Editorial
Special Focus Issue: Pediatrics

CLINICAL INVESTIGATION

Trials and tribulations of conducting medication trials: pediatric bipolar disorder as prototype

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Keywords: adolescent • bipolar • child • imaging • intervention • medication • pediatric • pharmacotherapy • treatment • trial

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"We must be the change we wish to see in the world." – Mohandas Gandhi.

It is understood that clinical trials are conducted with great care and tenacity toward publishing evidence-based results. In that pursuit, enormous barriers have to be overcome by those who lead such investigations to completion. These obstacles are not documented as part of manuscripts, yet they are silently experienced by all clinical investigators. Therefore, in an attempt to start dialog and to find realistic solutions, I am taking the plunge to candidly address some of the inevitable dilemmas faced by child psychiatrists that conduct clinical trials. I refer to pediatric bipolar disorder (PBD) as an example as it is one of the more complicated disorders to treat. One has to be conducting trials as a front-line clinically trained investigator in order to grasp the intricacies of intervention research trials in their entirety. Any advancement in eliminating these tribulations requires a deeper understanding of the reviewers, investigators, readers and decision-makers that are involved in the pipeline of decision-making, design, scientific approval, funding, oversight, troubleshooting and conduct of clinical trials. Revealing the complexities of this topic will help bring science to an authentic platform rather than forcing unworkable solutions.

Hidden problems of clinical trials & what they entail

Medicating children without adequate evidence is an appropriate concern of both clinicians and the general community alike [1]. The quagmire of industry or federally funded studies all come with a common set of difficulties in this line of research, as detailed below.

Reality with prior exposure to psychotropic medications

In the case of industry-designed trials, pharmaceutical companies tend to design and fund research based on questions that they want answered. They tend to be multisite studies and need careful oversight of procedures, especially given the number of sites recruiting patients and the highly variable levels of experience across the teams [2]. In the case of federally funded study applications, there is often a competitive peer-review process that expects the best-case scenario to bring a paradigm shift in science. Investigators are often eager to meet the challenge to ask the best questions through a rigorous design and deliver the product. Furthermore, in the case of pharmacological functional neuroimaging studies of medication's effect on brain function, a subject's exposure to any psychotropic medications prior to the trial is considered an 'unclean sample', as the brain is already exposed and affected by medications while you are trying to study the impact of a single study drug. If prior exposure to medications is allowed, withdrawing any medications (even if they are not continuing to be useful) can be considered an endangerment to child subjects by reviewers. This is especially the case if the subject's withdrawal is carried out as an outpatient. Having them free of medication effects prior to the recruitment

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may mean that a child has to be off medication for five half lives on average for any given drug. This amount of time without adequate medication can be unacceptable for parents or impossible to manage, such as in the case of PBD patients with severe manic episodes. Retaining these patients for recruitment in a single site in sizeable numbers becomes incredibly difficult. The alternate choice of washout in an inpatient unit or clinical practice toward recruitment for a study prior to consent is hard to decipher. Even if the washout is undertaken by a nonprincipal investigator prior to the trial toward referral, it is deemed a 'non-random process' since it is not common to wash out medications instead of cross tapering them to an effective regime. It goes to say that the difficulties in recruiting medication-naïve, medicated or unmedicated patients will all have their set of difficulties that need to be negotiated by the principal investigator (PI). It often seems impossible to push for perfect solutions in science through these treacherous routes and unattainable expectations.

Institutional review board compliance

Research is very different from clinical care. This preceding sentence needs to be engraved in every researcher's mind. Researchers, at least in the field of PBD, are often excellent and intuitive clinicians. However, empathy and intuitive understanding have minimal value and can even obstruct the requirement to follow impeccable research protocol. More than a decade ago, I began these conversations with my mentors and colleagues. In a real-life clinical scenario, optimal help would involve an evidence-based algorithm to take care of severely ill patients [3]. In research studies, it is imperative that grants, institutional review board (IRB) applications and clinical documents in the lab all match line to line. Each step of the study's procedures must be documented in detail and attested with signatures in a careful sequence such that someone reading it will know exactly what has occurred from the minute a subject is screened and until the study is terminated. Researchers tend to pool several studies under one IRB application as an 'umbrella application', avoiding the need to add, delete or modify clinical measures, staff and intake criteria. Unexpected difficulties should be ironed out, as it is rare for a study's IRB application to remain the same from the start to the finish. Every time there is any alteration in the study design of what is promised to the funding source, it needs to be discussed by all those involved in the pipeline. On occasion, PIs assume autonomy in adding pilot studies under the IRB approval and expanding the scope, pushing the envelope to forward science toward the next iteration of great ideas. However, things may become rapidly complicated if these secondary intentions are misunderstood by the granting agencies of such extended efforts. Poor communication may lead to confusion between granting agencies, PIs, the IRB and even the US FDA [4]. Another common problem occurs when PIs lack external or internal resources like senior research managers or auditors to help them with the paperwork. An experienced and efficient senior lab manager can be of great service to manage strict rules in aligning the grant, pilot expansions or adjustments to the grant, IRB application, informed consents and assents. This point cannot be underestimated, as research assistants that often work for 2- to 3-year terms may not be ideal to attend to comprehensive oversight alongside PIs with long-term research tenure. Research assistants simply cannot offer a solid continuity, especially if there are multiple studies going on simultaneously. However, hiring such senior lab managers can be very difficult with the time-limited research funds and without the promise of job continuity for that individual. This is an essential component of the infrastructure. In the end, the PI takes the final responsibility for operating the approved protocol, corresponding IRB and progress reports to the funding sources. That said, it is customary for the trainees, postdoctoral fellows, junior faculty or co-investigators to share the data and write manuscripts based on raw data. That is when the scope of responsibility broadens to the team level. All authors share the credit and the responsibility based on their role. A great example is that followed by the *Journal of American Medical Association* where it is required to specify who is responsible for each of the parts, that is, study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtaining funding, administrative, technical, or material support and study supervision. I believe that this is an excellent model for us all to follow no matter where we submit our manuscript. This documentation affords the team of authors on each manuscript, a sense of responsibility and ownership without any misattributions at the outset.

Recruitment

Recruitment of any specific subcategory of PBD patients requires considerable clinical expertise. In reality, it is the interpretation of symptomatology that leads to accurate diagnosis, rather than the short-term training and inter-rater reliability attained by conducting semi-structured research diagnostic interviews. Inter-rater reliability is still indispensable, but it is also important to keep in mind that each patient is incredibly unique in symptoms, ages, family dynamics, cognitive abilities and personal communication skills. If an experienced clinician interviews and selects the right patients

to refer to the study, less experienced researchers are likely to avoid any false positives or false negatives during screening or at the time of conducting the semi-structured diagnostic interviews as nuances are common, especially in diagnosing PBD. A distinct barrier to recruitment from the families who can afford private psychiatrists is their preference to seek immediate and active treatment for their children. They prefer that their child does not face a random chance of receiving placebo or being restricted to a specific monotherapy through a research study. Most parents understand the complexity of illnesses such as PBD and recognize the limitation of monotherapy or an extended period without treatment [5].

Extensive pressures

There are a number of pressures on researchers as they face several dilemmas in their work. For one, there exists a high pressure on researchers in a multi-site or a single-site study to fulfill the need to recruit patients based on a promise to the funding source or to the lead PI. Researchers have to keep the infrastructure alive by sustaining the revenue to honor the obligations and recruit patients. This also applies for federally funded researchers, but it becomes even more complicated by other added obligations, such as developing junior investigators and faculty, participating in academic publishing and working on multiple grant submissions. That aside, referring clinicians or those signed up to help the PIs as clinician co-investigators are also heavily under pressure due to increased computerized paper work of their own clinical patients outside of research. There are competing priorities and tensions in this interdependency. In the end, it ultimately falls on PIs to recruit and keep the research machinery running. If you have to run a trial where the granting agency is a small foundation offered on the promise on the existent federal grant of yours as the PI or where you are the PI's senior mentor (with the assumed responsibility to support junior faculty with pooled resources), expenses and responsibilities tend to multiply. These tensions must be predicted ahead of time and one needs to be prepared to manage them and to consider whether or not it is worth the effort in the absence of a sustainable infrastructure from central administration.

Another unavoidable problem is the insurmountable pressure that investigators experience from the parents of patients with PBD, as a parent's love for their child cannot simply be overridden by an informed consent document. Parents push research clinicians to obtain treatment for coexisting or disruptive problems in PBD, such as attention-deficit hyperactivity disorder, hyper-arousal, aggression and sleep problems. Clinician co-investigators may then feel conflicted between empathizing with parental concerns and objectively maintaining research protocol. When these researchers succumb to parental pressures, they avoid referring patients into treatment-restrictive studies, hence creating a non-random recruitment process. In the end, it is incredibly important that we support our diminishing pool of physician–scientists through these demands, as they are particularly sensitized to them given the nature of their training [6]. In this case, ignorance is not bliss and physician–scientists must be educated proactively on the potential tribulations of research responsibilities during their research training. One critical thing I try to teach research trainees over the years is, "You are helping millions through the discoveries. Therefore, take the comfort that you are helping the children and their families through rigorous protocols. There is also a good chance that study participation will help affected children despite some rigidity posed by the research protocol versus clinical care."

From study design to delivery of the findings: aim for perfection, or is being good enough acceptable?

An ideal and sustainable solution for a successful career in clinical investigation requires the following, in addition to basic expertise:

- Core university infrastructure support in expenses and expertise. It is especially useful to create a position of a senior lab manager that can count on an attractive salary, so that there is certain continuity in file management [7];
- PI must assume optimal responsibilities without over-extending in academia;
- Good symbiosis with referring clinical agencies. This is a continuous process and your work is never done;
- Write grants that are feasible to conduct rather than those that are perfect but impossible;
- Have funding agencies understand what is clinically feasible during the peer review;
- Training in excellent clinical judgment during recruitment;
- Avoid training excessive numbers of student researchers at the expense of the physician–scientist's primary responsibilities;
- Balance excessive empathy in foregoing nuances of clinical care with strict adherence to the protocol. It is worth repeating and reminding the researchers to remember that they are helping millions through credible research discoveries;

- Prioritize patient safety and maintain impeccable documentation and maintain a recipe-like approach to IRB rules;
- Ensure that you have well-oiled university support in all the above efforts, including IRB, department chair and clinical co-investigators.

That said, clear and open communication with full transparency and trust is important to facilitate the long and complicated pipeline in running clinical trials. Often, PIs or investigators starting research underestimate its complexity. That ought to be acknowledged and discussed at every level of the pipeline. Researchers must be rewarded by utmost understanding for the service they embrace in delivering evidence to help millions. It is not good enough to simply say that they signed up for it and they must be able to fulfill it. The entire scientific and clinical community must work together to grasp the imperfections and find thoughtful solutions for these intricate problems. Then, it would be possible to deliver scientific discovery that goes beyond being simply 'good enough' and actually offers our patients the very best.

Acknowledgments

The author thanks her medical students and Mamatha Challa for her editorial help.

Financial & competing interests disclosure

M Pavuluri has been funded by Berger-Colbeth endowment, NARSAD Foundation, DANA Foundation, AFSP Foundation and served as scientific advisor for Otsuka Pharmaceuticals. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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