NCATS Proposal — ALS Patients Demand

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

They really liked the Bayesian adaptive design.

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

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