NCATS Proposal — ALS Patients Demand
Richard J. Barohn MD, Jeffrey M. Statland MD,
University of Kansas Medical Center
Kansas City, KS

Keywords: ALS, Drug cocktails, Bayesian adaptive design

RFA/PRA: PAR15-172

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

Date of Review: May 10, 2016

Grant was: Not funded

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

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

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

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

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

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

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

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

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

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

We believed the study could create a model for multi-
center research studies seeking to more efficiently maxi-
mize network-level collaborations to study any rare disease.

This was an ambitious proposal that did get scored (41)
but this was not in a fundable range.
At the time these U01 grants allowed for direct costs of nearly 1 million dollars a year for 5 years.

We had to apply via an X02 preproposal mechanism to apply for the large study. The X02 was submitted in the summer of 2015 and was accepted in the fall of 2015. We submitted the full proposal in early 2016.

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

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

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

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

They really liked the Bayesian adaptive design.

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

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