Suicidality, Depression, and the FDA:
Health Inequities and the Ethical Conduct of Research

Ana S. Iltis, PhD[a,*]; William V. McCall, MD, MS[b]; and Riyan Deria[c]

ABSTRACT

Objective: Persons with mental health disorders, including suicidality, are underrepresented in clinical trials, undermining the generalizability of results and possibly contributing to health inequities. This report (1) documents the exclusion of persons with suicidality in trials used to secure US Food and Drug Administration (FDA) approval for antidepressants, (2) describes barriers to inclusion, and (3) identifies possible steps for overcoming barriers.

Methods: Inclusion and exclusion criteria for efficacy trials for depression or major depressive disorder described on FDA labels for 14 antidepressants approved from 1991 through 2013 were studied by reading the FDA labels, publications described on labels, and ClinicalTrials.gov entries for registered trials. Labels for drugs approved in or before 1998 were obtained through a Freedom of Information Act request filed June 26, 2018. For drugs approved after 1998, labels are on the FDA website. Publications based on the trials described on FDA labels were identified through a PubMed search on October 23, 2018, using each drug name and trial or study as the keywords and setting no date limit.

Results: For drugs approved from 1991 to 2000, of 36 publications identified, 26 did not mention suicidality, 7 excluded persons with suicidality but did not describe assessing suicidality with an instrument, 2 excluded persons with suicidality and described assessing suicidality using at least 1 instrument, and 1 included persons with suicidality. For drugs approved from 2000 through 2013, of 28 publications identified, 4 did not mention suicidality, 12 reported excluding persons with suicidality but did not describe assessing suicidality with an instrument, 12 excluded persons with suicidality and described assessing suicidality using at least one instrument, and none included persons with suicidality. More stringent criteria for assessing and excluding based on suicidality very likely were applied for drugs approved post-2000.

Conclusions: The exclusion of persons with suicidality from antidepressant trials is common, creating uncertainty about medication safety and efficacy in parts of the target population. Information about study populations can be beneficial for prescribing clinicians, but it is not always readily available.

J Clin Psychiatry 2020;81(2):19m13050

To cite: Iltis AS, McCall WV, Deria R. Suicidality, depression, and the FDA: health inequities and the ethical conduct of research. *J Clin Psychiatry.* 2020;81(2):19m13050.

To share: https://doi.org/10.4088/JCP.19m13050

[a]Center for Bioethics, Health and Society and Department of Philosophy, Wake Forest University, Winston-Salem, North Carolina

[b]Department of Psychiatry and Health Behavior, Medical College of Georgia at Augusta University, Augusta, Georgia

[c]Center for Bioethics, Health and Society, Wake Forest University, Winston-Salem, North Carolina

**Corresponding author:* Ana S. Iltis, PhD, Center for Bioethics, Health and Society, Wake Forest University, 1834 Wake Forest Rd, Winston-Salem, NC 27106 (iltisas@wfu.edu).

Health inequities are well documented in different populations, including persons with mental health disorders.[1] Exclusion from or underrepresentation in biomedical research as well as the underreporting of the inclusion and exclusion criteria and the relevant characteristics of enrolled participants, which masks information about the applicability of results to the target population, may contribute to these inequities.[2–4] Exclusion can be specified in the protocol or arise from selection biases in recruitment.[5,6] Research results might not apply to excluded or underrepresented groups, and assuming that findings apply to them could lead to harm.[2,3] This problem is well documented in women, children, and racial and ethnic minorities.[3,7–9] Persons with mental health disorders, including those with suicidality, often are excluded or underrepresented in biomedical research on both mental health conditions and medical conditions despite experiencing morbidity and mortality due to the conditions being studied.[10–16]

Reducing health inequities for persons with mental health disorders, especially persons with suicidality, requires increasing the generalizability of biomedical research, which is part of improving the ethical quality of research. In this report, we (1) document the exclusion and underrepresentation of persons with suicidality in trials used to secure US Food and Drug Administration (FDA) approval for antidepressants; (2) describe 4 barriers to inclusion of persons with mental health disorders, especially suicidality, in research; and (3) identify possible steps for overcoming those barriers to improve the generalizability of research.

Generalizability and the Ethical Conduct of Research

Generalizability refers to the extent to which research findings provide reliable grounds for predicting how knowledge gained applies to the target population, the group of people we reasonably anticipate might be candidates for the intervention studied.[17] Generalizability is an important measure of the ethical quality of research for two reasons. First, learning from research to benefit others in the future often is a primary justification for risks and burdens to participants.[18,19] Second, the Belmont Report's conception of justice requires the fair distribution of research risks and burdens.[20] When populations are systematically excluded, they fail to benefit "from access

Clinical Points

- Until recently, clinical trials for antidepressant medications have not provided easy access to information regarding their inclusion of patients with suicidal ideation and behavior, leaving prescribers with uncertainties regarding the effectiveness of many antidepressants in suicidal patients.
- Clinicians who treat depressed patients with suicidal ideation or prior suicide attempt ideally should favor antidepressant approaches with documented efficacy for suicidal ideation and behavior.

to the resources, knowledge, and benefits associated with research over time."[10(p31)] Thus, designing and conducting studies that yield generalizable knowledge, ie, knowledge that applies to the target population, is a requirement for the ethical conduct of research. Trial conditions, inclusion and exclusion criteria, selection biases, and biases in design and analysis of research affect generalizability.[6,17,21,22] Alternative designs might improve the applicability of findings.[17] However, research findings are not generalizable to excluded or underrepresented groups.

Generalizability depends on the extent to which the study population represents the target population. Clear reporting about inclusion and exclusion criteria and enrolled participants' characteristics is essential for understanding to whom research findings may be applied. When response differences are anticipated due to biological, social and economic, and epidemiologic or other factors, subgroup analyses also are required. It might be necessary to include more participants overall to allow for subgroup analyses and possibly even intragroup analyses.[9,17,23,24] The potential benefits of improved generalizability could help to justify the increased risk associated with exposing more people to research risks.

Generalizability, Mental Health Disorders, and Exclusion From Research

Studies on common medical conditions and mental health disorders routinely exclude members of the target population based on mental health diagnoses.[10] For instance, Wong et al[16] reviewed publications on bipolar disorder treatment trials and found that the exclusion criteria for these studies would exclude 55% to 96% of the population with bipolar disorder.

Of special concern is exclusion of persons with suicidality, which includes those with suicidal ideation, self-injurious behavior, suicide attempts, and suicide.[25] The term *suicidality* is ambiguous and not recommended for use in clinical trials.[25] We use it here because the materials reviewed often referred to suicide risk without distinguishing among ideation, behavior, and attempts, and our goal was to identity attention to any of these categories. Suicidality is a serious condition often with fatal outcomes, and the majority of persons with suicidality have a mental health disorder.[26] Yet, studies on physical and mental health disorders often exclude individuals with suicidality, reducing their generalizability and leaving persons with a serious medical condition treated with inadequate or unproven interventions.[27] Exclusion may contribute to health disparities that persons with suicidality experience. Recent research on prazosin demonstrates the importance of inclusion and prospective evaluation of persons with suicidality to avoid harm. Some studies have demonstrated that prazosin can reduce PTSD-associated nightmares.[28] Yet, prazosin did not reduce PTSD-associated nightmares in persons with suicidality.[29]

A lifetime history of major depressive disorder is associated with suicidal ideation.[30] Approximately 16.5% of patients who experience a major depressive episode have a previous suicide attempt.[31] Thus, many people who are part of the target population for antidepressants very likely have suicidality. Adequate representation of such persons is especially important given recent findings that patients who have depression and suicidal behavior or ideation may respond less to antidepressant treatment than those without suicidal behavior or ideation.[32,33] Yet, many trials exclude persons with suicidality per protocol or through selection biases. Stanley[13] notes that most studies on commonly used medications to treat depression conducted between 1984 and 2001 excluded participants with any level of suicidality and, even when they were included, there was no subgroup analysis.[13] Khan et al[11] studied the rate of suicides and suicide attempts in the Integrated Safety Summary reports submitted to FDA as part of the initial drug approval process for 14 antidepressants approved between 1991 and 2013. They found no difference in rates between the placebo and active drug groups, but they found a significant decrease in rates of suicide and suicide attempts with drugs approved before 2000 versus in or after 2000. They hypothesized that the decline "may be partially due to implementation of stringent entry criteria for participation in these trials, including higher awareness of suicide risk by clinical investigators screening patients and pharmaceutical companies' physicians and scientists…[and] to the increased use of operationalized and systematic suicide risk assessment tools."[11(p1461)] We examined the clinical trial history for the antidepressants Khan et al[11] studied to evaluate whether antidepressant clinical trials had become increasingly restrictive regarding suicidality.

METHODS

We obtained inclusion and exclusion criteria for the efficacy trials for depression or major depressive disorder described on FDA labels for the 14 antidepressants Khan et al[11] studied to assess whether, as they hypothesized, exclusion criteria regarding suicidality had become stricter. For approvals in or before 1998 (7 studies), we filed Freedom of Information Act (FOIA) requests on June 26, 2018, and received information electronically on July 13, 2018. This information is available on the FDA's website for drugs approved after 1998 (7 studies). For the one drug approved in 1998, information was received as part of our FOIA request

Table 1. Inclusion and Exclusion Criteria for Efficacy Trials for Depression or Major Depressive Disorder Described on FDA Labels of Antidepressants Approved From 1991 Through 2013

Drug (Trade Name), Year Approved, and Related Publications	No Mention of Suicidality	Exclude Suicidality—No Instrument	Exclude Suicidality—Instrument	Include Suicidality
Sertraline (Zoloft), 1991[35–37]	2	1	0	0
Paroxetine (Paxil), 1992[38–53]	15	1	0	0
Venlafaxine (Effexor), 1993[54–58]	3	1	1	0
Nefazodone (Serzone), 1994[59–64]	3	2	0	1
Mirtazapine (Remeron), 1996[65–67]	2	1	0	0
Venlafaxine ER (Effexor ER), 1997[a]	NA	NA	NA	NA
Citalopram (Celexa), 1998[68–70]	1	1	1	0
Totals for drugs approved prior to 2000 (36 publications)	**26**	**7**	**2**	**1**
Escitalopram (Lexapro), 2002[71–74]	0	0	4	0
Duloxetine (Cymbalta), 2002[75–79]	4	1	0	0
Desvenlafaxine (Pristiq), 2008[80–89]	0	7	3	0
Trazodone ER (Oleptro), 2010[90]	0	1	0	0
Vilazodone (Viibryd), 2011[91–94]	0	2	2	0
Levomilnacipran (Fetzima), 2013[95,96]	0	0	2	0
Vortioxetine (Trintellix), 2013[97,98]	0	1	1	0
Totals for drugs approved in or after 2000 (28 publications)	**4**	**12**	**12**	**0**

[a]No corresponding publications found.
Abbreviations: ER = extended release, FDA = US Food and Drug Administration, NA = not applicable.

and also was available online. One of us (A.S.I.) conducted a PubMed search on October 23, 2018, for publications of clinical trials involving each of the 14 medications. Two of us (A.S.I. and R.D.) reviewed each publication to identify studies that matched the descriptions of the studies that were included on the FDA label as having been used to obtain approval of each drug for the treatment of depression. Factors considered in matching studies were drug name, the use of placebo or other comparators, duration, number of participants, sponsor, and participant population characteristics such as age, diagnosis, and inpatient or outpatient status.

The final list of publications included in our analysis reflects an informed guess based on all publicly available information. Since 2007, the FDA has required that clinical trials be registered on ClinicalTrials.gov, and the FDA is piloting a voluntary program to disclose some information from clinical study reports.[34] However, the FDA does not require publication of clinical trial results in peer-reviewed journals as part of the approval process. Thus, it is likely that some studies never were published, and it is not possible to establish definitively that the publications we have identified correspond to the trials that were used to secure FDA approval. It also is possible that more than one publication resulted from the same trial. We reviewed the inclusion and exclusion criteria in the publications identified for mentions suicidality. For the 15 publications associated with a ClinicalTrials.gov number, we reviewed the inclusion and exclusion criteria available in the entry for mentions of suicidality. We grouped the publications into 4 groups: (1) did not mention suicidality in the inclusion or exclusion criteria; (2) excluded persons with suicidality but did not report using an instrument to assess suicidality; (3) excluded persons with suicidality and reported using at least one instrument to assess suicidality; and (4) explicitly included persons with suicidality. Each publication was assigned to only 1 category. In one case, the publication did not report use of an instrument to assess suicidality, but the ClinicalTrials.gov entry did. We assigned that publication to category 3. We identified 2 publications listing at least 1 instrument used to exclude participants based on suicidality (category 3) for which the ClinicalTrials.gov listing included an additional instrument for assessing and excluding based on suicidality.

RESULTS

Table 1 summarizes the inclusion and exclusion criteria related to suicidality in publications and ClinicalTrials.gov. As evident in Table 1, for the period from 1991 to the 2000 cutoff that Khan et al[11] used, we identified 36 publications. Of those, 26 did not mention suicidality in the inclusion or exclusion criteria, 7 excluded persons with suicidality but did not describe assessing suicidality with an instrument, 2 excluded persons with suicidality and described use of at least one instrument to assess suicidality, and 1 included persons with suicidality. For drugs approved between 2000 and 2013, the second grouping of Khan et al,[11] we identified 28 publications. Of those, 4 did not mention suicidality in the inclusion/exclusion criteria, 12 reported excluding persons with suicidality but did not describe assessing suicidality with an instrument, 12 excluded persons with suicidality and described use of at least one instrument to assess suicidality, and none included persons with suicidality. Table 2 describes the instruments and scores reported in the inclusion and exclusion criteria with respect to suicidality. Typically, nonspecific measures such as investigator judgment supplemented instruments, leaving open the possibility that potential participants with ratings showing less severity on assessments also were excluded. Based on the reported information, as Khan et al[11] speculated, more stringent criteria for assessing suicide and excluding potential participants in clinical trials of antidepressants for the indication of major depressive disorder very likely were

Table 2. Assessment Instruments and Corresponding Scores Listed as Specific Exclusion Criteria Related to Suicidality in Studies Noted in Table 1[a]

Instrument	No. of Trials Reporting Use	Exclusion Criterion
MADRS	1	≥ 4 on item 10[57]
MADRS	11	≥ 5 on item 10[68,71–74,91,92,95–97]
$HDRS_{17}$	4	≥ 3[83,84,89,95]
C-SSRS	3	Exclusion score not reported[91,95,96,99,100,b]
MINI Suicide Scale	1	"High risk" (≥ 17)[90]

[a]The total number of trials noted in Table 1 reporting use of at least one instrument was 14. Some reported use of more than one instrument, which is why the total number listed in in this table is higher.
[b]These 5 citations refer to 3 trials; 2 listings in ClinicalTrials.gov provided exclusion information not reported in the journal publications.
Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MINI = Mini-International Neuropsychiatric Interview.

applied for drugs that were approved after 2000. It is possible that there has been no change in protocols requiring the use of instruments to assess suicidality but rather that reporting has improved. Whether the apparent growth in use of instruments to assess potential participants for suicidality and exclude them from clinical trials explains the dramatic decline in suicide attempts and deaths by suicide in antidepressant trials is impossible to determine, but our inquiry confirmed that there has been an increased use of or at least reporting of the use of more rigorous, systematic exclusion criteria regarding suicidality in depression research. The inconsistency among trials makes it difficult to compare medications for different members of the target population. It is possible that selection biases further restricted participation and that not all exclusion criteria were listed.

DISCUSSION

Increasing the generalizability of research to persons with mental health disorders, including persons with suicidality, is important for reducing health inequities and improving the ethical quality of research. Yet, this population has received less attention than others in discussions of generalizability. A recent FDA report[101] on making clinical trials more inclusive does not mention mental health disorders except to note that obtaining consent or assent from persons with mental illness is challenging. Draft FDA guidance issued in June 2018 states that "Patients with a history of suicidal ideation and behavior need not be systematically excluded from trials…..Sponsors should provide the rationale for restrictive inclusion and exclusion criteria."[102(p6)] Whether such guidance will significantly increase the generalizability of findings to persons with suicidal ideation and behavior remains to be seen. Previous efforts to make trials more inclusive include incentives (children) and requirements with reporting obligations (women and minorities).[7,103] History shows how difficult it can be to improve representation in trials.[104] We consider 4 barriers to the inclusion of persons with mental health disorders, especially suicidality, in research and practices that could help to overcome them (see Table 3). Improved representation, reporting, and subgroup analyses are important in research on common medical and psychiatric conditions. Additionally, more research targeting persons with suicidality to reduce suicide is needed. Research on preventing suicide has been limited, largely due to ethical and logistical concerns, and should be a public health priority.[105]

Participant Safety and Research Risks

Sponsors, investigators, and institutional review boards (IRBs) might believe that research participation is too risky for persons with various mental health disorders, particularly persons with suicidality or at risk for psychosis. IRBs might assume that any risk of suicide in a study is unacceptable and warrants exclusion despite accepting death as a possible outcome when participants have other often-fatal conditions.[26,105] The use of placebos, the possibility of delaying treatment because of trial requirements, and fear that research participation or merely mentioning suicide could exacerbate suicidality are barriers to inclusion.[106] Rather than assume that research poses unacceptable risks that require exclusion, risk-benefit assessments should be evidence based, and investigators should employ reliable methods to minimize and manage risks.[107]

Yanos et al reviewed risks associated with research on persons with mental health disorders and found that "many common types of research present minimal risk or only a minor increment over minimal risk for large segments of this population, as they do for persons in the general population."[108(p374)] Contrary to common belief, merely mentioning suicide does not appear to increase suicide risk.[106,108]

Protecting participant safety through planning and implementation of safety measures is critical.[107,110,111] With proper planning and implementation of risk mitigation and management strategies described elsewhere and tailored to individual projects, persons with suicidality may be included safely in research.[107,109–112]

Because washout periods for psychiatric medications and delays in intervention might increase risk, these should be minimized.[108] When necessary, supervised tapering of medications may be appropriate.[111]

Investigators should develop a plan to maintain contact with participants, monitor and assess suicide risks, and establish a plan for responding to changes, including when and how hospitalization will be managed.[110,111] Including family members or other caregivers or participant advocates might be important, especially for protecting participants whose decisional capacity fluctuates. Participants must be told about the limits of confidentiality.[110] Investigators should have a plan for managing expressions of suicidal intent and suicide attempts and pathways for addressing disclosures of suicide risk.[112,113]

Independent safety monitoring and preestablished criteria for withdrawing participants or stopping a study serve important functions in safety planning.[105,110]

Table 3. Barriers to Inclusion of Persons With Suicidality in Research and Mechanisms to Overcome Barriers

Barriers: The Belief That…	Overcoming Barriers
Research participation is too risky for persons with suicidality	Evaluate risks and potential benefits in light of evidence Plan and implement measures to minimize, monitor, and manage risks
Prospective participants with suicidality might lack decisional capacity	Assess capacity of potential participants using validated instruments Foster decisional capacity using tested methods
Inclusion of persons with suicidality would be too burdensome because: • it would be costly to minimize and manage risks and foster decisional capacity • persons with suicidality are unreliable and likely to be nonadherent • inclusion of persons with suicidality would increase liability	Measures required for safe inclusion with valid informed consent should be treated like all other requirements for the ethical conduct of research Recognize evidence that demonstrates history of adherence in research; use methods to promote adherence when necessary Employ measures to reduce liability
Statistical considerations: • Inclusion introduces variables that could compromise results • There is no incentive to undertake costs and burdens to make study population representative of the larger target population	Design inclusive studies and measure variability Incentivize inclusion

Institutional structures and culture as well as staff training are vital to supporting the safe inclusion of persons with suicidality in research.[107,108,112] Finally, investigators must facilitate continuity of care when the study ends.[111]

Measures to minimize and manage risk change the study setting so that it does not mimic clinical reality, thereby reducing generalizability. In studies designed to measure or reduce suicidality, such measures can undermine statistical power by reducing the ability to detect differences between study arms.[112] These limitations sometimes are inevitable because, without them, participants could not be included safely[114] and it would be impossible to pursue important research at all. At the same time, investigators must balance safety and statistical considerations in designing studies because research risks are justified only when studies can produce scientifically valid results that can advance knowledge. Increased risk exposure can be justified only by a corresponding increase in potential benefit.[114]

Before resorting to exclusion, investigators and sponsors should explore options for safe inclusion of persons with mental health disorders, including persons with suicidality, in research.

Decisional Capacity and Voluntary Informed Consent

IRB members, investigators, or sponsors might assume that persons with mental health disorders lack decision-making capacity and are unable to give valid informed consent, excluding them on this basis.[109,110,115] Sometimes they will have capacity, or it will be possible to foster their capacity and enable them to give voluntary informed consent.

Decisional capacity judgments should be evidence-based and determined by cognitive function, not diagnosis.[116] Although some differences exist in how potential participants with mental health disorders and psychiatrists assess research risks, significant concordance has been found.[106]

When decisional capacity might be diminished, investigators should assess it using validated instruments, such as Evaluation to Sign Consent[111,117]; the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC)[118]; or the MacArthur Competence Assessment Tool for Clinical Research,[119] rather than exclude people automatically. Third-party advocates and authorized representatives can help protect against changes in capacity.[107]

When participants face difficulties with decisional capacity, proven strategies to foster decisional capacity should be employed when possible. Often, people with various mental health disorders can understand and appreciate risk information and give voluntary consent with appropriate support.[120,121]

Exclusion should not be the preferred or default response to concerns about decision making capacity.

A Difficult Study Population That Increases Liability

Persons with mental health disorders, especially those with suicidality, are highly stigmatized and might be excluded because they are seen as unreliable and nonadherent, burdensome, or a liability to investigators, institutions, or sponsors.[112,122]

Investigators should not assume that persons with suicidality will be less adherent than other participants. Consider adherence rates in 2 studies involving participants with suicidality.[123,124] REST-IT compared the use of hypnotic medication to placebo for reducing suicidal ideation in participants taking SSRIs who had both suicidal ideation and insomnia.[111] Participants took 91% of all prescribed doses of antidepressant medication and 88% of all study drug, and they completed 90% of scheduled study visits.[123] InterSePT compared the risk of suicidal behavior in participants with schizophrenia or schizoaffective disorder taking clozapine versus olanzapine. Participants took approximately 95% of study medication.[124] When adherence is a concern, investigators may use evidence-based measures to improve adherence, though more work is needed in this area.[125] While such interventions could decrease generalizability, this decrease is among the limitations of much clinical research.

Implementing measures to minimize and manage risk or to assess and foster decisional capacity or promote adherence might be seen as overly burdensome or costly and not worthwhile. These measures should be treated like other requirements for the ethical conduct of research

that impose costs or burdens. Persons with mental health disorders should not be singled out as unworthy of the trouble.

Concern that inclusion of persons with suicidality might expose sponsors, investigators, or institutions to liability could further deter inclusion.[112] Mechanisms to reduce liability for clinicians treating patients with suicidality might help investigators as well.[112] These include the aforementioned measures to assess and monitor suicidal risk and include family members.[112]

Statistical Considerations

Sponsors and investigators might exclude persons with mental health disorders because of concerns about study design and results. Strict inclusion/exclusion criteria can minimize variability within groups, making it easier to show differences between study groups.[22] Because including persons with mental health disorders or more severe forms of disease could undermine power of the trial if they respond in markedly different ways, investigators and sponsors might exclude them.[10] Studies that fail to demonstrate safety and efficacy might cost pharmaceutical companies approval or require investment in additional trials, creating a disincentive for inclusion.

Sponsors might define target populations in unrealistically narrow ways because FDA approval permits it, and off-label prescribing of approved drugs expands the pool of patients taking a drug without the burden of costly research. This means that there are no requirements and typically no financial incentives for making the study population truly representative of the larger target population. The FDA and the US Congress should explore incentives to foster inclusion of persons with suicidality and measurement of suicide-relevant outcomes. Pharmaceutical companies might determine that including persons with suicidality and demonstrating the applicability of their findings to a broader population allows them to advertise an advantage over competing products, providing sufficient incentive to change practice.

CONCLUSION

Psychopharmacologic clinical trials data informing the care of persons with suicidal ideation are scarce. There is some evidence that clozapine, lithium, and electroconvulsive therapy have specific antisuicidal effects, but very few data exist regarding the effect of antidepressant medication in depressed patients with active suicidal ideation.[18,126,127] The exclusion of persons with suicidality from clinical trials of antidepressants limits the generalizability of the results, creating uncertainty about the safety and efficacy of those medications in parts of the target population. One limitation of this study is that we did not request the full protocols from pharmaceutical companies that sponsored the trials in question to determine their inclusion and exclusion criteria. Understanding the extent to which study populations represent the target population is important for prescribing clinicians, yet this information may be difficult to ascertain for patients with suicidality. Lack of ready access to this information despite the extensive measures we undertook and without requesting full protocols from pharmaceutical companies highlights the problem that clinicians cannot readily access information relevant to making treatment recommendations.

Reducing health inequities requires greater attention to the features of study design and reporting that make findings generalizable to target populations. It might be impossible to include in any one study enough people from every imaginable target group to conduct subgroup analyses on all of them. Exclusion may be warranted in some cases, such as when there is no safe way to include while also answering the research question. For example, an outpatient study must exclude persons who are so suicidal that they must be hospitalized. When exclusion is warranted, investigators should offer a robust justification for exclusion as part of independent review process and exclusion should be documented and transparent. When appropriate, it might be necessary to conduct multiple studies in different populations to assess safety and efficacy in the target population.

Submitted: August 16, 2019; accepted December 19, 2019.

Published online: February 4, 2020.

Potential conflicts of interest: **Dr McCall** has received research support from MECTA, Vistagen, and Merck; is a scientific advisor for Sage Therapeutics and Jazz; receives royalties from Wolters Kluwer Publishing; and is a member of the speakers bureau for CME Outfitters. **Dr Iltis** and **Ms Deria** report no financial relationships with commercial interests.

Funding/support: This research was completed without grant support.

Previous presentation: Portions of the research were presented at the Association for Practical and Professional Ethics; March 1, 2019; Baltimore, Maryland ▪ the International Association of Law and Mental Health; July 23, 2019; Rome, Italy.

Acknowledgments: The authors wish to acknowledge Mary Beth Lock, MLIS, Assistant Dean and Director of Access Services at the Z. Smith Reynolds Library at Wake Forest University, for her research support. Ms Lock has no conflicts of interest to disclose.

Additional information: This research did not involve human participants; thus, institutional review board approval was not needed.

REFERENCES

1. Thornicroft G. *Br J Psychiatry*. 2011;199(6):441–442.
2. Corbie-Smith G, St George DM, Moody-Ayers S, et al. *J Clin Epidemiol*. 2003;56(5):416–420.
3. Zhang T, Tsang W, Wijeysundera HC, et al. *Am Heart J*. 2013;166(1):52–57.
4. Porzsolt F, Wiedemann F, Becker SI, et al. *BMJ Evid Based Med*. 2019;24(3):92–94.
5. Hofer A, Hummer M, Huber R, et al. *J Clin Psychopharmacol*. 2000;20(6):699–702.
6. Ellenberg JH. *Stat Med*. 1994;13(5–7):557–567.
7. United States Congress Public Law. National Institutes of Health Revitalization Act of 1993. Public Law 103-43. https://history.nih.gov/research/downloads/pl103-43.pdf
8. Castillo-Mancilla JR, Cohn SE, Krishnan S, et al; the ACTG Underrepresented Populations Survey Group. *HIV Clin Trials*. 2014;15(1):14–26.
9. Liu KA, Mager NA. *Pharm Pract (Granada)*. 2016;14(1):708.
10. Humphreys K, Blodgett JC, Roberts LW. *J Psychiatr Res*. 2015;70:28–32.
11. Khan A, Fahl Mar K, Gokul S, et al. *Psychopharmacology (Berl)*. 2018;235(5):1455–1462.
12. Handong M, Weng C. Identification of questionable exclusion criteria in mental disorder clinical trials using a medical encyclopedia. Biocomputing 2016: Proceedings of the Pacific Symposium. 2016:219-30.
13. Stanley B. Interventions for suicidal patients with co-occurring alcohol use disorder. National Advisory Council on Alcohol Abuse and Alcoholism website. https://www.niaaa.nih.gov/about-niaaa/our-work/

advisory-council/agenda-minutes/advisory-council-meeting-minutes/national-15. 2007. Cited January 18, 2017.
14. Hoertel N, Le Strat Y, Blanco C, et al. *Depress Anxiety*. 2012;29(7):614–620.
15. Blanco C, Olfson M, Goodwin RD, et al. *J Clin Psychiatry*. 2008;69(8):1276–1280.
16. Wong JJ, Jones N, Timko C, et al. *Contemp Clin Trials Commun*. 2018;9:130–134.
17. Fuller J. *J Eval Clin Pract*. 2013;19(4):644–647.
18. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. Office for Human Research Protections website. https://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html. 1979. Cited June 13, 2019.
19. International Ethical Guidelines for Health-Related Research Involving Humans. Council for International Organizations of Medical Sciences website. Council for International Organizations of Medical Sciences. https://www.cioms.ch/ethical-guidelines-2016/. 2016. Cited June 13, 2019.
20. Dresser R. *Hastings Cent Rep*. 1992;22(1):24–29.
21. Fuller J, Flores LJ. *Stud Hist Philos Biol Biomed Sci*. 2015;54:49–61.
22. Stegenga J. *Stud Hist Philos Biol Biomed Sci*. 2015;54:62–71.
23. Shahar E. *J Eval Clin Pract*. 2003;9(2):151–159.
24. Dans AL, Dans LF, Guyatt GH, et al; Evidence-Based Medicine Working Group. *JAMA*. 1998;279(7):545–549.
25. Meyer RE, Salzman C, Youngstrom EA, et al. *J Clin Psychiatry*. 2010;71(8):1040–1046.
26. Goldsmith SK, Pellmar DC, Kleinman AM, et al. *Reducing Suicide: A National Imperative*. Washington, DC: The National Academies Press; 2002.
27. Fisher CB, Hoagwood K, Boyce C, et al. *Am Psychol*. 2002;57(12):1024–1040.
28. Kung S, Espinel Z, Lapid MI. *Mayo Clin Proc*. 2012;87(9):890–900.
29. McCall WV, Pillai A, Case D, et al. *J Clin Psychopharmacol*. 2018;38(6):618–621.
30. de Beurs D, Ten Have M, Cuijpers P, et al. *BMC Psychiatry*. 2019;19(1):345.
31. Claassen CA, Trivedi MH, Rush AJ, et al. *J Affect Disord*. 2007;97(1–3):77–84.
32. Pompili M, Baldessarini RJ, Tondo L, et al. *J Affect Disord*. 2010;122(1–2):154–158.
33. Lopez-Castroman J, Jaussent I, Gorwood P, et al. *Depress Anxiety*. 2016;33(6):483–494.
34. FDA Commissioner Scott Gottlieb, MD, on new steps FDA is taking to enhance transparency of clinical trial information to support innovation and scientific inquiry related to new drugs. US Food & Drug Administration website. https://www.fda.gov/news-events/press-announcements/fda-commissioner-scott-gottlieb-md-new-steps-fda-taking-enhance-transparency-clinical-trial. January 2018. Cited June 13, 2019.
35. Lydiard RB, Stahl SM, Hertzman M, et al. *J Clin Psychiatry*. 1997;58(11):484–491.
36. Fabre LF, Abuzzahab FS, Amin M, et al. *Biol Psychiatry*. 1995;38(9):592–602.
37. Reimherr FW, Chouinard G, Cohn CK, et al. *J Clin Psychiatry*. 1990;51(suppl B):18–27.
38. Rickels K, Amsterdam J, Clary C, et al. *Acta Psychiatr Scand suppl*. 1989;350(S350):117–123.
39. Peselow ED, Filippi AM, Goodnick P, et al. *Psychopharmacol Bull*. 1989;25(2):272–276.
40. Cohn JB, Crowder JE, Wilcox CS, et al. *Psychopharmacol Bull*. 1990;26(2):185–189.
41. Claghorn JL, Kiev A, Rickels K, et al. *J Clin Psychiatry*. 1992;53(12):434–438.
42. Claghorn JL, Feighner JP. *J Clin Psychopharmacol*. 1993;13(suppl 2):23S–27S.
43. Feighner JP, Cohn JB, Fabre LF Jr, et al. *J Affect Disord*. 1993;28(2):71–79.
44. Dunbar GC, Cohn JB, Fabre LF, et al. *Br J Psychiatry*. 1991;159(3):394–398.
45. Dunbar GC, Claghorn JL, Kiev A, et al. *Acta Psychiatr Scand*. 1993;87(5):302–305.
46. Feighner JP. *Int Clin Psychopharmacol*. 1992;6(suppl 4):31–35.
47. Smith WT, Glaudin V. *J Clin Psychiatry*. 1992;53(suppl):36–39.
48. Shrivastava RK, Shrivastava SH, Overweg N, et al. *J Clin Psychiatry*. 1992;53(suppl):48–51.
49. Fabre LF. *J Clin Psychiatry*. 1992;53(suppl):40–43.
50. Feighner JP, Boyer WF. *Acta Psychiatr Scand suppl*. 1989;350(S350):125–129.
51. Rickels K, Amsterdam J, Clary C, et al. *J Clin Psychiatry*. 1992;53(suppl):30–32.
52. Cohn JB, Wilcox CS. *J Clin Psychiatry*. 1992;53(suppl):52–56.
53. Claghorn JL. *J Clin Psychiatry*. 1992;53(suppl):33–35.
54. Schweizer E, Feighner J, Mandos LA, et al. *J Clin Psychiatry*. 1994;55(3):104–108.
55. Schweizer E, Weise C, Clary C, et al. *J Clin Psychopharmacol*. 1991;11(4):233–236.
56. Khan A, Fabre LF, Rudolph R. *Psychopharmacol Bull*. 1991;27(2):141–144.
57. Guelfi JD, White C, Hackett D, et al. *J Clin Psychiatry*. 1995;56(10):450–458.
58. Clerc GE, Ruimy P, Verdeau-Pallès J; The Venlafaxine French Inpatient Study Group. *Int Clin Psychopharmacol*. 1994;9(3):139–143.
59. Fontaine R, Ontiveros A, Elie R, et al. *J Clin Psychiatry*. 1994;55(6):234–241.
60. Cohn CK, Robinson DS, Roberts DL, et al. *J Clin Psychiatry*. 1996;57(suppl 2):15–18.
61. Rickels K, Schweizer E, Clary C, et al. *Br J Psychiatry*. 1994;164(6):802–805.
62. Feighner JP, Pambakian R, Fowler RC, et al. *Psychopharmacol Bull*. 1989;25(2):219–221.
63. Mendels J, Reimherr F, Marcus RN, et al. *J Clin Psychiatry*. 1995;56(suppl 6):30–36.
64. Feighner J, Targum SD, Bennett ME, et al. *J Clin Psychiatry*. 1998;59(5):246–253.
65. Smith WT, Glaudin V, Panagides J, et al. *Psychopharmacol Bull*. 1990;26(2):191–196.
66. Thase ME, Nierenberg AA, Keller MB, et al; Relapse Prevention Study Group. *J Clin Psychiatry*. 2001;62(10):782–788.
67. Nierenberg AA, Quitkin FM, Kremer C, et al. *Neuropsychopharmacology*. 2004;29(5):1012–1018.
68. Feighner JP, Overø K. *J Clin Psychiatry*. 1999;60(12):824–830.
69. Mendels J, Kiev A, Fabre LF. *Depress Anxiety*. 1999;9(2):54–60.
70. Montgomery SA, Rasmussen JG, Lyby K, et al. *Int Clin Psychopharmacol*. 1992;6(suppl 5):65–70.
71. Lepola UM, Loft H, Reines EH. *Int Clin Psychopharmacol*. 2003;18(4):211–217.
72. Wade A, Michael Lemming O, Bang Hedegaard K. *Int Clin Psychopharmacol*. 2002;17(3):95–102.
73. Burke WJ, Gergel I, Bose A. *J Clin Psychiatry*. 2002;63(4):331–336.
74. Rapaport MH, Bose A, Zheng H. *J Clin Psychiatry*. 2004;65(1):44–49.
75. Detke MJ, Lu Y, Goldstein DJ, et al. *J Psychiatr Res*. 2002;36(6):383–390.
76. Goldstein DJ, Lu Y, Detke MJ, et al. *J Clin Psychopharmacol*. 2004;24(4):389–399.
77. Goldstein DJ, Mallinckrodt C, Lu Y, et al. *J Clin Psychiatry*. 2002;63(3):225–231.
78. Perahia DGS, Wang F, Mallinckrodt CH, et al. *Eur Psychiatry*. 2006;21(6):367–378.
79. Detke MJ, Lu Y, Goldstein DJ, et al. *J Clin Psychiatry*. 2002;63(4):308–315.
80. Feiger AD, Tourian KA, Rosas GR, et al. *CNS Spectr*. 2009;14(1):41–50.
81. Tourian KA, Padmanabhan SK, Groark J, et al. *Clin Ther*. 2009;31(pt 1):1405–1423.
82. Septien-Velez L, Pitrosky B, Padmanabhan SK, et al. *Int Clin Psychopharmacol*. 2007;22(6):338–347.
83. Iwata N, Tourian KA, Hwang E, et al. *J Psychiatr Pract*. 2013;19(1):5–14.
84. Liebowitz MR, Tourian KA, Hwang E, et al; Study 3362 Investigators. *BMC Psychiatry*. 2013;13(1):94.
85. Liebowitz MR, Yeung PP, Entsuah R. *J Clin Psychiatry*. 2007;68(11):1663–1672.
86. Liebowitz MR, Manley AL, Padmanabhan SK, et al. *Curr Med Res Opin*. 2008;24(7):1877–1890.
87. Boyer P, Montgomery S, Lepola U, et al. *Int Clin Psychopharmacol*. 2008;23(5):243–253.
88. DeMartinis NA, Yeung PP, Entsuah R, et al. *J Clin Psychiatry*. 2007;68(5):677–688.
89. Rosenthal JZ, Boyer P, Vialet C, et al. *J Clin Psychiatry*. 2013;74(2):158–166.
90. Sheehan DV, Croft HA, Gossen ER, et al. *Psychiatry (Edgmont)*. 2009;6(5):20–33.
91. Croft HA, Pomara N, Gommoll C, et al. *J Clin Psychiatry*. 2014;75(11):e1291–e1298.
92. Mathews M, Gommoll C, Chen D, et al. *Int Clin Psychopharmacol*. 2015;30(2):67–74.
93. Khan A, Cutler AJ, Kajdasz DK, et al. *J Clin Psychiatry*. 2011;72(4):441–447.
94. Rickels K, Athanasiou M, Robinson DS, et al. *J Clin Psychiatry*. 2009;70(3):326–333.
95. Bakish D, Bose A, Gommoll C, et al. *J Psychiatry Neurosci*. 2014;39(1):40–49.
96. Asnis GM, Bose A, Gommoll CP, et al. *J Clin Psychiatry*. 2013;74(3):242–248.
97. Boulenger JP, Loft H, Olsen CK. *Int Clin Psychopharmacol*. 2014;29(3):138–149.
98. Jacobsen PL, Mahableshwarkar AR, Serenko M, et al. *J Clin Psychiatry*. 2015;76(5):575–582.
99. Relapse Prevention Study of Desvenlafaxine Succinate Sustained Release in Outpatients With Major Depressive Disorder. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT00887224.
100. Study Evaluating Desvenlafaxine Succinate Sustained Release in Adults With Major Depressive Disorder. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT00887224.
101. Food and Drug Administration. Evaluating Inclusion and Exclusion Criteria in Clinical Trials: Workshop Report. FDA News website. https://www.fdanews.com/ext/resources/files/2018/08-22-18-FDAsummary.pdf?1534970149. April 16, 2018. [Cited 13 Jun 2019].
102. Food and Drug Administration. Major Depressive Disorder: Developing Drugs for Treatment, Guidance for Industry—Draft Guidance. US Food & Drug Administration website. https://www.fda.gov/media/113988/download. 2018.
103. United States Congress. Best Pharmaceuticals for Children Act of 2002. Public Law. 107-109. https://www.congress.gov/107/plaws/publ109/PLAW-107publ109.pdf.
104. Mazure CM, Jones DP. *BMC Womens Health*. 2015;15(1):94.
105. Sisti DA, Joffe S. *JAMA*. 2018;320(16):1633–1634.
106. Cukrowicz K, Smith P, Poindexter E. *Suicide Life Threat Behav*. 2010;40(6):535–543.
107. Iltis AS, Misra S, Dunn LB, et al. *JAMA Psychiatry*. 2013;70(12):1363–1371.
108. Yanos PT, Stanley BS, Greene CS. *Psychiatr Serv*. 2009;60(3):374–383.
109. Saigle V, Séguin M, Racine E. *IRB*. 2017;39(1):1–9.
110. Conducting Research with Participants at Elevated Risk for Suicide: Considerations for Researchers. National Institute of Mental

Health website. https://www.nimh.nih.gov/funding/clinical-research/conducting-research-with-participants-at-elevated-risk-for-suicide-considerations-for-researchers.shtml. 2017. Cited June 13, 2019.
111. McCall WV, Benca RM, Rosenquist PB, et al. *Clin Trials*. 2015;12(3):189–198.
112. Pearson JL, Stanley B, King CA, et al. *J Clin Psychiatry*. 2001;62(suppl 25):17–26.
113. Mishara BL, Weisstub DN. *Int J Law Psychiatry*. 2005;28(1):23–41.
114. Reynolds CF 3rd, Degenholtz H, Parker LS, et al. *Int J Geriatr Psychiatry*. 2001;16(6):602–608.
115. Tait RC, Chibnall JT, Iltis A, et al. *J Empir Res Hum Res Ethics*. 2011;6(1):39–50.
116. Palmer BW, Jeste DV. *Schizophr Bull*. 2006;32(1):98–106.
117. DeRenzo EG, Conley RR, Love R. *J Health Care Law Policy*. 1998;1(1):66–87.
118. Jeste DV, Palmer BW, Appelbaum PS, et al. *Arch Gen Psychiatry*. 2007;64(8):966–974.
119. Appelbaum PS, Grisso T. *MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)*. Sarasota, FL: Professional Resource Press/Professional Resource Exchange; 2001.
120. Jeste DV, Palmer BW, Golshan S, et al. *Schizophr Bull*. 2009;35(4):719–729.
121. Palmer BW, Dunn LB, Depp CA, et al. *J Clin Psychiatry*. 2007;68(5):689–696.
122. Thornicroft G, Mehta N, Clement S, et al. *Lancet*. 2016;387(10023):1123–1132.
123. McCall WV, Benca RM, Rosenquist PB, et al. *Am J Psychiatry*. 2019;176(11):957–965.
124. Meltzer HY, Alphs L, Green AI, et al; International Suicide Prevention Trial Study Group. *Arch Gen Psychiatry*. 2003;60(1):82–91.
125. Zullig LL, Blalock DV, Dougherty S, et al. *Patient Prefer Adherence*. 2018;12:1225–1230.
126. Cipriani A, Pretty H, Hawton K, et al. *Am J Psychiatry*. 2005;162(10):1805–1819.
127. Fink M, Kellner CH, McCall WV. *J ECT*. 2014;30(1):5–9.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.