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Ethical challenges in global mental health clinical trials

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Mental health clinical trials, in which treatment as usual or waitlist condition can mean no treatment, raise important ethical concerns. Even if scientifically valid, such designs require substantial justification and efforts to minimise harm. The lag from research to clinical practice in global mental health trials further challenges the ethics of no-treatment control conditions.¹ Finding ethical ways to do robust mental health clinical trials in low-income and middle-income countries (LMICs) is essential to scale up evidence-based treatments adapted for use in low-resource settings, and to assess new treatment methods.

The first randomised psychotherapy clinical trial in Africa,² done during 2002, used a treatment as usual control condition to assess group interpersonal psychotherapy in Uganda. Group interpersonal psychotherapy is a time-limited intervention for depression that focuses on identifying and addressing the interpersonal problems most relevant to the current depression. Interviewees who reported current suicidality were referred to the study's clinical psychologist, a costly practice not feasible for scale up, whereas non-suicidal individuals in the severely affected control group effectively received no care for 6 months.³ All participants from the control and treatment villages could access any locally available services, such as accessing counselling provided by local HIV organisations, or speaking with friends, family, or church members. The study was groundbreaking: it was the first of its type to show that an evidence-based psychotherapy could be feasible, culturally adapted, and efficacious for treatment of depression in a LMIC. However, because of a lack of funding, the intervention was not made available in clinical practice in Uganda for more than 10 years (H Verdelli, Columbia University, personal communication).

The Council for International Organizations of Medical Sciences⁴ has developed several conditions under which placebo-controlled trials might be ethically justified. These can improve the ethical conduct of global mental health trials, in which enhanced treatment as usual is often the control condition. We believe that implementation science, collaborative

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partnerships, and capacity building can help to overcome ethical dilemmas by maximising the local relevance, feasibility, and scalability of interventions.

The Council requires an intervention to be responsive to the health needs or priorities of a country to prevent its testing without local relevance or feasibility for scale up.⁴ In global mental health, this requirement might preclude testing of expensive psychiatric medications or treatments that are reliant on highly trained mental health specialists. Ensuring that the intervention is responsive to the country's needs is best achieved through community-engaged research with key stakeholders, including service users who might benefit from the intervention.⁵ Involving local policy makers in all stages of research can increase the likelihood and feasibility of scale up.⁶ Global partnerships between researchers from high-income countries and LMICs that emphasise interdependency, bidirectional collaboration, and shared ownership are crucial for successful global mental health research trials.^{5,7}

Another requirement of the Council that an effective intervention is made available post-trial has received criticism for not clarifying the extent that an intervention can be made available, and for assuming other exploitations of the study population might not occur. The fair benefits framework⁸ suggests that research trials might include other types of benefits to the community that justify the risks, in addition to the availability of an intervention, such as improved health infrastructure. However, the subjective determination of fairness can be problematic owing to power imbalances between international researchers and local communities.⁹ Implementation science and community-partnered research can help to address these weaknesses. Hybrid effectiveness-implementation designs, in particular, can enhance the ethical reasonable availability mandate of an intervention,¹⁰ by examining both effectiveness and implementation outcomes of an intervention, and help global mental health researchers link research to clinical practice.¹⁰ Hybrid type 1 designs, for example, focus on effectiveness while gathering information on implementation. These designs allow researchers to identify clinical outcomes in a real world setting while also considering scale up. In LMICs, such designs require meaningful involvement of local partners, capacity building, and infrastructure development.⁵ Community-engaged research can help to address both fair benefits and reasonable availability criticisms by reducing power inequities, lessening risk of exploitation, and ensuring real benefits for local communities.

An additional challenge is that many global mental health trials are done in settings with few specialists, low mental health literacy, and much stigma. This challenge means that many research ethics committees might not have sufficient knowledge or awareness to assess the scientific necessity of a study properly (beyond approval), or the severity of risks apart from suicidality. In order for research ethics committees to ensure ethical practices, more training might be needed to enhance their capacity to assess the attendant risks and unique challenges of doing global mental health research in low-resource settings.

To address the global mental health treatment gap, researchers will need to continue grappling with doing ethical clinical research in low-resource settings. Thus, the next wave of global mental health research will require meaningful local partnerships with researchers, community advocates, and policy makers; a focus on capacity building; and plans to scale up effective interventions.

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