on 2,000 ALS subjects via the GPC on ALSFRS-DEMAND at home survey. It could be argued that this is a small step towards integrated computed phenotyping via EHRs, but a step in the right direction nonetheless, and a strength.
- The applicants propose two distinct data acquisition methods (RedCap alone; EHR/RedCap/Epic). While this is inclusive of heterogeneous sites, it also complicates the conduct of an already complex trial.

Weaknesses

- Typically clinical trials have a single coordinating center. The structure of three coordinating centers is unusual. While it is stated that this will share workload and gain efficiencies, this rationale is not entirely transparent.
- The applicants wish to promote combination therapy trials. These are often problematic, as the individual drugs may not have shown efficacy individually, optimization of doses is made much more challenging when studying multiple drugs simultaneously, and developing effective clinical trial designs to accurately monitor both safety and efficacy can be difficult. The investigators cite both HIV and cancer as success stories. While they are indeed success stories, one could argue that key biomarkers were critical to the successful testing of combination therapies in these (viral load in HIV; molecular targets in cancer). ALS seems to lack such key biomarkers, and thus the translation of success in HIV and cancer may not be easily accomplished in ALS.
- There are many well-established ALS clinical trial networks. The CREATE network is integrated into the proposed CTSI large network via University of Miami. However, the applicants should provide a clear contrast to these pre-existing resources, providing a justification for how the proposed CTSI network is value added. Indeed, there is considerable overlap in the proposed U01 project and these pre-existing ALS-focused networks.
- Including stake holders in the consideration of clinical trial designs, while innovative, is also risky. As the applicants describe, the patients would like combination therapies across a very broad range of disease severity. Of course, this same inclusiveness can make a trial very difficult to carry out, with the risk of disparate outcome measures with variable relevance to

specific disease subgroups. As the combination drug design (sans biomarkers) is already quite challenged, adding the broad inclusion criteria may lead to a trial stands a risk of not providing much interpretable data, and thus could become unethical in its broad inclusion. Similarly, the effort to promote patient communication during the trial with the ALS Portal is innovative, it stands the risk of introducing additional bias as well, further complicating interpretation of outcome data.

- The bulk of the proposed study is to carry out a three arm clinical trial of three drug combinations in ALS. The rationale for choosing these drugs, as well as the doses, is not well described. It is acknowledged that this is a short grant application, and there is not adequate room for a thorough justification. The choice of tamoxifien as an anti-inflammatory agent is not well justified. Moreover, each of the drugs individually has side effect profiles, and this is not discussed adequately. Tamoxifen is reported to cause reduced cognition. Mexiletine has been reported to show nausea in 40%, coordination problems in 10%, and tremor in 13% of patients. Memantine was halted in trials of multiple sclerosis due to problems with neurological impairment. Ranolazine shows dizziness in 10% and constipation in 10% of patients. All these side effects could be viewed as exacerbating the ALS disease process.

Environment

Strengths

- There are multiple proposed participants, and thus multiple environments. Overall, the combined environment is outstanding.

Weaknesses

- There are acknowledged challenges with integrating the multiple networks.

Protections for Human Subjects

Acceptable.

Inclusion of Women, Minorities and Children

Acceptable.

Vertebrate Animals

Not Applicable.

Biohazards

Acceptable.

Resource Sharing Plans

Acceptable.

Critique 3

Significance: 2

Investigator(s): 2

Innovation: 3

Approach: 4

Environment: 2

Overall Impact

The investigators propose to utilize CTSA-based national infrastructure to conduct a clinical trial to evaluate drug combination therapy to slow disease progression in ALS. They will take advantage to IRB agreements between sites to improve efficiency in regulatory oversight and hence expedite study start-up and mid-stream approval of protocol revisions. They will utilize existing data capture resources at the sites to recruit and collect data from patients. They also propose to use Bayesian adaptive design to treatment randomization and early stopping. The investigators will also include input from the community members (patients and caregivers) in their design, conduct and dissemination of study results. While the investigators propose a bold initiative to conduct a large trial in a rare disease with no real treatment option, there are limitations in their approach that will impact adaptation of their methodology to other rare diseases. Key limitations include informatics support and lack of an existing network with IRB agreements to expedite study start-up.

Significance

Strengths

- The investigators aim to test drug combinations to slow the progression of ALS using vast CTSA infrastructure. If successful, it will be a major breakthrough in providing treatment options to ALS patients.
- The investigators hope to provide an example of how to utilize CTSA infrastructure to conduct a multi-site trial.

Weaknesses

- The methods proposed to implement the trials may not be readily transferable to other trials or disease areas.

Investigator(s)

Strengths

- The applicants have put together a strong team of experienced researchers that are likely to succeed in their efforts. The role of each CTSA hub is well defined.

Innovation

Strengths

- The investigators propose to utilize several existing approaches to successfully conduct an important trial in ALS patients. These concepts that have been tested and evaluated in other settings include: use of central IRB or use of existing IRB agreements in a network of sites; incorporating patient and community input in design, conduct and dissemination of study results; use of EHR to screen potential patients; use of two-way web based video to reach and capture key data from patients with mobility issues; and use of adaptive design for randomization and early stopping for efficacy or futility.

Weaknesses

- Some of these concepts may not be easily transferable to other rare disease populations.

Approach

Strengths

- The overall study design is reasonable with a good likelihood of achieving the objective of testing the hypothesis that the proposed drug combinations will slow the progression of ALS.

Weaknesses

- The key weakness, a function of independent databases at each CTSA hub, is the data collection and management system. The lack of a central data system makes the study implementation very in-efficient, resource intensive and potentially error prone. There is no real time central database with monthly downloads of data from individual sites. There are no centralized data quality check tools. Safety reports cannot be real time either. Every update of CRFs will be time consuming and cannot be pushed from a central system. These will have an impact on the ability to implement adaptive randomization and interim analyses. This is not an ideal model to emulate for other studies.
- It is not clear why the KUMC IRB is developing informed consent forms and disseminating updates to study protocols. This is a task typically held by lead study PI and their staff.
- The use of time from IRB approval to first enrollment to evaluate IRB performance does not make sense. The application suggests that they expect some sites will not enroll any participant hence the need to censor time to first enrollment.
- While the idea of expanding inclusion criteria makes sense, it would be good to account for patient's baseline status in primary analysis or use some sort of stratified randomization approach. The impact of patient's functional status at baseline on primary endpoint is not addressed.
- While the proposed Bayesian adaptive design seems reasonable, the investigators should have presented why this method is preferable over other adaptive designs.
- The study timeline should allow for at least six months of data analyses after last patient last visit. The current plan can have patients in follow-up in Year 5 of the grant.
- The timing of interim analyses (100 in some places and 90 in other) and statistical descriptions are confusing. It is not clear whether the primary outcome change from baseline or functional rating scale at 12 month follow-up.
- It is not clear if all interim data from a patient will be used to predict 12 month score or just the six month value.
- Risk based monitoring is not at all described.
- It is not clear if the drug will be labeled for the study and also if patients are expected to pay for the drug costs.

Environment

Strengths

- The environment is adequately suited for successful completion of the trial.

Protections for Human Subjects

Acceptable.

Inclusion of Women, Minorities and Children

Acceptable. Children are not expected to be in this study as the median age of disease diagnosis is around 60 years.

Vertebrate Animals

Not Applicable.

Biohazards

Not Applicable.

Select Agent Research

Not Applicable.

Resource Sharing Plans

Acceptable.

Budget and Period of Support

Adequate.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): UNACCEPTABLE

Though the drugs proposed for combination are FDA approved, with the subsequent large amount of available safety information, their systematic long term combination is unique to this study and has not undergone rigorous toxicology evaluation. Though AEs reporting is clearly delineated, there is a lack of systematic and centralized laboratory and AEs pharmacovigilance, which could identify safety signals before they become an issue. This is an unacceptable risk to humans.

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 U01 TR001815-01; PI Name: Barohn, Richard J.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.