Lost in Translation:
The Value of Psychiatric Clinical Trials

John C. Markowitz, MD,[a,b,*] and Barbara L. Milrod, MD[c]

What value do clinical research trials have in psychiatry? The US National Institutes of Health (NIH) define a clinical trial as "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."[1] Clinical trials long represented the height of psychiatric research, the defining tests of which of our treatments worked for particular diagnoses, how well they worked, how tolerable patients found them, and which interventions worked comparatively best for whom. Our current armamentarium of pharmacologic, somatic, and psychotherapeutic treatments derives from such trials comparing specific, well-defined, time-limited treatment interventions to control conditions or to one another. Comparative trials of active treatments yield crucial information about differential treatment effects, mediators, moderators, dropout rates, and optimal treatment populations.[2]

The National Institute of Mental Health (NIMH)

For the first 6 decades after its founding in 1949, the NIMH provided the world's great source of psychiatric clinical research funding, its budget roughly divided between pre-clinical and clinical studies.[3] Helping individuals suffering from mental illness was its principal charge.[3] Funded clinical trials included large and invaluable projects like the NIMH Treatment of Depression Collaborative Research Program, the first randomized trial to compare cognitive behavioral therapy, interpersonal psychotherapy, antidepressant medication, and pill placebo as treatments for major depressive disorder[4]; the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) algorithmic progression of trials for increasingly treatment-resistant depression[5]; and the Multicenter Panic Disorder Study comparing psychotherapy and pharmacotherapy.[6]

Abruptly and without precedent more than a dozen years ago, as if current treatments sufficed, NIMH changed policy, consigning the vast preponderance (~90%[6]) of its budget to neuroscience.[3,7–11] The chief engineer of this shift, former NIMH Director Thomas Insel, MD (tenure 2002–2015), recently conceded that neuroscience has yet to yield meaningful clinical advances, yet his advice to his successor, Joshua Gordon, MD, is to further "double down" on neuroscience.[12] This funding shift has devalued psychiatric clinical trials and the carefully crafted, crucial methods such trials require, largely extinguishing them and halting clinical progress.

Good treatments exist for psychotic, mood, anxiety, eating, and trauma-related disorders, but none are panaceas. Americans continue to suffer from psychiatric illness resistant to available proven treatments, with psychopathology rising in the context of the COVID-19 pandemic and other stressors.[13,14] We do not yet know which treatments work best for whom, and our environment is changing radically. We here renew our plea for reassessment of the narrow neuroscience NIMH agenda. Notably, no other NIH institute has drastically curtailed clinical research funding as NIMH has. Across the rest of medicine, clinical trials remain the scientific gold standard for evaluating treatment interventions.

Research Domain Criteria (RDoC),[15] the vague, poorly articulated[16] orthodoxy NIMH promulgated 13 years ago, rang the death knell of the traditional clinical trial in mental health. In substituting this new, untested, clinically distant (if not irrelevant) classification system for the admitted heterogeneity of more clinically useful *DSM* diagnoses,[17] the Institute shifted its research focus from helping people with mental illness to explicating translational neuroscience. RDoC explore associations between genes, neurotransmitters, neuroanatomical circuits, and ultimately—but often almost as afterthought—behavior. Its domains comprise phenomena like positive or negative valence, or arousal/regulatory systems, rather than psychiatric diagnoses of suffering people.

The RDoC system neither rescues nor addresses the suicidal teen hanging a noose from his ceiling. Indeed, much neuroscience research involves no humans, exploring animal brain analogs with sometimes dubious relation to human psychopathology. Although the NIMH website states that "RDoC is not meant to serve as a diagnostic guide, nor…

[a]Department of Psychiatry, Vagelos College of Physicians & Surgeons, Columbia University, New York, New York
[b]New York State Psychiatric Institute, New York, New York
[c]Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, New York, New York
*Corresponding author: John C. Markowitz, MD, Columbia University/New York State Psychiatric Institute, 1051 Riverside Dr, Unit #129, New York, NY 10032 (jcm42@cumc.columbia.edu).

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intended to replace current diagnostic systems,"[15] RDoC have replaced clinical diagnoses in their research funding. Henceforth, when NIMH has funded clinical research in humans, it has done so to test mechanistic concepts *rather than* clinical outcomes. Some NIMH grant mechanisms, eg, the R61/R33, seem almost engineered to minimize assessment of meaningful clinical outcomes.

Neuroscience matters, and will continue to evolve, but is not the only route to progress. It has not provided and may never provide practical routes to answering clinical questions. In turning away from treating psychopathology, RDoC may indeed be taking the wrong route to helping people. In contrast, clinical trials can test both treatments and patient brain mechanisms (eg, with neuroimaging). They can address the myriad important clinical situations that may lack translational neuroscience roots[3]—eg, complexities of parent-child relationships contributing to early onset mood and anxiety disorders. They can test treatments that can help suffering people, not just neural mechanisms.

In discouraging use of *DSM* diagnoses, RDoC create their own heterogeneity, partly explaining the lack of clinical utility of most RDoC-framed studies. Subjects with "negative affect," for example, may range from achieving clinical diagnostic thresholds to nearly asymptomatic, subclinical presentations. Developed to supplant imprecise *DSM* diagnoses, RDoC may in fact mix them, compounding heterogeneity. Diagnostic major depression and colloquial mild subjective "depression" may now coexist in subject samples, yielding results that may or may not address neuropathological mechanisms but in any event lack clinical generalizability and applicability. This approach thus sacrifices clinical utility to pursue abstract concepts.

The insular view that psychopathology research requires neuroscience ignores the manifest global medical importance of the environment. Clinical research has ground to a halt at the moment that psychopathology rates have risen dramatically[13] in the context of the COVID pandemic,[14] political polarization, the trauma of rising gun violence in the US, and global instability (eg, the Russo-Ukrainian war). One would think NIMH might fund studies comparing in-person treatment to telepsychiatry, an understudied, previously little-used treatment modality that the pandemic abruptly made ubiquitous.[18] Does teletherapy have advantages or disadvantages relative to in-person interventions? For which patients, with which disorders and ages? (Child teletherapy presents particular concerns.[19]) Although these questions have far-reaching public health implications, NIMH appears uninterested.

Research might address the problems of the hundred thousand Ukrainian immigrants arriving in the US with high rates of depression, PTSD, and other disorders and explore numerous other psychopathological treatment questions that may arise largely unrelated to one's genes,[3] including broader effects of systemic racism.[20,21] Do Black lives matter to NIMH? How to develop, test, and improve mental health interventions to target systematically oppressed people deserves research that addresses toxic cultural environments rather than, say, their neurosignatures or genetic epiphenomena.

The NIMH budget appears intentionally opaque. NIMH concedes that the NIH definition of clinical trials has led to classifying some basic experimental research under that rubric, even though basic science research is ordinarily considered to lack direct clinical import.[1] Despite budget opacity, E. Fuller Torrey, MD, has demonstrated the drastic decline in NIMH clinical trial funding for serious *DSM* disorders.[10,11] The NIMH funding descriptions obscure easy enumeration, limiting our certainty, but the National Cancer Institute and National Institute of Diabetes and Digestive and Kidney Diseases, cognizant that psychiatric comorbidities affect their primary targets, may each currently fund more clinical trials for psychiatric disorders like major depression than NIMH does. That this is even a possibility is scandalous.

The Patient-Centered Outcomes Research Institute (PCORI, https://www.pcori.org/) funds patient-focused comparative effectiveness research, but PCORI grant submissions require treatments of already demonstrated efficacy. If NIMH funds no clinical trials, there will be few innovative interventions for PCORI to test in mental health at a time of escalating mental health crisis. NIMH appears to have no plan for this.

Broader Mental Health Consequences

Beyond ignoring patient care, stifling clinical advancement, and impoverishing a rich area of intellectual endeavor, NIMH cuts in clinical grant support have profound educational consequences for mental health care trainees. Absent research support, it is nearly impossible for clinically focused junior faculty to sustain research careers. A decade without clinical grant funding is impairing academic departments, shifting young faculty members away from their clinical interests and promoting a clinically distant research faculty. The complex skills required to conduct scientifically rigorous, reproducible clinical trials risk being lost.

A further casualty might be the personnel capable of conducting clinical trials at academic centers. If academic faculty in psychiatry and psychology departments become primarily neuroscientists, these centers may have to opt out of clinical trials. In the past, academics have often served to ensure a measure of equipoise and counter bias in pharmaceutically sponsored trials, a balance that may be lost if such trials are simply farmed out to contract research organizations.

Beyond research itself, the NIMH funding shift affects clinical training. Who will train not only future clinical researchers but future clinicians? It will no longer be faculty invested in the subtleties and experienced in exploration of clinical care. Rising faculty are more focused on laboratories than patients. Psychiatry and psychology departments are noticing this dearth of clinically focused junior faculty, whose loss will have profound long-term effects on graduate training and thereby on the mental health care of patients for the next generation.

Clinical Critique

NIMH is not alone in disparaging clinical trials. Clinicians have worried that randomized controlled trials have overly restrictive inclusion and exclusion criteria and hence do not translate to the patients they see in their practices.[22] This perception partly explains the lengthy time lag[23] preceding dissemination and integration of meaningful clinical research discoveries into clinical practice.

The Well-Conducted Clinical Trial

Which research skills does this funding dearth threaten? Conducting good clinical trials is complex and labor intensive. To ensure data validity, studies must define patients by an operationalized diagnosis or other reliably reproducible clinical target determined by inclusion and exclusion criteria. Researchers provide, and patients give, informed consent for randomization and treatment. Consenting eligible patients are evaluated by independent evaluators, then assigned randomly to treatment and treated by trained adherent therapists. Raters blinded to treatment and trained to consensus scoring use standardized instruments to serially assess treatment benefits and side effects.

Psychopharmacologic adherence is measurable by pill counts or serum levels. Psychotherapy adherence requires therapists to follow a defined, manualized treatment (eg, cognitive behavioral therapy), with treatment-blinded adherence raters sampling randomly chosen taped treatment sessions to ensure treatment is delivered as intended. Trial design and conduct must ensure equipoise and avoid researcher and therapist bias.[24] This complex technology risks being lost through growing disuse: senior clinical researchers are aging, and junior faculty lack opportunity to master it.

Discussion

There is no alternative. Clinical trials are expensive, but lack of optimal treatments and differential therapeutics for many patients is more so, in both money and suffering. No other scientific mechanism rigorously tests clinical treatments to ascertain what works best for whom. Losing clinical trials strips psychiatry of an essential mechanism for testing innovative clinical observations, leaving it to rely on the tortuous path from laboratory to clinic. To abandon the randomized clinical trial turns time back a century, to the era of the interesting but unsubstantiated case report. It pushes clinicians to rely on theory—always dangerous, as it is often incomplete or wrong—in the absence of rigorous data. Some enterprising researchers have found wealthy donors to fund clinical projects, but in our experience these often study fringe therapies, research undertaken more on donor whim than clinical priority. The United States cannot afford to relegate its mental health treatment agenda to its plutocrats.

It is not too late to resume what, in retrospect, was a golden age of clinical advance in mental health. Some researchers have publicly objected to the current NIMH policy,[3,7–11,16] but complaints from clinical researchers sound self-serving and NIMH has ignored them. Too many academics, wary of offending NIMH, have ambivalently accommodated to the RDoC funding stream.

Congress founded NIMH to improve treatment of psychiatric illness,[3,11] and NIMH should be held accountable for having abandoned it. The field needs outcry from academic departments, professional organizations like the American Psychiatric Association, and patients and their families. The larger public may be unaware that NIMH now pursues only neuroscience: within the medical academy, our research and clinical colleagues in oncology, cardiology, and other fields react with disbelief when informed of the NIMH stance. NIMH might learn from the PCORI model, which involves patients, caretakers, and other stakeholders in formulating its research agenda. Psychiatric clinical outcome research is too valuable to lose. Allowing the current situation to persist harms patients and research both.

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