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De-risking Psychiatric Drug Development: The NIMH's Fast Fail Program, a Novel Precompetitive Model

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Abstract

The lack of success of psychiatric drug research and development has increased attention on the use of precompetitive models of early stage clinical drug development, whereby foundations, companies and academic researchers led by NIH, work together to advance a pipeline of potential novel therapeutics. This commentary presents an example of such an approach through which the National Institute of Mental Health contracted a network of academic researchers to work with other stakeholders to investigate AZD7325, a drug targeting the GABA-A α2/α3 receptor subtype, in young adult subjects with autism spectrum disorder using an experimental medicine approach. Instead of relying on traditional clinical measures, electroencephalography was used to evaluate pharmacodynamic responses and was established as the primary outcome measure, in order to objectively identify dose ranges that can modulate central nervous system activity in the absence of significant side effects. Many trial considerations and "lessons learned" were identified through the process of setting up and performing the trial. These considerations are important to present to the research community more broadly, to emphasize what processes and resources are needed to integrate pharmacodynamics measures into multisite trials in research areas which have traditionally relied on clinical rating scales alone. The goal is to design and implement studies that will provide sufficient objective data of brain effects to make go/no-go decisions to clinical efficacy studies in which one is confident that the underlying mechanistic hypothesis of drug action is being tested. We here provide a real life example of what is required to execute this strategy.

In the last several years, psychiatric drug development has been plagued by multiple failures of novel mechanisms to show efficacy in late stage clinical trials in depression, psychosis,

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Study drug provided by AstraZeneca.

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anxiety, Fragile X, and autism spectrum disorder (ASD). Underlying this worrying trend, it has become clear that positive studies in early clinical development have failed to translate to positive outcomes in pivotal efficacy studies [1]. In response to this emergent situation, several reports have been published from academic and industry researchers calling for a redesign of early stage (Phase Ia through Phase IIa) clinical trials to better inform crucial strategic decisions in the development process [2–10]. The principal goal is to increase the success rate of late Phase II and III trials leading to compound approvals, given current estimates that approximately only 35% of Phase II and 65–70% of Phase III trials generate new approvals, with the high number of failures adding to the overall ultimate cost of successful drug development. The increased risk of failure in Central Nervous System (CNS) drug development coupled with improved success rates in other therapeutic areas has led to a dramatic re-focusing of pharma investment [1, 11].

How can early phase trials be improved? Most agree that psychiatric drug development has suffered from several heretofore inadequately solved scientific challenges: clinical heterogeneity, limited knowledge of sufficient dosing to effect, high placebo response rates, and lack of objective measures of response. Some techniques have already proven useful in early CNS drug development including determining the maximally tolerated dose in patients during Phase I trials to establish the dose range in subsequent efficacy studies [12]. More recently, when radiolabeled ligands for a targeted site are available, measures such as receptor occupancy (RO) utilizing positron emission tomography (PET) can be incorporated into early studies in order to establish the dose for clinical trials [13, 14]. But for many compounds PET ligands are not available and maximal tolerated dose approaches do not necessarily assure that a target is adequately engaged in the brain to test the compound's mechanism of action in question. To meet the challenges, a model of early phase clinical trial design has been proposed: the "experimental medicine" approach, where known biological information about the CNS disorder and the mechanism of the investigational drug is considered in stratifying subjects, identifying which subjects would most benefit from the agent, and, selecting robust pharmacodynamic and intermediate outcome readouts (endpoints that are proximal to the ultimate clinical or behavioral change, e.g. blood pressure for cardiovascular disease). In such trial designs, it is expected that trial endpoints establish whether the investigational drug demonstrates a dose dependent CNS effect by incorporating biomarkers. Ultimately, trial results should yield go/no go decisions for the target under study. The intent is that for trials that meet "go" criteria, future efficacy trials for that indication would be more precisely informed of the dose ranges necessary to yield desired CNS effects. Compounds unable to generate sufficient target engagement would be dropped, reducing the number of expensive, later stage failures. If such enhancements, successes, and savings in CNS drug development can be achieved, interest in CNS programs could be restored; supporting industry's pursuit of well-powered Phase II studies and eventually registration trials, i.e. mitigating the risk of CNS trials. Additionally, the establishment of networks and partnerships, between government, industry and non profits, could share in the risk by contributing relevant expertise and resources to help re-stimulate the field and to help define an optimal trial design that might not be created when an organization works alone. Precompetitive public/private partnerships focused in the CNS space have successfully been developed in the US, with examples including the Foundation for NIH's Biomarkers

Consortium Neuroscience Steering Committee, the Psychiatric Genomics Consortium, the NIH-Industry New Therapeutic Uses Program, and the Innovative Medicines Initiative NewMeds Consortium, all which have been described in more detail in a previous review [15]. Networks developed to support early stage drug trials are simply another way to bring all relevant parties together to fill an existing gap, and potentially advance methodology and knowledge more rapidly. In this model, the government can take part in organizing the networks, providing funding, managing the trials and retaining all data to be shared with the public. Likewise, non profits can also provide funding, expertise in their patient populations, assist with advertising (patient lists), and provide input on feasibility of the trial design from a practical level.

Based on these experimental medicine concepts, the National Institute of Mental Health (NIMH) established a contract program in 2013 called “The Fast Fail Program” to support testing of novel, high quality investigational drugs in early stage trials, using new trial designs and enhancements, in a precompetitive collaboration with compounds provided by industry. Using this model, the government assumes some of the risk of early development and validation of novel approaches that ultimately will benefit the entire field. Additional values of this precompetitive model include the continued utilization/investigation of the experimental medicine strategy, and the possible identification of new endpoints, which can also benefit the field. “Fast Fail,” coined by Paul et. al. (2010) refers to the goal of reducing the number of investigational drugs advancing to late stages of development by only advancing ones with a high probability of success. These trial designs focus on achieving either “quick wins”, identifying safe, mechanistically effective compounds worthy of further testing, or “fast fails”, agents which lack desired target properties or safety. In fiscal year 2013, three contracts were awarded with each targeting different disorders, including: mood/anxiety disorders, psychosis and autism spectrum disorders.

The first trial to complete its active trial phase is supported under the Fast Fail Autism Spectrum Disorders (Fast-AS) contract, and the authors believe it provides an excellent illustration of the unique approach taken in performing early stage psychiatric drug trials through federal funding of academic research institutions. In this first completed trial, we encountered several issues leading to ” lessons learned” along the way that are important to share to help establish standards in NIMH supported academic clinical trials going forward.

Sponsors often are faced with difficult choices regarding compound selection, given multiple possible targets, various available agents, and other considerations. Due diligence was undertaken to select which investigational drugs to test in the Fast trials program. The NIMH established a subcommittee of the National Advisory Mental Health Council, with additional outside advisors and consultants from government, industry and academia, including those with drug development, clinical trial and regulatory expertise, to help rank drug targets of importance based on the ASD preclinical and clinical literature. This subcommittee worked with NIMH staff and the lead clinical trialist as well as the scientific team that was awarded the Fast-AS contract, on compound selection. The biological underpinnings of ASD are incompletely understood and no drugs have been approved for treating the core symptoms which could provide some framework for consideration of new agents. Some of the initial targets considered included: serotonin 5HT2A, γ-Aminobutyric acid-A (GABA-A),

histamine H3, and the nicotinic α4/β2 or α7 receptors, as well as the glycine transporter-1 (GlyT1) transporter. The subcommittee recommended the GABA-A receptor as a lead drug target for an agonist based on literature pointing to a GABAergic-glutamatergic mismatch in CNS function observed in both human and animal studies (ASD rodent models, post mortem tissue analysis, in vivo brain imaging), a concept that has continued to gain support [16–20]. The subcommittee felt the other targets could be considered in future ASD trials, as more relevant data emerges. They also felt a potential GABA deficiency in some forms of autism might be addressed through a selective GABA potentiator that is not effectively addressed using existing, non-selective benzodiazepines, due to side effects.

Once this drug target was identified, the subcommittee evaluated investigational drugs, identified through the *Pharmaprojects Pipeline* database and from the list of investigational drugs available through NIH's National Center for Advancing Translational Science (NCATS) New Therapeutic Uses Program https://ncats.nih.gov/ntu/assets/current, based on the safety, preclinical and clinical data provided by industry. One particular focus was to find a GABA-A compound with less sedation and reduced risk of cognition impairment, believed mediated via α1 subtype activation, than traditional benzodiazepines. The AstraZeneca GABA-A α2/α3 subtype selective positive modulator (AZD7325) was available through the NCATS repurposing program; importantly, critical legal agreements for making the drug available were already in place and drug supply more assured. These considerations, coupled with the lack of sedation seen with AZD7325, brought it to the top of the list. Another attractive aspect of this compound is that AstraZeneca had acquired considerable safety data in human volunteers and patients with Generalized Anxiety Disorder. Finally, they had demonstrated target engagement using PET RO as well as pharmacodynamic data using EEG, which provided a framework for incorporating this latter measure into the protocol. The Contract PI (Dr. McCracken, UCLA), in collaboration with the subcommittee, the other site investigators, NIMH and AstraZeneca scientists, designed the protocol, including the selection of biomarkers for the pharmacodynamic and intermediate outcomes, the clinical outcomes, and other early stage trial design aspects. The specific protocol design for this initial trial will be described in a subsequent paper of results; one unique feature highlighted here was the selection of EEG variables as the primary outcome metrics for the clinical trial, along with safety assessments.

After the general protocol design was identified, a central IRB agreement across the independent research sites was established. A central rating system for performing key clinical assessments with rapid feedback was also established to minimize rater variability. The sites designated for conducting the trial were all experienced sites for both academic ASD trials and industry-sponsored ASD trials, but not all of the trialists and their staff had experience with EEG data collection in industry-sponsored trials, and likewise, the EEG researchers generally were not experienced in industry-sponsored trials. Therefore, training and coordination across the various teams was crucial and within this set-up phase, significant time and effort went into establishing standardization of the EEG systems and biomarkers across sites. The lead trial site (UCLA) was instrumental in establishing the biomarker standardization procedures, monitoring of all sites' biomarker performance, the (blinded) processing and analysis of EEG data, and providing feedback quickly to help sites stay within the designated quality standards during set up and throughout the trial in near

real-time. All of these processes were essential and since now established, they should enable the start-up phases of subsequent trials that use EEG to be more streamlined.

A further enhancement that was explored in this first trial was to determine if EEG could be used as a stratification measure (enrichment strategy), in an attempt to define a biologically more homogenous subject sample, given the recognition that ASD is a very broad, heterogeneous group of disorders. A results paper will describe the EEG stratification composite that was identified and selected for use in the trial as an inclusion criterion for subjects with ASD, based on comparisons to data obtained in 38 control subjects (baseline data), used to define a “normal EEG baseline” composite compared to ASD baseline EEGs. The development of this stratification measure was a novel aspect of the trial design. More generally, this entailed an iterative team approach involving sequential modification of inclusion criteria, where the multiple parties involved provided input into the measures to include, and then reviewed and discussed the analyzed data before moving forward with subject randomizations. This model of iterative collaboration is not practically possible under traditional investigator initiated RO1 type grants.

Overall, the timeline for trial set up using this new NIMH trial model required approximately the same period as the trial itself. While the set-up was not short, the planning and partnership were essential to establish a collaborative, team-based approach to drug ranking and selection, trial design and assistance in monitoring to enable the trial itself to move in a more streamlined fashion compared to traditionally funded NIMH drug trials, and more consistent with aspects of industry run trials. Once the trial was launched, the NIMH staff were much more actively involved in interacting with sites to meet goals and identify potential issues early than has traditionally been the case in NIMH funded studies. This involved weekly clinical coordinator calls and meetings with the lead investigator and team, closer to the model of industry/contract research organization (CRO) run studies.

The trial length was one year in duration (44 randomized subjects) and within the first three months of the trial, we brought in an industry experienced project manager to help with site specific issues around recruitment, by evaluating internal staffing responsibilities and processes, potential competing trials at the institution, and the site’s use of advertising, and then provided action plans for improvement. NIMH initially set up the lead trial site as the study Investigational New Drug (IND) sponsor. However, NIMH has determined there is value in centralizing this role to take the regulatory burden off of the lead academic site; and therefore plans on being the sponsor moving forward. One of the additional values of the project management role will be to bring the industry sponsor (regulatory) experience in house. In addition, as NIMH further refines its role as a sponsor we will determine how best to provide resources to cover trial operations issues.

Industry does not rely solely on academic sites for their CNS trial data collection, but uses CROs as well. This first trial was important in that it demonstrated that a very small number of academic clinical trial sites (n=3) could successfully maintain a high standard of technical fidelity with EEG and apply consistent cross-site EEG biomarker standards established at the beginning of the trial. It was also essential to recruit subjects within a limited timeframe (the active trial was completed in one year) to minimize problems of drift and reduce the

need to recruit additional sites, a recognized disadvantage in clinical trial management. As far as we are aware, this is the first multisite psychiatric early stage trial (testing an investigational drug that is not approved for use in any indication) to use EEG as a stratification measure and as a primary outcome measure. It will be important for future trials to validate this and potentially other interesting stratification measures. Overall, we propose this Fast Fail type of model, including all of the components described here and in a future results paper, as providing important considerations for early stage psychiatric clinical trials.

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