EE2: 3,4-Diaminopyridine Phosphate for AAL—The EEDAPP-ALS Trial

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Submitted to: National Center for Advancing Translational Sciences/NIH
In response to RFA/PA: PAR 19-099

The genesis of this unfunded NIH proposal was two-fold. First Dr. Raghav Govindarajan (at University of Missouri at the time), and Dr. Stanley Iyadurai, a neuromuscular neurologist at Catalyst Pharma, had the idea that 3,4-diaminopyridine phosphate (DAPP) might be beneficial for ALS. The theory was that DAPP, working at the presynaptic terminal of the neuromuscular junction (NMJ) might enhance function by increasing the release of acetylcholine vesicles. One of our colleagues at the University of Kansas Medical Center (KUMC), Dr. Hiroshi Nishimune, had been developing data that the NMJ was critical in ALS and that ways to preserve function at the NMJ could prolong survival time in SOD mice.

The second factor going on at this time was that I was learning about efficacy to effectiveness (E2E) studies by Dr. Harry Selkar, the principal investigator of the clinical and translational science program at Tufts University. Dr Selkar had been telling me about how a subtype of E2E studies called efficacy and effectiveness too (EE2) made a lot of sense in trial design. The overall concept of EE2 trials is that a phase 3 efficacy study is nested in a larger effectiveness study. The idea is to simultaneously prove efficacy in a narrow more homogenous population of subject, and at the same time enroll additional patients who do not meet the criteria for the efficacy study to get a sense on how the intervention has an effect in a larger population.

For enrollment criteria for the efficacy portion of the study, we planned to use a slight modification of the fairly rigid entry guidelines used in the edavarone pivotal study for ALS. For the effectiveness portion of the study, we allowed ALS patients to be randomized who did not meet these criteria. We proposed to enroll 200 study participants into the efficacy component and an additional 100 study participants into the effectiveness component and planned to use 24 sites that were part of the CTSA consortium or the IDeA-CTR consortium of trial sites. In the months leading up to the submission we had utilized the NCATS CTSA Trials innovation network (TIN) consultation process to vet and refine their proposal.

We had applied and were accepted to present the proposal to experts at an in-person TIN meeting in Boston in April 2019. At this meeting there were experts from the NIH, FDA, pharma and a number of clinical trial experts that provided useful feedback. What happened to this valiant effort to repurpose a new drug for ALS? Two things. As the grant was being reviewed, we got data back from a study that one of our other colleagues, John Stanford, PhD, was performing for us at KUMC. He did a controlled trial of DAPP in SOD mice. The results are reported in this issue of the RRNMF NM Journal.

Unfortunately, DAPP did not have any benefit in the animal model of ALS. Then we got the critiques back from NCATS/NIH which are attached. We were not funded to do this innovative EE2 trial. The reviewers seemed to be uncomfortable funding this unconventional trial design.

To date, we do not believe the NIH has funded a EE2 trial. There also was some hesitancy about the DAAP hypothesis for ALS. We wanted to publish the proposal and the critiques in the RRNMF Neuromuscular Journal under "Proposed Stuff" as the grant outlines what an EE2 trial design is, and this may be a new concept for many readers of the journal. We also wanted to have readers understand the thought process on why we believed DAPP should be studied in ALS.

Project Summary/Abstract
The overall goal of this application is to perform an innovative Efficacy Effectiveness -Too trial design (EE2) in Amyotrophic Lateral Sclerosis (ALS) in which we can simultaneously enroll a homogenous population to determine efficacy and a wider population to determine effectiveness in a broader population. ALS is a rare, relentlessly progressive and fatal neurodegenerative disease affecting cortical and spinal motor neurons. The exact mechanism of ALS is unknown. This clinical trial will study the efficacy and effectiveness of 3,4-Diaminopyridine Phosphate (3,4-DAPP) in patients with ALS. The mechanism of action of 3,4-DAPP is at the presynaptic terminal of the neuromuscular junction (NMJ) to enhance function by producing an increase in the release of acetylcholine vesicles. This drug was recently approved by the FDA for the treatment of the Lambert -Eaton myasthenic syndrome and may improve the function at the NMJ in ALS patients the same way exercise does. This proposal would be the first time an EE2 trial is done in a rare disease and will include 20 CTSA sites and 4 IDeA State CTR sites dispersed across the United States. There are five sites (Kansas, Missouri, Nebraska, California-Irvine, and Florida-Gainesville) that are designated as lead sites for the study. The specific aims for this study are as follows: **1.** Perform an EE2 study in ALS at 20 CTSA sites and 4 IDeA CTR sites and simultaneously enroll a cohort to determine efficacy and a more heterogenous cohort which combined with the efficacy cohort will determine effectiveness in a broader population. This will serve as a blueprint for the CTSA consortium to perform EE2 studies on rare diseases. **2.** Determine if 3,4-DAPP can alter the course of the disease in ALS patients. **2a.** Assess the efficacy of 3,4-DAPP by measuring changes in the slope of ALSFRS-R in a well-defined progressing cohort of ALS as previously defined in the edavarone study. We hypothesize that 3,4-DAPP will slow down the progression of ALS by 30% as measured by the slope of the ALSFRS-R at the end of 6 months in this well-defined narrow cohort. The dose of 3,4-DAPP will be 80mg/day or the highest tolerated dose up to that level. **2b.** Simultaneously recruit ALS patients with a more heterogenous entry criteria to more likely reflect a general ALS population and determine effectiveness. The aim is to determine if there are trends when looking at a more heterogenous population that suggest 3,4-DAPP may have a benefit **2c.** Measure secondary outcome measures in both populations: survival, the slope of decline of FVC, the change in an ALS specific quality of life measure (ALSAQ-40) and a patient reported ALS outcome measure, PADL ALS. At the conclusion of the study, there will be an open-label extension study which will allow all ALS patients who consented to participate in the study to have access to the active research drug. This will be funded by a different mechanism through a partnership with Catalyst Pharmaceuticals.

Contact PD/PI: Barohn, Richard Jude

Project Narrative

We will test an innovative trial diesing in amyotrophic lateral sclerosis (ALS), a rare, relentlessly progressive, fatal disease, by conducting a clinical trial, **EE**2: 3,4-**Dia**mino**p**yridine **P**hosphate for **ALS** - The EEDAPP-ALS Trial to determine 3,4-Diaminopyridine Phosphate versus placebo benefits patients with ALS by slowing down disease progression. In addition to performing a Phase III efficacy study in ALS with narrow inclusion criteria, we will simultaneously enroll a more heterogenous ALS group to determine effectiveness in a more generalizable population. 20 CTSA and 4 IDeA State CTR sites dispersed throughout the USA will be leveraged for this unique proposal.

Contact PD/PI: Baronn, Richard Joel

EE2: 3,4-Diaminopyridine Phosphate for ALS - The EEDAPP-ALS Trial

Amyotrophic lateral sclerosis (ALS) is a rare relentlessly progressive and fatal neurodegenerative disease affecting cortical and spinal motor neurons. The exact mechanism of ALS is unknown. The prevailing theory is that ALS is a dying forward phenomenon, in which primary damage occurs in the motor neurons and then extends in an anterograde fashion. Alternatively, multiple animal studies (such as SOD1 mice, drosophila and zebra fish ALS models) have demonstrated a distal axonopathy in which motor neuron degeneration starts at the nerve endings and progresses toward the cell bodies in a dying back manner leading to muscle denervation. Clinical and electrophysiologic correlates of muscle fatiguability suggest and element of neuromuscular junction transmission (NMJ) transmission dysfunction. In SOD mice there is loss of laminin beta2 which is believed to produce the dying back phenomenon. There is an interaction between laminin beta2 and the P/Q type VGCC that causes NMJ denervation and cause a decreased number of active zones. Adult ALS patients show decreased active zone size in spinal cord synapses. Therefore, the loss of laminin beta 2 can cause NJM denervation in SOD1 mice. Exercise as an intervention for ALS has been performed in SOD mice and ALS patients and recovers laminin beta 2 levels at NMJs and ameliorates NMJ denervation in SOD1 mice and rats.

The mechanism of action of 3,4-Diaminopyridine Phosphate (DAPP) is at the presynaptic terminal of the NMJ to enhance function by producing an increase in the release of acetylcholine vesicles. This drug was recently approved by the FDA for the treatment of the Lambert -Eaton myasthenia syndrome, Firdapse® may improve the function at the NMJ in ALS patients the same way exercise does. Several small studies of 3,4-DAPP in ALS included a placebo controlled cross over study and two open label studies. Overall, small but significant improvements in function were seen.

Many phase 3 ALS trials have failed to show efficacy and one of the possible explanations is that the populations enrolled are too heterogenous. This problem was solved recently in the study of edavarone for ALS in which they had a narrow inclusion criterion in order to enroll a relatively homogenous population. Edavarone (Radicava®) was efficacious in slowing ALS Functional Rating Scale by 30% and the drug was approved by the FDA in 2017.

While we now have a pathway to perform efficacy studies in ALS, patients and families want the option to be part of the drug research process and it is important to obtain knowledge of the effectiveness of the drugs in a larger more generalized population of ALS patients. One way to address this seeming dichotomy of crossed purposes is to use the innovative Efficacy Effectiveness -Too trial design (EE2) in which we can simultaneously enroll a homogenous population to determine efficacy and a wider population to determine effectiveness in the broader population. The EE2 trial design has never been attempted in a rare disease population.

AIMS:

1. Perform an EE2 study in ALS at 20 CTSA sites and 4 IDeA CTR hubs and simultaneously enroll a cohort to determine efficacy and a more heterogenous cohort which combined with the efficacy cohort will determine effectiveness in a broader population. This will serve as a blueprint for the CTSA consortium to perform EE2 studies on rare diseases.

2. Determine if 3,4-DAPP can alter the course of the disease in ALS patients.

2a. Assess the efficacy of 3,4-DAPP by measuring changes in the slope of ALSFRS-R in a well-defined progressing cohort of ALS as previously defined in the edavarone study. We hypothesize that 3,4-DAPP will slow down the progression of ALS by 30% as measured by the slope of the ALSFRS-R at the end of 6 months in this well -defined narrow cohort. The dose of 3,4-DAPP will be 80mg/day or the highest tolerated dose up to that level.

2b. Simultaneously recruit ALS patients with a more heterogenous entry criteria to more likely reflect a general ALS population and determine effectiveness. The aim is to determine if there are trends when looking at a more heterogenous population that suggest 3,4-DAPP may have a benefit

2c. Measure secondary outcome measures in both populations: survival, the slope of decline of FVC, the change in an ALS specific quality of life measure (ALSAQ-40) and a patient reported ALS outcome measure, PADL ALS

RESEARCH STRATEGY

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

The overall goal of this application is to employ novel trial methodology through an Efficacy and Effectiveness Too (EE2) design in a rare disease, amyotrophic lateral sclerosis (ALS). Using the EE2 design will allow a heterogenous group of patients to be on the study medication but also allowing the measurement of drug efficacy in a narrow subgroup of participants that is typical of many standard clinical trial designs.[1] This novel trial design can serve as a blueprint for similar studies in other rare diseases and it has the potential to improve enrollment and accelerate therapy development. Importantly, this trial design responds precisely to the priorities of ALS patients and caregivers by addressing their concern over the slow pace of generalizable treatments that can impact quality of life and slow progression. To our knowledge our EE2 trial has never been performed in a rare disease. This multi-center study will be performed exclusively at CTSA and IDeA State CTR sites. These are sites with expertise to accomplish this innovative rare disease trial design. In addition, we are testing a novel mechanism of action for treating ALS through the use of 3,4-Diaminopyridine Phosphate (3,4-DAPP) which works at the neuromuscular junction (NMJ). The investigators are partnering with a pharmaceutical company, Catalyst Pharmaceuticals, which will provide the drug recently approved by the FDA for Lambert-Eaton Myasthenic Syndrome, another rare disease indication. This will be a unique partnership of ALS clinics at CTSA/CTR sites, the National Institutes of Health, and industry to complete a combined phase 3 (efficacy) and phase 4 (effectiveness – in generalizability) in a rare disease that could have an immediate impact to benefit ALS patients if the drug can be shown to slow progression of this rare and fatal disease.

Challenges for rare diseases: A rare disease is defined in the US as having < 200,000 people affected. There are approximately 7000 rare diseases in the US, so taken together that represents 25-30 million people.[2-5] Rare diseases are complex, chronic, and often have inadequate or no treatment options available. Therefore, rare diseases represent a major unmet medical need and can result in a large share of US health care spending.[6] Barriers to developing new therapies for rare diseases include: 1) needing to use multiple sites to recruit sufficient numbers of patients for statistical rigor; 2) difficulties with regulatory oversight for large multicenter studies causing delays in start-up and increasing study costs; 3) identifying and contacting eligible participants; 4) repeated and often lengthy study visits; 5) lack of patient and caregiver input into study design and conduct; and 6) geographic distance or medical infirmity.[7] The National Clinical and Translation Science Award (CTSA) and Institutional Development Award (IDeA) - CTR programs gives us an opportunity to overcome these barriers and enhance our existing national ALS infrastructure by adapting existing CTSA models for IRB reliance and leveraging the Trial Innovation Network (TIN) Vanderbilt University Recruitment Innovation Center. This NCATS Innovation award initiative allows to pursue a phase 3 and 4 trial in the CTSA/CTR consortiums for a rare disease.

Challenges for ALS: Riluzole, an oral drug, was approved as a treatment of ALS in 1993 because it has shown a modest benefit in survival, with most studies showing a three-month survival benefit.[8] Edaravone was shown to reduce rate of decline in function by 30% (as measured by ALSFRS-R)[9]; however, it is expensive, requires intravenous therapy 14 days a month, and is often denied by insurance companies due to a lack of evidence showing effectiveness studies in a more general ALS population. Our own experience shows only about 15% of patients are receiving both medications, despite over 70% being on riluzole during the edaravone clinical trial. Many phase 3 ALS trials have failed to show efficacy and one of the possible explanations is that the populations enrolled are too heterogenous.[10] This problem was solved recently in the edaravone study in which they used a very narrow inclusion criterion in order to enroll a relatively homogenous population (see below).[11-12]

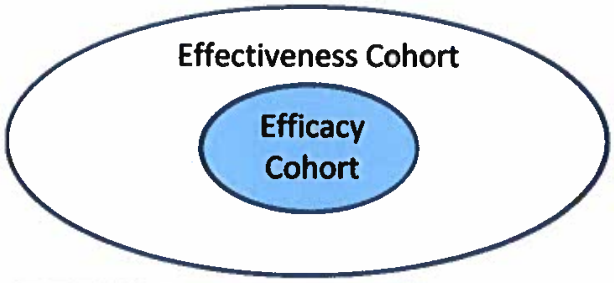

Figure 1: Reprinted from published article - Selker HP, Eichler H, Stockbridge NL, McElwee NE, Dere WH, et al. Efficacy and effectiveness Too Trials: Clinical Trial Designs to Generate Evidence on Efficacy and on Effectiveness in Wide Practice. Clin Pharm & Therapeutics. 2019; 105(4):857-866.

In the Efficacy-Effectiveness Too Trial of 3,4-Diaminopyridine Phosphate (3,4-DAPP) in Amyotrophic Lateral Sclerosis (EEDAPP-ALS) study we will be measuring the drug's efficacy in a narrow subgroup

and will simultaneously include a heterogenous population which will allow us to study the effects of the drug on a more diverse group of ALS patients (Figure 1). This will be measuring the drug's effectiveness in a more generalized ALS population. This will be responsive to the patients and families with ALS who have reportedly told researchers that they do not want to be excluded from trials.

B. Rationale:
There is increasing interest in determining both efficacy of a drug in a Phase 3 study as well as effectiveness of the drug in a more generalizable, real world, diverse population. However, effectiveness studies, while often contemplated, are seldom performed after a positive Phase 3 efficacy study when the drug is FDA approved and on the market. Thus, patients and payers, two key stakeholders, never have additional information on how the drug will perform in patients in a general population who may not have met the original entry criteria in the Phase 3 labeling study.

At least two approaches have been suggested to a prior plan for an efficacy and effectiveness study when a phase 3 study is first designed. One is to perform an Efficacy to Effectiveness study (E2E) (Figure 2) when an effectiveness study is designed to begin immediately after enrollment is complete or after the final patient has finished a phase 3 trials. The effectiveness study, in this case, is launched before the final results of the phase 3 study are available.[1] An even more expeditious design is the EE2 study (Figure 3). In an EE2 study, the patients for the phase 3 study and a more generalizable population of patients with the disorder are enrolled simultaneously.[1] Therefore, at the conclusion, there is an immediate answer to both the efficacy question as well as the effectiveness question. This is beneficial to multiple stakeholders on the research and health care spectrum – patients, caregivers, clinicians, and payers. All would like to know the answer to both clinical research questions as quickly as possible. Pharmaceutical stakeholders on the other hand may see an EE2 approach as risky for two reasons – they are investing financially in the effectiveness study before an answer to efficacy is known and the results could show the drug is efficacious in the narrow group of patients who meet study entry criteria but did not have the same effect in the wider more heterogenous patient group. In this case it is possible insurers may elect not to reimburse for the drug unless the strict efficacy criteria are met.

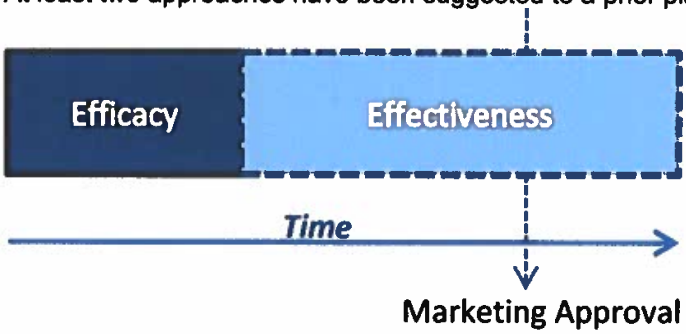

Figure 2: Example of E2E design: Reprinted from published article – Selker HP, et al. Efficacy and effectiveness Too Trials: Clinical Trial Designs to generate Evidence on Efficacy and Effectiveness in Wide Practice. Clin Pharm & Therapeutics. 2019; 105(4): 857-866.

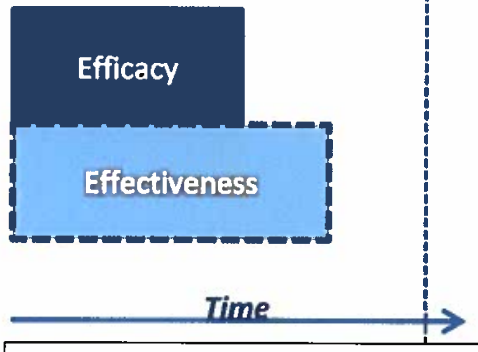

Figure 3: Example of EE2 design: Reported from published article – Selker HP, et al. Efficacy and Effectiveness Too Trials: Clinical Trial Designs to Generate Evidence on Efficacy and Effectiveness in Wide Practice. Clin Pharm & Therapeutics. 2019; 105(4): 857-866.

Innovation Opportunity for Trial Design in ALS:
Many phase 3 ALS trials have failed to show efficacy, and one of the possible explanations is that the populations enrolled are too heterogeneous. This problem was solved recently in the study of edavarone for ALS in which they used a narrow inclusion criterion to enroll a homogenous population. The cohort that was enrolled showing efficacy consisted of patients aged 20 to 80 years; ALS -Functional Rating Scale-Revised (ALSFRS-R) of at least 2 points on all 12 items; forced vital capacity (FVC) of 80% or more; definite or probable ALS according to the revised El Escorial criteria; disease duration of 2 years or less; and who had a 1 to 4 point decrease in ALSFRS-R during a 12 week lead-in period before randomization.[11] In this narrow ALS population, edavarone was efficacious in slowing ALSFRS-R by 30% and the drug was approved by the FDA

in 2017. This makes edavarone only the second drug approved for ALS since 1993 (riluzole) which has only a minimal effect on ALS survival. Currently only about 30% of patients seen in the clinic meet these selective criteria and many ALS trials have similar strict criteria. Therefore, many ALS patients that do not meet the strict inclusion criteria have minimal to no options in terms of treatment (in the case of edaravone) or participation in a clinical trial.[12]

While we now have a pathway to perform efficacy studies in ALS, patients and families want the option to be part of the drug research process and it is important to obtain knowledge of the effectiveness of the drugs in a larger more generalized population of ALS patients. One way to address this seeming dichotomy of crossed purposes is to use the innovative Efficacy Effectiveness -Too trial design (EE2) in which we can simultaneously enroll a homogenous population to determine efficacy and a wider population to determine effectiveness in the broader population.[1] The EE2 trial design has never been attempted in a rare disease population.

C. Strategy and Methodology

Aim 1: Perform an EE2 study in ALS at 20 CTSA sites and 4 IDeA CTR hubs and simultaneously enroll a cohort to determine efficacy and a more heterogenous cohort which combined with the efficacy cohort will determine effectiveness in a broader population. This will serve as a blueprint for the CTSA consortium to perform EE2 studies on rare diseases.

Collaboration:

We will leverage our existing ALS patient-centered clinic and clinical trial research infrastructure and national CTSA and IDeA-CTR programs and collaborating with the TIN (see letters of support). For this study, the University of Kansas Medical Center is the sponsoring institution and will serve as the data coordinating center (DCC) as well as the clinical coordinating center (CCC): responsible for managing implementation of the central IRB, site management, data quality assurance, and project management. We applied for and obtained initial TIN consultation and then we obtained full TIN support. We used the Recruitment Innovation Center (RIC) resources and our engaged ALS patient experience to design the study and to identify potential sites. Our organizational structure will include a national network of 24 ALS specialty clinic sites—all at existing CTSA/CTR hubs. The University of Kansas Medical Center (KUMC) has experience running large multi-site studies—most recently completing a 40-site study in small fiber neuropathy and 2 national phase II studies of rasagiline in ALS, and with an ongoing dose ranging study of ranolazine in ALS, and a national multi-center phase II study of memantine in ALS. To maintain efficient communications and coordination, we will have four regional lead sites to accomplish the study. KUMC has primary responsibility as the study sponsor and will co-lead the central U.S. hubs with the University of Missouri-Columbia. The University of Nebraska Medical Center will

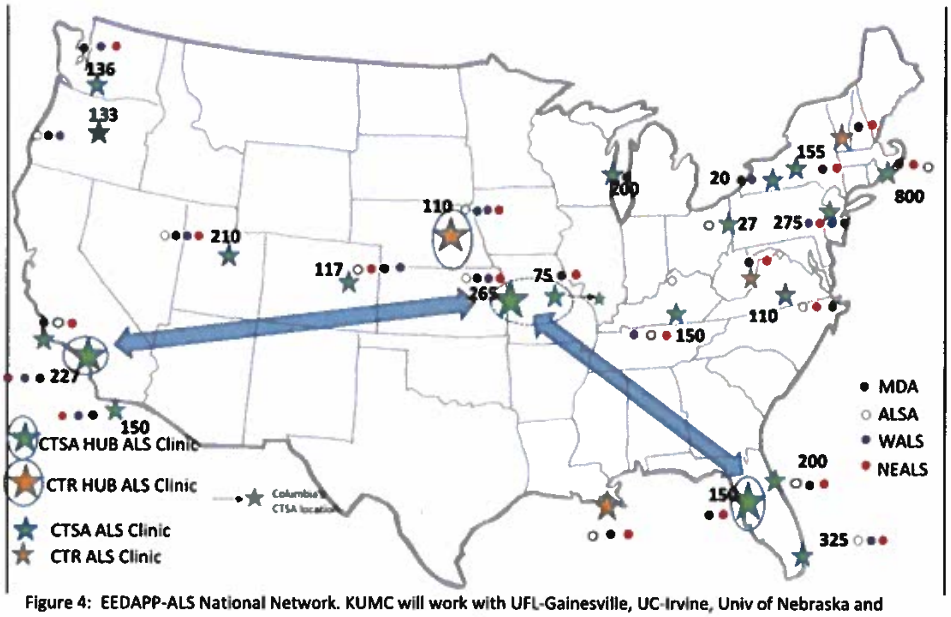

Figure 4: EEDAPP-ALS National Network. KUMC will work with UFL-Gainesville, UC-Irvine, Univ of Nebraska and Oklahoma University to manage network recruitment and implementation. Numbers represent estimated ALS participants. Green star=CTSA ALS Clinics, Brown star=CTR ALS Clinics; MDA = Muscular Dystrophy Association Clinic, ALSA = Amyotrophic Lateral Sclerosis Association Clinic; WALS = the Western ALS Study Group; NEALS = the Northeast ALS Consortium. CReATe = member of the NCATS Rare Disease Clinical Research Network for ALS

serve as the IDeA-CTR lead and the University of Florida-Gainesville and University of California-Irvine will serve as CTSA leads for the east and west coast regions, respectively (see Figure 5). A prior analysis of ALS clinical trials showed the most successful sites in recruitment, retention, and protocol adherence were sites that were experienced in clinical trials, with improved efficiencies with each trial and full-time coordinator.[13] We will use multiple existing ALS infrastructures to conduct this study. First is the national network of ALS multi-disciplinary clinics funded by the Muscular Dystrophy Association and ALS Association. Second, most of these sites are members of existing ALS research consortia, which requires baseline level of clinical trial preparedness and includes NEALS and WALS. Together the 24 sites we preselected have over 5,000 ALS patients. We estimate that 30% would qualify for the efficacy component and about 40-50% would qualify for the effectiveness component.

EEDAPP-ALS is a multi-PI project led by Dr. Richard Barohn (Contact PI- University of Kansas Medical Center) and Dr. Raghav Govindarajan (PI- University of Missouri Medical Center). Other ALS lead Co-investigators are Dr. Miguel Chuquilin (CTSA site investigator – University of Florida - Gainesville), Dr. Tahseen Mozzafar (CTSA site investigator- University of California-Irvine), and Dr. Americo Fernandes (CTR site investigator- University of Nebraska). This team will oversee all aspects of trial implementation and has over 85 years of demonstrated, collaborative research across their institutions. Andrew Heim (Project Lead, KUMC) will report to the PI's and will oversee all operations of the project as it relates to the trial responsibilities while ensuring smooth integration with the other sites. Leveraging these existing relationships with the TIN resources greatly enhances this proposed national multi-site study, and improves clinical trial processes, such as regulatory oversight, patient identification and recruitment, and study retention.

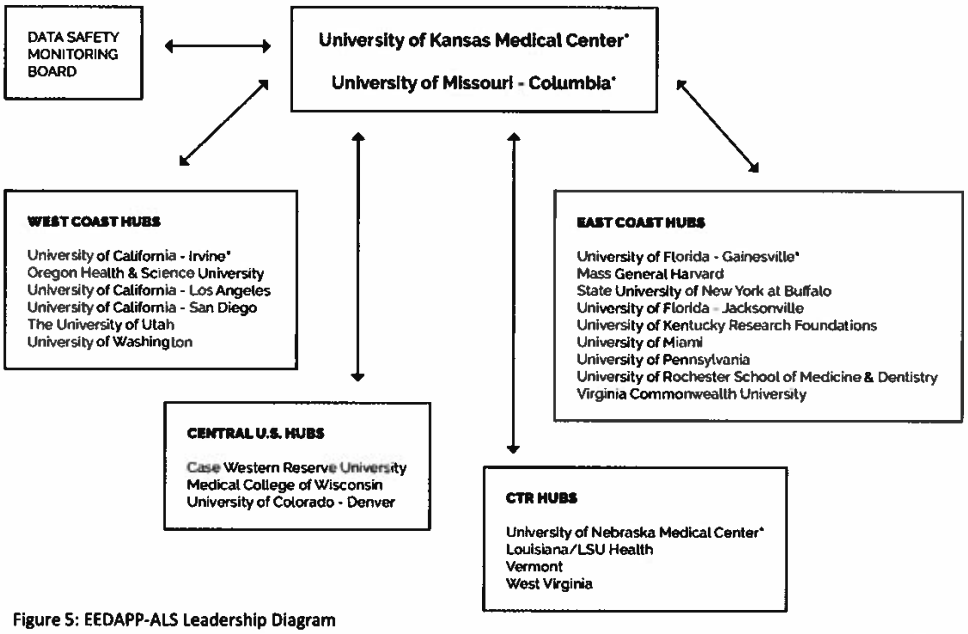

Figure 5: EEDAPP-ALS Leadership Diagram

* lead site

The proposal went through a rigorous consultation through the Johns Hopkins University (JHU)-Tufts TIC and Vanderbilt RIC of the TIN network, including a 2-day live meeting at the JHU-Tufts TIC Design Lab held in April 2019. Dr. Barohn and his team (Drs Govindarajan, Karanevich, Statland, and Ms Herbelin) were invited by the TIN to present their EE2 concept and proposal. Representatives from industry, payers, NIH, FDA and a number of clinical trial experts participated and provided useful advice and recommendations. The research team made significant revisions to their protocol resulting in the current proposal. We obtained advice from experts in the EE2 design field. We will leverage the TIN's design studio experience in conducting a first of its kind EE2 study in a rare disease. After the design studio event, we applied for an initial TIN consultation which occurred over several calls. We then asked for a comprehensive consultation which was granted (see letters of support).

Our industry partner, Catalyst Pharmaceuticals, was also essential in the development of this proposal. Stanley Iyadurai, Vice President of Clinical Affairs at Catalyst Pharmaceuticals, played a vital role in this collaboration by supporting our proposal and assisting us in the development of the specific aims, trial

design, and study medication dose limits and titration schedules.

Our comprehensive framework for patient, caregiver and family collaboration This study is responsive to the input received from patients and families over the course of ongoing patient engagement at KUMC. Figure 6 displays the operating model of engagement that guides the activities to ensure patient- and family/caregiver-centeredness for ALS research. Each engagement element depicted informs the other, and each makes a unique contribution. The model is a visual tool that ensures investigators fully use the unique contributions of non-academic team members. It also helps address organizational and representational issues for decisions at all levels for the design and execution phases of the study. To maintain engagement throughout this study, our Patient and Family Advisory Council (PFAC) will be reconfigured to include participants from all of the collaborating sites. Our track record for maintaining an active group using only phone and video connections (vs. in person meetings) is strong, and using an online communication platform (i.e., Zoom) lets the group build trust and familiarity with one another and with the research team as the study progresses. The PFAC is facilitated by a patient engagement expert, Kim Kimminau, PhD, who ensures the group stays focused on the research challenges and progress of the study over time.

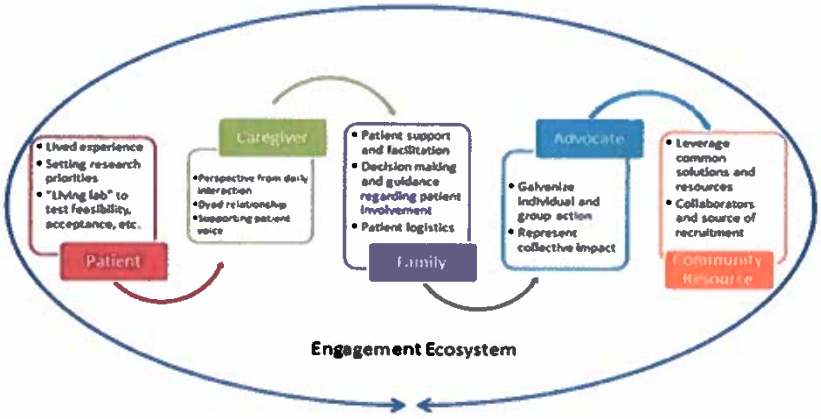

Figure 6: ALS Engagement Ecosystem

The innovative trial design for this project stemmed from ongoing dialogue with patients, families and the industry given the desperate need for more treatments options for ALS. While edaravone has shown to slow the progression, it is expensive, has a cumbersome infusion protocol, and is not widely used.[14] Riluzole has shown to prolong survival by three months without any significant effect on function. Data from two sources show that there is a high variability in the use of these medications.[2] A report was ran in March 2019 in the Mid-America ALS Chapter's Patient Reported Database which showed that out of 515 total patients, 74 patients (14%) are on riluzole alone, 66 (13%) are on edaravone alone, 124 (24%) are on both, and 251 (49%) are on neither.[3]

The Greater Plains Collaborative, PCORNet is based at the University of Kansas Medical Center and has 11 partner sites. We queried the electronic medical records of 10 sites (Medical College of Wisconsin, Marshfield Clinic, University of Utah, University of Nebraska Medical Center, University of Kansas Medical Center, University of Iowa, University of Texas Southwestern Medical Center, University of Indiana, University of Missouri, and University of Texas Health Sciences Center at San Antonio) and found that out of 2160 active ALS patients, 998 are on riluzole alone (46%), 11 on edaravone alone (5.2%), 146 on both (6.7%). The 11th site was a pediatric site. The reasons for this wide variability in use of two FDA approved drugs remains unclear. Using this information, we convened a patient and patient/caregiver dyad focus group. Two key findings from this helped shape the approach for this study. First, patients shared enthusiastic support for a new drug study targeting a novel mechanism of action. Second, patients and caregivers were passionate about ensuring the study would be available to as many patients as possible—a topic discussed at length. They understood opening inclusion criteria produces broader patient participation and potentially generalizability but at the same time might reduce the efficacy of the trial. Thus, having a trial design that can allow a heterogenous group of patients to participate without compromising the efficacy was an ideal solution and responsive to their priorities.

Innovation:
The key innovations for Aim 1 are: 1) exploring the EE2 model in a rare disease like ALS, a first of its kind trial in ALS and any rare disease; 2) building an EE2 trial experienced CTSA/CTR network which can be

used for other rare diseases and non-rare diseases. Aside from being the first randomized trial of 3,4-DAPP in ALS, this trial allows studying the effects of 3,4-DAPP in a homogenous patient population similar to what was used in other phase 3 studies and led to FDA approval in those drugs. The use of an efficacy and effectiveness too (EE2) trial design will ensure that 3,4-DAPP will also be tested under conditions relevant to usual clinical care.

Efficacy trials, typically designed to gain regulatory marketing approval, evaluate drugs in optimally selected patients under advantageous conditions. Effectiveness trials, designed to evaluate use in usual practice, assesses treatments among more typical patients in real-world conditions. However, this risks that the data collected on the narrower more homogenous group of patients will not be realized when implemented in real-world care. The innovative "efficacy and effectiveness too (EE2) trials," which simultaneously satisfy the requirements of both efficacy and effectiveness trials, would be used for the first time in a rare disease condition. Thereby, this trial's design addresses the problem that most new treatments are tested in highly selected samples that are not representative of how it would be used in widespread practice. Thus, this trial will include the broader group of patients with ALS who wouldn't qualify for the efficacy cohort because they don't meet certain inclusion criteria.

An EE2 trial is an ideal innovation for the CTSA and IDeA CTR consortium to embark on as it is a novel and unique trial design concept. At this time, the design has not been widely adopted in any disease area. Our exploration to take on these types of projects has met with some hesitancy and reluctance from potential funders. One NIH Institute Director, when approached on whether that Institute would be open to funding an EE2 trial, responded "We like to fund one trial at a time". Clearly, there is some equipoise regarding EE2 trials. Our contention is that the NCATS Innovation Awards RFA is the ideal mechanism to fund the early attempts at innovative EE2 trial and that this example is of particular interest as it involves a rare disease. We are able to perform this innovative Phase 3 trial in a CTSA/CTR consortium with NCATS funding because we are targeting a rare disease.

Translation:
Applying new innovative trial design in the conduct of clinical trials in rare diseases has the potential to speed the translation of trial results into practice by appealing to a larger group of patients with limited options for participating in clinical trials, and therefore encouraging faster enrollment. Patients and families with ALS are desperate for new therapies to be translated quickly from research trials. Since 3,4-DAPP is FDA approved already for another disease, if we can show efficacy in ALS, the drug can quickly become available to ALS patients.

Statistical considerations:
As described in the paper by Selker et al [1], an EE2 trial is designed to test the primary efficacy hypothesis/es in the efficacy cohort according to a plan prespecified in the protocol and statistical analysis plan. The results of these pre-specified analyses will determine the success of the study and are used for regulatory decision. The effectiveness cohort may have prespecified statistically powered endpoints or may be considered exploratory. The effectiveness cohort will also be the main population used for safety analyses.

Recruitment:
The study is a collaboration of 20 CTSA and 4 IDeA-CTR ALS centers that care for more than 5000 patients with ALS. The University of Kansas Medical Center will work with sites to establish recruitment strategies that will work for each local setting. Each site investigator will submit a recruitment plan and agree to screen every eligible participant referred to or seen at the site. The University of Kansas Medical Center will review recruitment performance metrics, and screening logs will explicitly identify the key criteria for enrollment. In addition, trial metrics reports from the University of Kansas Medical Center will be inspected regularly to look for trends and abnormalities within the data. The reports will include: monthly screened, consented, and enrolled participants including a ratio of hospital/registry statistics vs. number screened. Most solutions to poor recruitment performance are local and depend on the efforts of motivated, capable personnel who understand the protocol and have adequate resources to recruit participants into the trial. Richard Barohn, Raghav Govindarajan, and staff will maintain close working relationships with site investigators and coordinators to understand local problems and help ensure site

investigators quickly implement local solutions. This will be carried by having monthly site investigator and study coordinator calls. Scheduled contact with the study Patient and Family Advisory Council (PFAC) will ensure connectivity and relevance of patient and family input to the PI and scientific leads on the study.

Data Management:
Data Management will be overseen by the Department of Biostatistics and Data Science Department. For this study, we will be using the VELOS/CRIS database system that is a 21 CFR Part 11 Compliance database. Data Management will ensure site database training, will produce site level metrics on data quality and queries, and will create reports for the Data Safety Monitoring Board (DSMB) and for EE2 randomization in Aim 2.

Barriers:
Rolling out a new trial design such EE2 across multiple CTSAs and CTRs will be challenging as many investigators are not familiar with this design and IRBs will be scrutinizing the protocol closely. However, we will be leveraging TIN experience of designing and conducting EE2 trials in this study, particularly the expertise of Drs Cohen and Selker. Recruitment difficulties also may be challenging in this rare disease, but our combined networks, covering ~5000 ALS patients, can be used to disseminate study information.

Defining Success:
We will demonstrate the ultimate clinical success of this project if we: 1) demonstrate the feasibility of doing EE2 trial in a rare disease like ALS 2) meet our enrollment and study completion timeline 3) build a CTSA/CTR network that can do EE2 trial in rare diseases. This will be discussed in our Aim 2 section below.

We will disseminate the results of this study using our CTSA and IDeA infrastructure, patient engagement networks, and relationships with advocacy groups. If we are able to successfully complete the trial it will provide a blue print for EE2 trial for other rare diseases.

Aim 2:
We will determine if 3,4-DAPP can alter the course of the disease in ALS patients. In this aim, we will assess the efficacy of 3,4-DAPP by measuring changes in the slope of ALSFRS-R in a well-defined progressing cohort of ALS as previously defined in the edavarone study (Aim 2a). We hypothesize that 3,4-DAPP will slow down the progression of ALS by 30% as measured by the slope of the ALSFRS-R at the end of 6 months in this well -defined narrow cohort. The dose of 3,4-DAPP will be 80mg/day or the highest tolerated dose up to that level (Aim 2a). Simultaneously, we will recruit ALS patients with a more heterogenous disease status to more likely reflect a general ALS population and determine effectiveness (Aim 2B). The aim 2B is to determine if there are trends when looking at a more heterogenous population that suggest 3,4-DAPP may have a benefit (Aim 2b). We will also measure secondary outcome measures in both populations: survival, the slope of decline of forced vital capacity (FVC), the change in an ALS specific quality of life measure (ALSAQ-40) and a patient-reported ALS outcome measure, PADL ALS (Aim 2c). We will use our Patient and Family Advisory Council (PFAC) to inform and interpret the patient outcomes associated with this aim.

Rationale:
Neuromuscular Junction Pathology in ALS: The exact mechanism of ALS is unknown. The prevailing theory is that ALS is a dying forward phenomenon, in which primary damage occurs in the motor neurons and then extends in an anterograde fashion. Alternatively, multiple animal studies (such as SOD1 mice, drosophila and zebra fish ALS models) have demonstrated a distal axonopathy in which motor neuron degeneration starts at the nerve endings and progresses toward the cell bodies in a dying back manner leading to muscle denervation.[15-18] Clinical and electrophysiologic correlates of muscle fatiguability in ALS patients also suggest an element of neuromuscular junction (NMJ) transmission dysfunction.[19-20] Several studies of muscle biopsies from ALS patients suggest muscle denervation develops prior to significant motor neuron loss indicating early NMJ involvement.[19-20] In SOD1 mice, there is loss of laminin β2 which is believed to produce the dying back phenomenon. In SOD1 mice, the loss of an interaction between laminin β2 and the P/Q type voltage gated calcium channel (VGCC) causes NMJ denervation. This is because the interaction between laminin β2 and P/Q type VGCC anchors this channel at presynaptic terminals and organizes NMJ presynaptic active zones, the synaptic

vehicle release sites. Decreased levels of laminin β2 and P/Q type VGCC at ALS NMJs cause a decreased number of active zones.[21]

NMJ denervation in SOD1 mice:
ALS patients show decreased active zone size in spinal cord synapses.[22-23] Chronic inhibition of laminin β2 causes decreased number of active zones and NMJ denervation in wild type mice. Therefore, the loss of laminin β2 can cause NMJ denervation in SOD1 mice. Exercise as an intervention for ALS has been performed in SOD1 mice and ALS patients. Exercise recovers laminin β2 levels at NMJs and ameliorates NMJ denervation in SOD1 mice and rats. When SOD1 mice are crossed with transgenic mice expressing laminin β2 in muscle, transgenic expression of laminin β2 without exercise ameliorated NMJ denervation in SOD1 mice. Thus, laminin β2 ameliorates dying back neuropathy in ALS can improve the NMJ structure and function.[21]

Why could 3,4-DAPP benefit patients with ALS?
The mechanism of action of 3,4-DAPP is at the presynaptic terminal (at the voltage gated potassium channel) of the NMJ to enhance function by producing an increase in the release of acetylcholine vesicles.[24] This drug was recently approved by the FDA for the treatment of the Lambert-Eaton myasthenia syndrome, a disorder of the presynaptic terminal in which antibodies are directed against the P/Q voltage gated calcium channel.[25] 3,4-DAPP may improve the function at the NMJ in ALS patients the same way exercise does.[26] Benefit of exercise for ALS patients is an increase in laminin β2. We think this is a *druggable phenomena* and that 3,4-DAPP may produce this. There have been several small clinical studies of 3,4-DAPP in ALS. Aisen **et al.** demonstrated that 3,4-DAPP was well tolerated in all ALS patients, but limited by gastrointestinal side effects.[27-28] They also found a statistically significant improvement in Functional Independence Measure and speech assessment scores in addition to providing data on the pharmacokinetic properties of 3,4-DAPP in ALS patients. The standard outcome of ALS clinical trial namely ALSFR-R was **not** measured in this study.[27-28] Bertorini et al. in a double-blind, crossover design of 17 ALS patients, demonstrated that 3,4-DAPP was well tolerated with only four subjects reporting tingling of lips and fingers during the active drug period.[29] The subjective scores for fatigue and weakness showed a mild improvement after 4 weeks on DAP compared with placebo. A significant benefit of **3,4-DAPP** was also demonstrated in the timed verbal scores. The study was underpowered to demonstrate a measurable change in ALSFRS-R.[29]

We believe we have sufficient justification with the current information to move directly to a Phase 3/4 EE2 trial. The justification is as follows: 1) **3,4-DAPP** has been FDA approved for another severe neuromuscular disorder and have been shown to be safe and efficacious and **there is extensive clinical experience with this drug even prior to FDA approval as an off-label use. There is also strong pre-clinical and clinical evidence of neuromuscular junction pathology in ALS** 2) there have been three prior small phase 2 ALS studies with 3,4-DAPP as noted above; 3) patients and families and the ALS community are anxious to show that another drug (in addition to riluzole and edaravone) can slow the progression of ALS. Repeating another phase 2 trial is an unneeded delay; 4) Industry (Catalyst Pharmaceuticals) is very supportive and interested in the current phase 3/4 EE2 trial. They may use this data to go to the FDA to obtain a labeling indication for ALS if the study is positive.

Collaboration:
TIN, TIC, and RIC collaborations as well as the PFAC were previously described. Using a national infrastructure of 20 CTSA sites and 4 IDeA CTR sites, we will enroll ALS participants in a prospective 6-month placebo-controlled trial. All sites have ALS specialty clinics sponsored by MDA or ALSA, and experience with ALS clinical trials, being affiliated with WALS and NEALS. ALS patients seen in these clinics represent the full spectrum of disease, both sexes, all races/ethnicity, urban and rural dwelling, and diverse socioeconomic status. To ensure all eligible patients have a chance to participate, we will also reach out to patients directly using national registries, which include the advocacy organizations.

Innovation:
The key innovations for Aim 2 are: 1) exploring a novel mechanism of action for ALS at the neuromuscular junction in a large trial 2) conducting a drug trial with new inclusion criteria for ALS that was put forth in edaravone study and has not been reproduced in any other clinical trial 3) exploring the correlation between

patient reported PADL-ALS with ALSFRS-R in a real world clinical trial, with input and augmented interpretation of findings by patients and caregivers.

Translation:
Methodological issues for conducting the first of its kind EE2 study in a rare disease was discussed in Aim 1. Here we discuss implementation of the EE2 study design with 3,4-DAPP through a multi-center, double blind, prospective placebo controlled 6-month trial. We will enroll patients to both efficacy component and effectiveness component simultaneously. If positive, the result of this study will have enormous implications for ALS patients and their families.

Trial design: This will be a multi-center, double blind, prospective placebo controlled 9-month trial. Patients will be randomized to medication vs. placebo in a 1:1 ratio stratified by cohort (efficacy and effectiveness) and edaravone (yes/no). We will enroll patients to both efficacy component and effectiveness component simultaneously. Participants will be seen in clinic every 3 months to coincide with their standard of care visits and participants are allowed to be on the two FDA approved disease modifying medications (riluzole and edaravone). The drug will be provided in 20 mg tablets that is scored. Patients will start at 1 tablet 4 times a day for 1 week (total of 40 mg week). They will increase the dose to 1 ½ tablet (15 mg) four times a day for 1 week (total of 60 mg week). The last dose will be ramped up to 20 mg four times a day of the active drug or placebo (for a total of 80 mg). Following completion of the blinded portion of the study, all interested participates will have an opportunity to participate in an open label extension study (for patients in both efficacy and effectiveness components) for at least 6 months which will provide more longitudinal data of 3,4-DAPP in the ALS population and will allow all ALS patients who consented to participate in the study to have access to the active research drug. A full description of the trial design is located in the HUMAN SUBJECTS section of the grant.

Patient characteristics: 200 study participants will be enrolled into the efficacy component and 100 study participants will be enrolled into the effectiveness component.

Inclusion criteria:
Efficacy Cohort (Specific Aim 2a)
18 years of age who meet the diagnosis of "definite" or "probable" ALS according to the El Escorial revised Airlie House diagnostic criteria, forced vital capacity (%FVC) of at least 80% or more, duration of disease from the first symptom (any ALS symptom) within two years or less, scores of at least 2 points on all 12 items of ALSFRS-R bilaterally, change in revised ALS functional rating scale (ALSFRS-R) score during a 12-week observation period of –1 to –4 points. These are a slight deviation from the pivotal labelling indication trial for edaravone, that we dropped the Japanese ALS rating system as a criterion.

Effectiveness Cohort (Specific Aim 2b)
18 years of age who meet the diagnosis of "definite" or "probable" or "lab supported" ALS according to the El Escorial revised Airlie House diagnostic criteria, forced vital capacity (%FVC) of at least 70% or more, duration of disease from the first symptom (any ALS symptom) within three years or less, subjects who initially attempted to get into the efficacy phase, but failed the lead-in drop of the ALSFRS-R over the 12 -week period.

Exclusion criteria:
Hypersensitivity to any component of this medication, history of past or current seizures, history of asthma, evidence of prolonged QT syndrome. There is no absolute upper limit of normal for the QTc interval, family history of prolonged QTc syndrome, history of unexplained syncope, seizures or cardiac arrest.

Recruitment:
See the recruitment plan in Aim 1 and Human Subjects section. A search of local CTSA electronic health records identified >5000 ALS patients covered by the 24 CTSA sites and 4 IDeA CTR sites chosen for this study. We will leverage our relationships with advocacy organizations,

Interventions: While neuromuscular pathology has been implicated in ALS, they have not systematically been explored in a large multicenter trial. 3, 4-DAP acts at the presynaptic terminal (at the voltage gated potassium channel) of the NMJ to enhance function by producing an increase in the release of acetylcholine vesicles. This drug was recently approved by the FDA for the treatment of the Lambert-Eaton myasthenia syndrome, a disorder of the presynaptic terminal in which antibodies are directed against the P/Q voltage gated calcium channel. 3,4-DAPP may improve the function at the NMJ in ALS patients the same way exercise does.

Primary outcome:
We hypothesize that 3,4-DAPP will slow down the progression of ALS by 30% as measured by the slope of the ALSFRS-R at the end of 6 months in the efficacy cohort. The primary outcome of this study is the slope of decline in ALSFRS-R a validated patient reported 12-item survey that measures impairment of limb, bulbar and respiratory functions. The scale is measured as a part of routine clinical care across centers in the study. The slope of decline of each arm will be compared at baseline at randomization, 3 months and at the end of 6 months. The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) is a validated questionnaire-based scale that assesses the ability of ALS patients to perform physical tasks across four main domains: gross motor activity, fine motor activity, respiratory function, and nutrition. The scale has been designed to be a clinical rating instrument that could be readily administered for monitoring the progression of patients in routine clinical practice as well as serve as an outcome measure in clinical trials. The ALSFRS-R is composed of 12 questions regarding aspects of daily functioning, and the answers given on a 5-point scale (0-4). The spheres measured are: 1) speech, 2) salivation, 3) swallowing, 4) handwriting, 5) cutting and handling utensils (with two subtypes depending on gastrostomy status), 6) dressing and hygiene, 7) turning in bed and adjusting bed clothes), 8) walking, 9) climbing stairs, 10) dyspnea, 11) orthopnea, and 12) respiratory insufficiency. ALSFRS-R is a strong predictor of survival, declining with disease progression at a rate that is quite consistent across clinical trials- 0.92 units per month with a relatively small variance (standard error of 0.08). Further, values of Cronbach's alpha for ALSFRS-R were greater than 0.67 for all individual ratings and the association between the ALSFRS-R and the Sickness Impact Profile (SIP), a well-accepted quality of life measurement, was strong, with Spearman coefficient of r= -0.71.[30]

Secondary Outcomes (Specific Aim 2c):
The secondary measures include assessing the survival, the slope of decline of forced vital capacity, the change in an ALS specific quality of life measure (ALSAQ-40) and a patient reported ALS outcome measure, PADL ALS. Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 is a disease-specific measure, designed specifically to assess health related quality of life. The content of the measure was designed on the basis of patient self-report. The instrument contains 40 questions that measure five areas of health state: physical mobility, activities of daily living and independence; eating and drinking; communication; and emotional functioning.[31] The questionnaire addresses experiences of importance to individuals with ALS in such diverse areas as fear of falling when walking, difficulties cutting and eating food, participating in conversations, feelings of isolation, social embarrassment, as well as measuring feelings of fear and hopelessness about the future, that are all quite distinctively associated with it. Dimension scores are coded on a scale from 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure). Cronbach's alpha for ALSAQ-40 exceeded 0.9 for all individual ratings and the ALSAQ-40 total score to item correlation ranged from 0.61 to 0.92 (Spearman's r, $P<0.001$). PADL-ALS is a patient-centric revision of the ALSFRS designed specifically to conduct large pragmatic trials in ALS using the EMR patient-portal which has added questions about pseudobulbar affect, pain, and faith.[32]

Statistical analysis:
Power and Sample Size: Sample size was derived assuming a t-test with equal variance across treatment arms. We expect patients who don't receive any treatment to progress at roughly -1.25 ALSFRS-R per month, and that those on edaravone will decrease at 70% of this rate, with a standard deviation of 5 (as was seen in the 6-month edaravone pivotal phase 3 trial). We further assume that 3/4 DAP will slow progression by an additional 30%, and that the common standard deviation between baseline and 12 months will stay roughly 5. Assuming 45% of patients in the efficacy cohort will be on edaravone, using a weighted average to obtain the average six-month decline in the placebo arm (-6.5 ALSFRS-R) and the treatment arm (-4.55 ALSFRS-R), and estimate the six-month standard deviation of 5, which results in needing N = 210 patients per treatment group with 80% power at alpha = 0.05 via a two-sided test.

Reporting: Categorical measurements will be summarized by raw number observed and percent. Continuous measurements will be summarized by mean, median, standard deviation, minimum and maximum. For efficacy measurements (including coefficients associated with statistical modelling), 95% confidence intervals will be provided for the mean.

Primary Analysis: The null hypothesis that in the efficacy cohort there is no difference in change of six-month slope in the ALSFRS-R, from baseline, between treatment groups. The alternative is that the change of six-month slope in the ALSFRS-R, from baseline, is smaller in the treatment group compared to the placebo group.

The difference in change of six-month slope in the ALSFRS-R, from baseline, between treatment groups will be evaluated via a linear mixed effects model. Time, treatment group, and edaravone use will be included as fixed effects, and time and intercept will be included as random effects. An unstructured covariance structure will be utilized. In the event of convergence issues, a first-order autoregressive covariance structure will be utilized instead.

The null hypothesis will be rejected if the coefficient associated with treatment group (the indicator of being treated 3,4-DAPP) is statistically significantly greater than 0 with a type I error rate of 0.05.
Secondary Analyses: Survival from baseline will be analyzed using Kaplan-Meier across treatment arms. Analysis of the six-month slope in change of forced vital capacity (FVC) from baseline will be performed in the same fashion as that of the primary analysis. Six-month change in ALSAQ-40 from baseline will be evaluated using ANCOVA, with treatment group and edaravone use included as covariates.

Missing data: Observed cases only will be used, with no imputation.

Sensitivity Analyses: If modelling assumptions are violated, all six-month slopes may instead be evaluated via a Wilcoxon Rank-Sum test which solely looks at the raw difference between the six-month endpoint or last-observed endpoint and the baseline value. Similarly, the Six-month change in ALSAQ-40 from baseline may also be evaluated via Wilcoxon Rank-Sum test.

Safety monitoring and Safety analysis:
Drug Safety: All drugs used in this study are FDA-approved and have considerable safety data available for the use in humans. Possible drug interactions for this study would include the study medications and existing standard of care medications, which includes riluzole, and edaravone. Drug interactions were reviewed with the pharmaceutical company and no major interactions were noted. The study doses chosen are within the FDA labeling dose ranges for both drugs (the FDA safety labels for each drug are available at drugs@FDA.gov).

For this study we propose real-time safety monitoring which will include AE reporting monthly during the run-in phase, then weekly as the dose is ramped up and then monthly. Participants safety will be monitored by our investigators and coordinators, Medical Safety Monitor and by our DSMB. The Medical Safety Monitor (MSM) and DSMB will receive periodic safety reports of all adverse events including serious adverse events (SAEs) if necessary. All clinical safety endpoints and SAEs will be summarized by AE code in terms of frequency of the event, number of subjects having the event, severity, and relatedness to the study treatment.

Partnership:
This study is a partnership among the ALS research teams, and the patients and caregivers who have had, and will have, an active role in study design, conduct, and dissemination of results and industry. We are partnering with Catalyst Pharmaceuticals to provide the drug and placebo and allowing us to cross file on their IND for 3,4-DAPP. We will continue to use a Patient and Family Advisory Council during the conduct of the study to help give feedback on recruitment, retention, results interpretation and dissemination; and we will collaborate with the advocacy organization (MDA, ALSA) to help with recruitment and study results dissemination.

Barriers:

Rolling out a new trial design such EE2 across multiple CTSAs and IDeA CTRs will be challenging. However, we will be leveraging TIN experience of designing and conducting EE2 trials in this study. **The inclusion criteria for the efficacy cohort has never been tested in a clinical trial outside Japanese clinical trial. Patients fulfilling that inclusion criteria might be hard to recruit but our combined networks, covering** ~5000 ALS patients, can be used to disseminate study information. The MDA and ALSA and Catalyst Pharmaceuticals will assist us in getting the word out about the study to patients and families. **The absence of good biomarkers to monitor treatment response and disease progression has plagued ALS clinical trials. In particular to this study the lack of suitable biomarkers for monitoring neuromuscular junction pathology might prevent us from measuring treatment responders and non-responders. This is a known barrier in all ALS clinical trials and ALSFRS-R continues to be the universally accepted biomarker of treatment response.**

Defining Success:
We will demonstrate the ultimate clinical success of this project if we: 1) are able to show a slowing down of ALSFRS-R slope by 30% in the efficacy component; 2) to determine if there are trends of efficacy (either with primary end point or secondary end points) when looking at a more heterogenous population which provides data for generalizability which traditional trial designs lack; 3) demonstrate correlation between patient reported ALSFRS-R(PADL-ALS) with ALSFRS-R in a real world clinical trial. We will disseminate the results of this study using our CTSA and CTR infrastructure, patient engagement networks, and relationships with advocacy groups. If the drugs tested prove efficacious, it will have an immediate impact on patients with ALS and their family members and will become only the second drug to have a disease modifying effect on ALS. If the trial is positive, our partner, Catalyst Pharmaceuticals, may elect to file with the FDA for labeling indication for 3,4-DAPP for ALS.

SUMMARY STATEMENT

PROGRAM CONTACT:
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(Privileged Communication)

Release Date: **04/25/2020**
Revised Date:

Application Number: **1 U01 TR003420-01**

Principal Investigators (Listed Alphabetically):
BAROHN, RICHARD J. (Contact)
GOVINDARAJAN, RANGASWAMY

Applicant Organization: UNIVERSITY OF KANSAS MEDICAL CENTER

Review Group: **ZTR1 CI-4 (01)**
National Center for Advancing Translational Sciences Special Emphasis Panel
CTSA Collaborative Innovation Awards Review Meeting

Meeting Date: **02/20/2020**
Council: **MAY 2020**
Requested Start: **07/01/2020**

RFA/PA: **PAR19-099**
PCC: **1CCIA12**

Project Title: **EE2: 3,4-Diaminopyridine Phosphate for ALS - The EEDAPP-ALS Trial**

SRG Action: **++**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: 48-At time of award, restrictions will apply
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Age: 3A-No children included, scientifically acceptable

Project Year	Direct Costs Requested
1	749,957
2	749,288
3	749,977
4	749,898
TOTAL	2,999,120

++NOTE TO APPLICANT: Members of the Scientific Review Group (SRG) were asked to identify those applications with the highest scientific merit, generally the top half. Written comments, criterion scores, and preliminary impact scores were submitted by the assigned reviewers prior to the SRG meeting. At the meeting, the more meritorious applications were discussed and given final impact scores; by concurrence of the full SRG, the remaining applications, including this application, were not discussed or scored. The reviewers' comments (largely unedited by NIH staff) and criterion scores for this application are provided below. Because applications deemed by the SRG to have the highest scientific merit generally are considered for funding first, it is highly unlikely that an application with an ND recommendation will be funded. Each applicant should read the written critiques carefully and, if there are questions about the review or future options for the project, discuss them with the Program Contact listed above.

ADMINISTRATIVE NOTE
1U01TR003420-01 Barohn, Richard
ADMINISTRATIVE NOTE – RESOURCE SHARING
PROTECTION OF HUMAN SUBJECTS UNACCEPTABLE

DESCRIPTION (provided by applicant): The overall goal of this application is to perform an innovative Efficacy Effectiveness – Tool trial design (EE2) in Amyotrophic Lateral Sclerosis (ALS) in which we can simultaneously enroll a homogeneous population to determine efficacy and a wider population to determine effectiveness in a broader population. ALS is a rare, relentlessly progressive and fatal neurodegenerative disease affecting cortical and spinal motor neurons. The exact mechanism of ALS is unknown. This clinical trial will study the efficacy and effectiveness of 3,4-Diaminopyridine Phosphate (3,4-DAPP) in patients with ALS. The mechanism of action of 3,4-DAPP is at the presynaptic terminal of the neuromuscular junction (NMJ) to enhance function by producing an increase in the release of acetylcholine vesicles. This drug was recently approved by the FDA for the treatment of the Lambert -Eaton myasthenic syndrome and may improve the function at the NMJ in ALS patients the same way exercise does. This proposal would be the first time an EE2 trial is done in a rare disease and will include 20 CTSA sites and 4 IDeA State CTR sites dispersed across the United States. There are five sites (Kansas, Missouri, Nebraska, California-Irvine, and Florida-Gainesville) that
are designated as lead sites for the study. The specific aims for this study are as follows: 1. Perform an EE2 study in ALS at 20 CTSA sites and 4 IDeA CTR sites and simultaneously enroll a cohort to determine efficacy and a more heterogenous cohort which combined with the efficacy cohort will determine effectiveness in a broader population. This will serve as a blueprint for the CTSA consortium to perform EE2 studies on rare diseases. 2. Determine if 3,4-DAPP can alter the course of the disease in ALS patients. 2a. Assess the efficacy of 3,4-DAPP by measuring changes in the slope of ALSFRS-R in a well-defined progressing cohort of ALS as previously defined in the edavarone study. We hypothesize that 3,4-DAPP will slow down the progression of ALS by 30% as measured by the slope of the ALSFRS-R at the end of 6 months in this well-defined narrow cohort. The dose of 3,4-DAPP will be 80mg/day or the highest tolerated dose up to that level. 2b. Simultaneously recruit ALS patients with a more heterogenous entry criteria to more likely reflect a general ALS population and determine effectiveness. The aim is to determine if there are trends when looking at a more heterogenous population that suggest 3,4-DAPP may have a benefit 2c. Measure secondary outcome measures in both populations: survival, the slope of decline of FVC, the change in an ALS specific quality of life measure (ALSAQ-40) and a patient reported ALS outcome measure, PADL ALS. At the conclusion of the study, there will be an open-label extension study which will allow all ALS patients who consented to participate in the study to have access to the active research drug. This will be funded by a different mechanism through a partnership with Catalyst Pharmaceuticals.

PUBLIC HEALTH RELEVANCE (provided by applicant): We will test an innovative trial design in amyotrophic lateral sclerosis (ALS), a rare, relentlessly progressive, fatal disease, by conducting a clinical trial, EE2: 3,4-Diaminopyridine Phosphate for ALS - The EEDAPP-ALS Trial to determine 3,4-Diaminopyridine Phosphate versus placebo benefits patients with ALS by slowing down disease progression. In addition to performing a Phase III efficacy study

in ALS with narrow inclusion criteria, we will simultaneously enroll a more heterogenous ALS group to determine effectiveness in a more generalizable population. 20 CTSA and 4 IDeA State CTR sites dispersed throughout the USA will be leveraged for this unique proposal.

CRITIQUES

Critique 1
Significance: 6
Investigator(s): 3
Innovation: 4
1 U01 TR003420-01 3 ZTR1 CI-4 (01)
BAROHN, R
Approach: 6
Environment: 3

Overall Impact: This is an interesting application in terms of a new trial design, which seems to
address the issue of whether a drug that "works" in a restricted group of patients will also work in a larger, more generalized population. However, the data supporting the testing of this drug, 3,4-Diaminopyridine Phosphate (DAPP), are quite weak. Though there are data arguing for a primary pathology at the neuromuscular junction (NMJ) in Amyotrophic Lateral Sclerosis (ALS), the rationale for the use of this particular drug is not encouraging. Two previous small trials of 3,4-DAPP did not show any significant positive effect, and the underlying science provided by the Principal Investigator (PI), Richard Barohn, M.D., regarding laminin beta 2 is unreferenced other than a single abstract that can be found as a seminar title at Queensland University, Australia. Other than the selection of the drug to be used in the trial, there are also problems with the statistical arguments and inconsistencies with the power analyses. In summary, the overall impact is low.

Significance
Strengths
- This is a novel approach to a clinical trial in ALS that may be informative for future trials in ALS and other rare disorders.

Weaknesses
- The proposed hypothesis is not well supported by preliminary data, preclinical studies, or the literature.
- The expected outcome, given previous experience with this drug, will not lead to significant improvement in the lives of ALS patients.
- The argument that the success of edaravone makes a good target for efficacy for an ALS drug places a very low bar on the definition of success for patients.

Investigator(s)
Strengths
- The Contact Principal Investigator (PI), Richard Barohn, M.D., is a leader in the field of neuromuscular disease and clinical trials. His administrative experience will certainly be a positive for this project.

• The roles of other consortia participants are those of a typical multicenter clinical trial group, and the skillsets involved are likely adequate.

Weaknesses

• The Multiple PI (MPI), Raghav Govindarajan, M.D., is much less experienced, has few publications and no track record for this level of leadership in such a large consortium.

Innovation

Strengths

• The Efficacy Effectiveness-Too (EE2) design is certainly innovative, as it has not previously been used in ALS or other neurodegenerative diseases.

Weaknesses

• The outcome measures are standard; no innovative outcomes specific to the proposed mechanism of action of the drug are presented.

• The description of the statistical basis for the EE2 design is unclear.

Approach

Strengths

• A strength is the use of the CTSA hubs and established ALS clinical sites to form an integrated consortium that can work together to provide the numbers of patients necessary to support a clinical trial of a rare disease with very restrictive entry criteria.

Weaknesses

• The choice of 3,4-DAPP for this EE2 trial is weak, due to a lack of preclinical data supporting this drug in ALS and the previous negative (but clearly small) trials of 3,4-DAPP in ALS.

• The EE2 design, as described, seems a bit counterintuitive. One would expect that if the drug works in the less restrictive trial population (effectiveness cohort), then it will necessarily work in the more restrictive cohort (efficacy), unless one believes that these represent different disease mechanisms.

• From a power analysis perspective, typically the number of patients needed for a cohort with less restrictive inclusion criteria would be more than that for a cohort with more restrictive entry criteria. However, the trial design states 200 participants in efficacy and 100 in effectiveness (page 228). This seems backwards.

• The section on power and sample size states that N=210 patients/treatment group. This is not consistent with the previous statement of 300 total participants and makes the statistical plan suspect.

• The patients are being separated on and off edaravone, but they are not being stratified for riluzole. Given that any clinical effect of 3,4-DAPP is unlikely to be better than either of these two approved drugs, multiple groups would need to be compared: placebo only, DAPP only, DAPP + riluzole, DAPP + edaravone, DAPP + both, and possibly even placebo plus each of the other drugs. This is not addressed in the statistical discussion.

• The doses and dose escalation schemes are confusing. 3,4-DAPP will be provided in 20 mg tablets and started at one tablet 4x/day for one week. This is 80 mg not “40mg week” (page 228). Similarly, the escalated doses of one and a half tablets 4x/day is 120 mg, not 80 mg. This may be a typographical error, repeated in the statistics section.

• Scant data are presented demonstrating that the numbers of patients fitting the entry criteria will be recruited and that those numbers might range from 200 to >500. Stating that there are 5,000 ALS patients in their region is fine, but it does not provide data on how many patients are at each center, what each center's population looks like (early vs. late disease, slow vs. fast disease) and what the other centers have done previously in ALS clinical trials. This is not a trivial problem, since the majority of patients will not meet the entry criteria and many patients will choose not to participate.

Environment

Strengths

• The CTSA hub infrastructure at the University of Kansas Medical Center (UKMC) is impressive.

• The collaborative network is in place.

Weaknesses

• More data are needed to assure that the adequate numbers of patients will be recruited.

Study Timeline

Strengths

• A reasonable clinical trial timeline is included.

Weaknesses

• Assurance is needed that enough patients with appropriate inclusion criteria can be recruited.

Protections for Human Subjects: No issues.

Data and Safety Monitoring Plan: Adequate.

Inclusion of Women, Minorities, and Individuals Across the Lifespan:

• Sex/Gender: Distribution justified scientifically.

• Race/Ethnicity: Distribution justified scientifically.

• For NIH-Defined Phase III trials, Plans for valid design and analysis: Scientifically acceptable.

• Inclusion/Exclusion Based on Age: Distribution justified scientifically.

Adequate.

Vertebrate Animals: [No reviewer comments].

Biohazards: [No reviewer comments].

Select Agents: [No reviewer comments].

Resource Sharing Plans: Adequate.

Authentication of Key Biological and/or Chemical Resources: [No reviewer comments].

Budget and Period of Support Recommend as Requested.

Critique 2
Significance: 4
Investigator(s): 2
Innovation: 3
Approach: 5
Environment: 2

Overall Impact: ALS is a fatal disease for which limited disease-modifying therapies are presently available. This proposed national consortium will test the medication 3,4-DAPP as a potential diseaseslowing agent, employing the EE2 trial design. The medication 3,4-DAPP, through its action at the presynapsis of the NMJ, is approved for use in Lambert-Eaton myasthenic syndrome, which is physiologically centered at the presynaptic terminal of the NMJ; it has been tested in limited ways in ALS over the past several decades. The EE2 design will use highly constrained criteria for enrollment into the efficacy arm, emulating what was performed for the Japanese edaravone trial, while also including research participants representing the broader real world spectrum of ALS in the effectiveness arm of the study. The Contact PI at KUMC is a well-recognized leader of multisite trials, the various consortium sites chosen are appropriate, and the lead site at KUMC has a strong track record in directing multicenter clinical trials in neuromuscular disease. Strengths include the clear need for disease-modifying therapies in this fatal disease; the first such EE2 clinical trial design in a rare disease population; appropriately chosen primary and secondary outcome measurements; and the fact that there will be eventual access to the drug for all participants in the clinical trial. Weaknesses include the limited preclinical data to support 3,4-DAPP as potentially beneficial in ALS; concern that while the efficacy component of the study is effectively powered, the effectiveness component may not be; and the absence of a well-delineated plan for how the University of Florida and the University of California Irvine will lead the East and West coast sites, respectively, for this study.

Significance
Strengths

- ALS is a fatal disease for which very limited disease-modifying therapies are presently available, thus there is a clear need for disease-modifying therapies.
- Success in the field demands multi-center studies like this and the idea of an EE2 trial via a multi-center consortium has merit.

Weaknesses

- While the trial medication 3,4-DAPP is approved for use in Lambert-Eaton myasthenic syndrome, which is pathophysiological centered at a site of action of the medicine, the presynaptic terminal of the NMJ, the scientific premise for its use in ALS is not nearly as well developed or justified.

Investigator(s)
Strengths

- Dr. Barohn is an established clinician scientist with a strong track record in clinical research and human clinical trials in neuromuscular disease.

- As Director of the CTSA hub at the University of Kansas, the PI is well-positioned to coordinate activities that are related to this.
- The University of Kansas team has a solid track record working with multisite consortia in ALS.
- MPI of the Kansas Missouri leadership team is Dr. Govindarajan, a neuromuscular specialist who recently was promoted to Associate Professor at the University of Missouri.
- Co-investigator Theodora Cohen, Ph.D., at Tufts University, who will provide statistical input to the EE2 study proposed, has appropriate experience in clinical trial design, analysis and reporting.
- The leadership plan makes it clear that the Contact PI will be mentoring the MPI in the conduct of large multicenter clinical trials.
- Participating sites have over 5,000 ALS patients, which should readily fill enrollment needs.

Weaknesses

- The 0.6 calendar months requested effort for Dr. Govindarajan may not be sufficient for the work required since the application states on p. 157 that the MPI "will provide oversight of the entire project and development implementation of all policies, procedures and processes."
- There is some concern that little is specifically described about both the ALS clinical efforts and clinical research at the University of Missouri, which is a lead institute in this application.
- Details are missing regarding how the University of Florida and UC-Irvine sites will be the lead sites for the East and West Coast institutions, respectively.

Innovation

Strengths

- This is the first such EE2 clinical trial design in a rare disease population. It is likely appropriate that an EE2 design be used in rare neurodegenerative diseases that have significant clinical heterogeneity, like ALS.

Weaknesses

- [No reviewer comments].

Approach

Strengths

- Incorporation of the Great Plains Institution for Clinical Translational Research spanning the North Central states is an encouraging step in collaboration across CTSA hubs and similar IDeA entities.
- The preparatory work to explore the Greater Plains collaborative electronic medical records (EMRs) to assess use of riluzole and edaravone by current ALS patients gives some confidence for the collaborative nature of the study.
- The EE2 design is appealing. While efficacy may be established for a narrow subset of ALS patients in the efficacy study, there may be supportive data for the broader ALS community through the combined study. In that sense, the impact of a positive result would be much higher.
- Appropriately chosen primary and secondary outcome measurements.

• KUMC will serve as the single IRB of record for the study; KUMC has a track record serving as a single IRB for collaborative initiatives like this one.
• Data safety and monitoring plan is adequate and includes remote monitoring through the KUMC quality assurance department.
• Data safety monitoring board will meet three times yearly with appropriate inclusion of a member of the ALS community.
• The University of Florida and the University of California Irvine will serve as regional leads for the east and west coast respectively, and the University of Nebraska will serve as lead regionally for the IDeA Centers.
• Primary endpoint will be measured using, appropriately, a linear mixed effects model to estimate the slope of the ALS Functional Rating Scale-Revised (ALSFRS-R).
• The drug, 3,4-DAPP is available. It is manufactured by Catalyst pharmaceuticals (letter indicates their support) and the IND application was submitted last fall.
• The Patients and Family Advisory Council will be kept informed at least every four months of the status of the study and as needed when pertinent information becomes available.
• Study results will be disseminated in the ALS Association and Muscular Dystrophy Association newsletters and posted on the web to broadcast to a wider community.
• Appropriate letters are in place from the various collaborating sites and coinvestigators to document involvement.
• Eventual access to the drug for all participants in clinical trial.
• Timeline is feasible.

Weaknesses

• Quite limited preclinical/human subject data to support 3,4-DAPP as potentially beneficial in ALS.
• Concern that while the efficacy component of the study is effectively powered, the effectiveness component may not be, thereby undercutting the goal of the EE2 trial.
• Absence of a well-delineated plan for how the University of Florida and UC-Irvine will lead the east and west coast sites, respectively, raises some concern for connectedness across sites.
• The following sentence in exclusion criteria on p. 228 is difficult to discern: “There is no absolute upper limit of normal for the QTC interval, family history of prolonged QTC syndrome, history of unexplained syncope, seizures or cardiac arrest.”

Environment

Strengths

• The neuromuscular research clinical trials unit at KUMC is highly ranked and has strong track record of success.
• The various collaborating sites are all established in clinical research neuromuscular diseases including ALS. Most participate in existing regional or national ALS consortia and are expected to be able to easily recruit participants for the EE2 design study.
• Appropriate use of the CTSA network and builds on existing strengths within the network.

Weaknesses

• Details are not explicitly provided regarding how the University of Florida and UC-Irvine sites will be the lead sites for the east and west coast institutions.

Study Timeline: Adequate description of timeline.

Protections for Human Subjects: Acceptable.

Data and Safety Monitoring Plan: Acceptable.

Inclusion of Women, Minorities, and Individuals Across the Lifespan:

- Sex/Gender: Distribution justified scientifically.
- Race/Ethnicity: Distribution justified scientifically.
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Scientifically acceptable.
- Inclusion/Exclusion Based on Age: Distribution justified scientifically.

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Vertebrate Animals: Not Applicable (No Vertebrate Animals).

Biohazards: Not Applicable (No Biohazards).

Select Agents: [No reviewer comments].

Resource Sharing Plans: Acceptable.

Authentication of Key Biological and/or Chemical Resources: [No reviewer comments].

Budget and Period of Support: [No reviewer comments].

Critique 3
Significance: 2
Investigator(s): 4
Innovation: 5
Approach: 5
Environment: 3

Overall Impact: This is a comprehensive collaborative effort spanning 20 CTSA hubs and four IDeA centers to rapidly study a novel treatment for ALS. The clinical trial is a major undertaking and having leadership distributed across multiple CTSA hubs with regional leadership roles, particularly given the limited experience collaborating on such a complex trial, the likelihood of success is questioned. The use of placebo and risks with the study design do not appear objectively discussed. The sample size appears like it is larger than required had a design effect been applied accounting for repeated measures. Overall, the treatment approach to ALS is considered significant; this approach to get to that point is not as well received.

Significance

Strengths

- ALS is a critical, neurodegenerative disease that warrants rapid, structured testing of new treatments.
- Leverages some unique CTSA hubs with existing infrastructure.

Weaknesses

- The EE2 design appears premature for this treatment in this population. There appears to be limited pilot data and the likelihood of success is uncertain.

Investigator(s)

Strengths

- The senior leadership and the co-investigators are well trained and bring broad expertise to the trial.
- The idea of regional hubs helps logistics of the study, but more details would have enhanced this plan.

Weaknesses

- Beyond PI-level investigators, it is unclear if all of the sites will have the resources needed to manage the study.
- Investigator effort in the consortium is too low to have viable engagement.

Innovation

Strengths

- None noted.

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Weaknesses

- The whole application is built around the EE2 approach. As the investigators likely are aware, this is a bit of a polarizing approach in that some will love it and others will be more guarded. The inclusion and exclusion study does not define an effectiveness subgroup; this appears as a treatment failure. Given some subjects could be on placebo, this is a significant design flaw.

Approach

Strengths

- Potential for diverse, representative enrollment into the ALS study. Accelerates the testing of a novel indication for an existing compound in ALS.
- Data management plans using the VELOS database; central IRB plans are in place. The approach is described very briefly. More details are required, but the basic framework should meet the study's needs.

Weaknesses

- The application is unbalanced in technical details and promoting the EE2 study design.
- The EE2 study design is not likely the panacea being suggested. There are ethical considerations about interactions with standard of care, withholding standard of care, what level of evidence is needed before expanding use, etc. that warrant more attention. While there needs to be an acceleration of treatments and testing in rare diseases, there are also important methodological and resource considerations that warrant more

attention. The study design still closely resembles a post hoc subgroup analysis of any clinical trial. Planned or unplanned, it is still basically the same approach.
• On page 228 the effectiveness cohort is defined and importantly it is not an effectiveness cohort. This would almost appear as non-responders vs. broad inclusion criteria.
• It is unclear if there is any dissemination product available for this study. This is a large simple trial. This is very well established. Pragmatic trials are also well established. What specific attributes of the CTSA hubs are being leveraged for this award?
• The methods speak of obtaining the full Trial Innovation Network (TIN) support for this application. It is unclear what this means objectively. A summary of some of the discussions and how this protocol design has been chosen relative to alternatives would have increased the scientific rigor of the application.
• A more objective recruitment feasibility assessment is expected. This would have included justification for the individual sites selected as well as discussion of incident cases. It is expected that moving treated patients to this trial may not be a certainty; the calculations do not address this concern.
• Preliminary data for Specific Aim 2 are non-quantitative and lacking in figures and tables. Important questions about dosing are unresolved. It is not clear why the "extensive off label use" data is not presented directly in the application. If this data is so extensive, does this raise concerns for the need of the EE2 study design?
• Sample size calculations do not appear to account for the longitudinal data being available. The repeated measures and comparisons of slopes over time could have increased the "effective sample size" and reduced the overall number of participants studied. Given the cost and complexity of this first randomized trial in a rare disease, optimization of the sample size is expected.
• The analysis plan specifies a mixed model, which would be a strength. The investigators state, however, that the primary test is the treatment parameter. There would still be a treatment by time interaction terms that would be needed to be tested to summarize the differential slope relative to placebo. Likewise, model-based contrasts comparing the final timepoints estimated means is expected.

Environment

Strengths

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• The CTSA consortium, builds on an existing Central IRB and data management center expertise.

Weaknesses

• There is limited collaboration of these sites to date. The geographic spread will make the trial more difficult to coordinate due to time zone and travel demands.

Study Timeline

Strengths

• There is an attempt to mine I2B2 records across many of the sites. There is some indication of a prevalent pool of participants.

Weaknesses

• The recruitment still feels ambitious and hard to manage across the sites. Each site is expected to enroll, on average, about three participants per year. This does not seem to be enough volume to maintain much visibility and consistency of the site investigative teams.
• A more detailed accrual feasibility section that accounts for a study enrollment fraction (say 1/10 of all newly diagnosed patients) may have provided a more objective assessment of accrual feasibility.

Protections for Human Subjects: Unacceptable.
Overall, the human subject plan is repetitive and unfocused. There is not enough discussion on the consent process and consideration for starting standard of care in newly diagnosed patients.
The use of pure placebo is not justified. More information on the risks of placebo in a degenerative disease should have been addressed in the protocol. It is unclear if this protocol, as written, would pass the IRB process.

Data and Safety Monitoring Plan: Acceptable.
Basic DSMB structured in the application. More details on the charter, particularly around early monitoring of the study and evaluation of the "effectiveness" arm is warranted going forward.

Inclusion of Women, Minorities, and Individuals Across the Lifespan:
• Sex/Gender: Distribution justified scientifically.
• Race/Ethnicity: Distribution justified scientifically.
• For NIH-Defined Phase III trials, Plans for valid design and analysis: Scientifically acceptable.
• Inclusion/Exclusion Based on Age: Distribution justified scientifically.
Statistical plan is basic, but coverage of key elements is generally acceptable. More details are included in the trial protocol, which is welcomed, but this extended the length of the application considerably.
Vertebrate Animals: Not Applicable (No Vertebrate Animals).
Biohazards: Not Applicable (No Biohazards).
Select Agents: Not Applicable (No Select Agents).
Resource Sharing Plans: Unacceptable.
The primary concern is the general premise of disseminating the EE2 study model. This is viewed as a
weak alignment to the PAR.
Authentication of Key Biological and/or Chemical Resources: Not Applicable
(No Relevant Resources).
Budget and Period of Support: Recommend as Requested.
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THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:
PROTECTION OF HUMAN SUBJECTS: UNACCEPTABLE
Overall, the human subject plan is repetitive and unfocused. There is not enough discussion on the consent process and consideration for starting standard of care in newly diagnosed patients.
The use of pure placebo is not justified. More information on the risks of placebo in a

degenerative disease should have been addressed in the protocol. It is unclear if this protocol, as written, would pass the IRB process.

ADMINISTRATIVE NOTE – Resource Sharing Plans: UNACCEPTABLE.
The primary concern is the general premise of disseminating the EE2 study model. This is viewed as a weak alignment to the PAR.
Footnotes for 1 U01 TR003420-01; PI Name: Barohn, Richard J.
NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.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.

MEETING ROSTER
The roster for this review meeting is displayed as an aggregated roster that includes reviewers from multiple TR Special Emphasis Panels Meetings
for the 2020/05 council round.
This roster for TR is available at:
http://public.era.nih.gov/pubroster/Reports?DOCTYPE=SEP&DESFORMAT=PDF&AGENDA_SEQ_NUM_P=387632