



VU Research Portal

Suicide risk management in research on internet-based interventions for depression

Sander, Lasse; Gerhardinger, Katharina; Bailey, Eleanor; Robinson, Jo; Lin, Jiaxi; Cuijpers, Pim; Mühlmann, Charlotte

published in Journal of Affective Disorders 2020

DOI (link to publisher) 10.1016/j.jad.2019.11.045

document version Publisher's PDF, also known as Version of record

document license Article 25fa Dutch Copyright Act

Link to publication in VU Research Portal

citation for published version (APA) Sander, L., Gerhardinger, K., Bailey, E., Robinson, J., Lin, J., Cuijpers, P., & Mühlmann, C. (2020). Suicide risk management in research on internet-based interventions for depression: A synthesis of the current state and recommendations for future research. Journal of Affective Disorders, 263, 676-683. https://doi.org/10.1016/j.jad.2019.11.045

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
 You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address: vuresearchportal.ub@vu.nl Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

Suicide risk management in research on internet-based interventions for depression: A synthesis of the current state and recommendations for future research

Lasse Sander^{a,*}, Katharina Gerhardinger^a, Eleanor Bailey^{b,c,d}, Jo Robinson^{b,c}, Jiaxi Lin^e, Pim Cuijpers^f, Charlotte Mühlmann^{g,h}

^a Department of Rehabilitation Psychology and Psychotherapy, Albert-Ludwigs-University Freiburg, Institute of Psychology, Engelbergerstr. 41, D-79085 Freiburg, Germany

^b Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, Australia

^c Centre for Youth Mental Health, University of Melbourne, Australia

^d Swinburne University of Technology, Melbourne, Australia

e Department of Psychiatry and Psychotherapy, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Hauptstrasse 5, D-79104 Freiburg, Germany

^f Department of Clinical, Neuro-, and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, BT 1081, Amsterdam, the Netherlands

⁸ Danish Research Institute for Suicide Prevention, Mental Health Centre Copenhagen, Hellerup, Denmark

h The University of Copenhagen, Denmark

ARTICLE INFO

Keywords: Internet interventions

E-Health

Review

Depression

Suicidal ideation

ABSTRACT

Background: The number of studies examining internet-based interventions (IBIs) for depression is increasing. Although many individuals with depression experience suicidal ideation, there is only insufficient information available on how to manage and support individuals at risk of suicide in IBI trials. Here, we examined the current practice regarding the management of individuals experiencing suicidal thoughts or behaviors in studies of IBIs for depression.

Methods: Information pertaining to the management of suicidality was extracted from 24 studies. Additionally, researchers in the field completed a questionnaire (n = 13) before being interviewed (n = 11) about their procedures and considerations regarding the management of suicidality.

Results: In most trials (N = 17; 71%), individuals at risk of suicide were excluded based on varying criteria. N = 7 studies used structured interviews and N = 5 studies used single items of self-report questionnaires for assessing suicidality. The nature and degree of support provided to individuals at risk of suicide varied and only one intervention comprised suicide-specific content.

Limitations: Most experts referred to research on interventions with some level of human support (e.g. written feedback) which might limit the representativeness of the results of the interviews for unguided interventions. *Conclusions:* Suicidality is often treated more as an exclusion criterion rather than a treatable condition in research on IBIs for depression. This paper provides an overview of the current practice and gives recommendations for the design of future trials.

1. Introduction

Depression is highly prevalent, affecting approximately 350 million people worldwide at any given moment and is associated with a range of negative outcomes, including suicide (Ferrari et al., 2013). Indeed, individuals with depression are at 25 times increased risk of suicide compared to the general population (American Association of Suicidology, 2014). The assessment and management of suicidality, suicidal ideation and behavior (Silverman, 2006), is therefore a major consideration in treating individuals suffering from depression, and best-practice guidelines for the treatment of depression regularly provide information on the management of suicidal ideation and behavior (American Psychiatric Association, 2003; DGPPN, 2015; National Institute for Health and Care (NICE), 2009).

Over the past two decades, the use of the internet in health care has continuously evolved (Ebert et al., 2018; Wicks et al., 2014), and in

* Corresponding author.

https://doi.org/10.1016/j.jad.2019.11.045

Received 3 September 2019; Received in revised form 5 November 2019; Accepted 9 November 2019 Available online 12 November 2019 0165-0327/ Crown Copyright © 2019 Published by Elsevier B.V. All rights reserved.





E-mail address: lasse.sander@psychologie.uni-freiburg.de (L. Sander).

recent years there has been an increasing number of randomized controlled trials (RCTs) showing good evidence for the efficacy of internetbased interventions (IBIs) for the treatment and prevention of depression (Karyotaki et al., 2018, 2017; Königbauer et al., 2017; Sander et al., 2016). IBIs can either be provided with human support and guidance via e-mail, chat, webcam or telephone or as strictly selfhelp interventions without human support (Barak et al., 2009). Human guidance has repeatedly been shown to improve the effectiveness of IBIs (Baumeister et al., 2014; Domhardt et al., 2019).

Given that IBIs differ in many aspects from face-to-face interventions, for example in the amount and nature of contact with therapists (Baumeister et al., 2014; Ebert et al., 2018), recommendations for the management of suicidality in face-to-face practice might not be applicable to the online setting. This can lead to uncertainties in the application of correct management of suicide risk in IBIs in clinical practice, but also in research in this area. In intervention research, issues like concerns for participant safety, methodological complications, resistance from review boards and burden on researchers are well known and have led to the exclusion of participants who experience suicidal ideation (Fisher et al., 2002; Hom et al., 2017; Lakeman and FitzGerald, 2009; Oquendo et al., 2004; Pearson et al., 2001; Raison et al., 2007; Sisti and Joffe, 2018). Regarding IBI for depression, the exclusion of such individuals, however, can lead to the creation of an evidence base that is not representative of individuals who experience depression (Sisti and Joffe, 2018; Zimmerman et al., 2005). To the best of our knowledge, there is to date no systematic research on how to manage suicidality in the novel field of internet-based therapy. A better understanding of how to best manage participants with suicide thoughts may help researchers, clinicians and review boards as well as depressed individuals with suicide thoughts that seek help from IBIs.

Thus, this study aimed to: (a) examine current inclusion and exclusion practices pertaining to individuals at risk of suicide in IBIs for depression; (b) consult researchers in the field on their experiences and recommendations regarding the management of suicidality in their studies; and (c) provide recommendations for future research on internet interventions for depression.

2. Methods

This study is based on a review of current literature, an online questionnaire, and subsequent telephone interviews. We used a mixed methods approach including a qualitative content analysis and descriptive statistics.

2.1. Sample and recruitment

Literature review. We reviewed two recent and comprehensive metaanalyses of RCTs of IBIs for depression (Karyotaki et al., 2018, 2017). To ensure the currency of the studies, we included only studies published within the last five years prior to the first meta-analysis (since 2012) (N = 24) (Buntrock et al., 2015; Carlbring et al., 2013; Choi et al., 2012; Ebert et al., 2014; Geraedts et al., 2014; Gilbody et al., 2015; Hallgren et al., 2015; Imamura et al., 2014; Johansson et al., 2012b, 2012a; Kenter et al., 2016; Kivi et al., 2014; Kleiboer et al., 2015; Klein et al., 2016; Meyer et al., 2015; Mira et al., 2017; Moritz et al., 2012; Newby et al., 2013; Nobis et al., 2015; Phillips et al., 2014; Sheeber et al., 2012; Titov et al., 2015; Ünlü Ince et al., 2013; Williams et al., 2013).

Online survey and interview. All first- and senior authors of the included studies from the literature review (n = 41) were invited to take part in an online survey and a subsequent interview. All researchers provided informed consent prior to participation in the study. Fig. 1 provides a detailed description of the examination procedure and dropouts.

2.2. Instruments

Questionnaire. The questionnaire was delivered using an online survey software for academic research (*unipark*) and consisted of up to 14 questions (number of questions varied depending on given answers) about the management of suicidality in research on IBIs for depression (Appendix A). Topics included assessment and monitoring of participants experiencing suicidal thoughts, inclusion and exclusion procedures, safety procedures and ethical considerations. Both open and closed questions were used. The researchers were asked to refer to a recent study on IBIs for depression they had conducted since 2012.

Interview. The semi-structured interviews were individually tailored to the researcher's answers in the questionnaire (Appendix B). They were conducted and recorded using Adobe Connect Meeting, a software package for online meetings. The interviewed researchers were asked about their experiences with their chosen suicide risk assessment, monitoring and risk management procedure.

2.3. Data extraction and analysis

For the literature review, we extracted the inclusion and exclusion criteria regarding suicidality, the type and nature of suicidality-specific content of interventions and the implemented management procedures for suicidality from the articles or the respective study-protocols.

Regarding the questionnaire and interviews, for closed questions, we performed a descriptive analysis to determine the frequency of different features of the management of suicidality. Answers to open questions were analyzed by KG, following the qualitative content analysis according to Meuser and Nagel (2009). This method aims to reduce the quantity of data by paraphrasing the given answers and rearrange passages by thematically linked general terms. For the case of this study, the method was used to extract the essential opinions of the researchers on how to manage suicidality in RCTs on IBIs for depression. All of the coding of the survey and interviews were performed by KG. LS afterwards sense-checked the extracted codes by reading the transcripts.

3. Results

Literature review. Table 1 provides an overview of the suicidalityrelated information of the 24 included studies. Seven studies did not exclude individuals at risk of suicide. With regard to the assessment of suicide risk, five studies exclusively used single items of self-report rating scales of the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) or the Beck Depression Inventory (BDI) (Beck et al., 1961), four studies exclusively used structured clinical interviews (e.g. Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), Structured Clinical Interview for DSM (SCID) (First et al., 2015) and three studies combined self-report scales with the MINI.

One study (Kleiboer et al., 2015) used the suicide questionnaire developed by Gega et al. (2005) and one study assessed suicidality by clinical judgment of a general practitioner (Gilbody et al., 2015). Three studies assessed and excluded individuals at risk of suicide, but did not state specifications regarding in- or exclusion criteria (Johansson et al., 2012a; Kenter et al., 2016; Williams et al., 2013). A suicide attempt in the past was an additional exclusion criterion in three studies (Kivi et al., 2014; Newby et al., 2013; Titov et al., 2015).

The studies differed in the level of suicidal ideation (different cut-off scores) that they would accept for inclusion of participants. For the studies that used clinical interviews, the respective cut-offs were unclear.

Information about intervention modules that specifically targeted suicidal thoughts or behaviors could not be found in any article or respective study protocol.

Eight trials reported support options for participants with suicidal



Fig. 1. Flow diagram for the recruitment of the sample of this study.

thoughts or an increased suicide risk. These included information about health services and emergency contact details, the advice to seek professional help or the referral to an online portal for suicide prevention. In one study, trained personnel were available within 24 h. In another study, a personal emergency plan was discussed during the initial telephone interview. One study used a standardized safety protocol for participants with suicidal ideation.

Expert interview and questionnaire. Thirteen researchers (comprising 54% of included trials) filled out the online questionnaire and eleven researchers took part in the subsequent interview. The researchers were from eight different countries: Germany, Australia, United States of America, England, Spain, Turkey, Sweden, and The Netherlands. All researchers worked in different labs and commented on different studies.

3.1. Assessment and monitoring of suicidal thoughts and behaviors

With regard to the time of measurement, all thirteen researchers reported that they assessed the risk of suicide before the beginning of the intervention. Additionally, nine researchers assessed suicide risk during the intervention.

The researchers used different instruments for assessing the risk of

suicide equivalent to the results of the literature review (Table 1). Using item nine of the PHQ-9 suicide item was seen as a pragmatic approach for assessing suicidality but insufficient if being used as a stand-alone measurement because it does not differentiate the wish to die from the intent of self-harm. A combination of PHQ-9, BDI, and a subsequent diagnostic interview was suggested by four researchers to be the most adequate, but – due to a lack of resources – this procedure was not always feasible.

3.2. Exclusion or inclusion of individuals at risk of suicide

Nine researchers had excluded individuals based on their level of suicide risk. A positive scoring on a self-report scale or in an interview and a prior suicide attempt were the most common exclusion criteria. Seven researchers reported that the final decision to exclude individuals was based on clinical judgment.

Of those researchers who had excluded individuals based on suicide risk, four reported they did not inform individuals of these criteria prior to participation. They believed that informing individuals about the suicide-related exclusion criteria might result in them withholding information and therefore preventing the research team from providing adequate help. In contrast, four other researchers stated that it is the

Table 1

Suicidality-specific modules, support for participants at risk of suicide and exclusion criteria regarding suicidality in research trials on internet interventions for depression.

Study	Level of human support	Exclusion criterion/instrument regarding suicidality	Support for participants at risk of suicide
Buntrock et al., 2015	Feedback after each module by trained and supervised	BDI suicide item >1	No information given
	graduate students and health care professionals		
Carlbring et al., 2013	About 15 min per week administration and feedback by clinical psychology MSc students	Suicidality was no exclusion criterion	No assessment of suicidality
Choi et al., 2012	Weekly telephone/email contact to clinical	Item nine of the PHQ-9 >1	Information about how to access other mental health services
Ebert et al., 2014	Weekly written feedback by psychologists and MSc psychology students	BDI suicide item >1	No information given
Geraedts et al., 2014	Weekly written feedback by MSc students in clinical psychology	Suicidality was no exclusion criterion	No information given
Gilbody et al., 2015	All participants were subject to usual GP care. Weekly phone calls by trained technicians	Actively suicidal, assessed by GP	Participants at risk were referred to the GP or designated psychiatrist/psychologist.
	for technical/motivational Support		
Hallgren et al., 2015	Initial call, contact on demand to and weekly monitoring by a psychologist	Suicidality was no exclusion criterion	Individuals could receive additional help
Imamura et al., 2014	Email reminders	Suicidality was no exclusion criterion	Free e-mail address and phone number of a clinical psychologist that participants could contact
Johansson et al., 2012a Johansson et al., 2012b	Continuous online support from MS. students in clinical psychology Continuous email support from MSc-level clinical psychologist students	Own assessment of suicidal ideation → exclusion, cut-off not specified MADRS-S suicide item >4	Possibility for therapists to consult psychiatrist if suicidal ideation was expressed No information given
Kenter et al., 2016	Brief weekly emails by a masters-level students	Assessed and excluded, not specified	No information given
Kivi et al., 2014	Email/telephone call by licensed psychologists or licensed psychotherapists	Previous suicide attempt, or MADRS- $S > 3$, MINI Part B – Suicide > 9	No information given
Kleiboer et al., 2015	Email support by MSc students: Intervention group 1: no support Intervention group 2: support on request Intervention group 3: weekly support	Reported active suicidal plans (\geq 3) based on a 4- item self-report screening questionnaire (SQ) by Gega et al. (2005)	Excluded participants with suicidal plans were advised to contact their GP
Klein et al., 2016	In case initial PHQ-9 score between 10 and 14: Continuous contact option and weekly feedback through email by psychotherapists in training or MSc students in clinical psychology	Acute suicidality assessed clinically based on a structured assessment of current suicidal ideation and past suicide attempts	Encouragement to seek professional help. Advice on how to receive professional help in case of a suicidal crisis and development of a crisis plan which included an address of a local psychotherapist, psychiatrist, general practitioner or hospital they could contact in case of an acute crisis. Email hotline was available every weekday in case
Meyer et al., 2015	Unsupported	MINI via telephone	Personalized crisis plan were developed during telephone interview
Mira et al., 2017	Intervention group 1: no human support Intervention group 2: brief weekly support phone call without clinical content by clinical psychologists	MINI via telephone (presence of suicidal ideation or plan)	No information given
Moritz et al., 2012	Unsupported	Suicidality was no exclusion criterion but participants with acute suicidal ideas were discouraged from participation, based on Suicide Behaviours Questionnaire-Revised (SBO-R)	Automatically displayed telephone numbers and contact addresses from institutions specialized in the treatment of suicidal ideation
Newby et al., 2013	Regular contact to clinician or therapist up to session 2. Afterwards contact on demand and in case of symptom deterioration	Online screening questionnaire (Suicidal ideation/ history of suicidality), MINI (suicidal or recent self- harm)	Telephone contact to clinician or therapist
Nobis et al., 2015	Graduate students or psychologists provided weekly feedback by email. Phone call in cose of inoctivity	SCID-I via telephone, attached suicide protocol, BDI suicide item >1	Email with the advice to seek professional help and detailed information on available services.
Phillips et al., 2014	Weekly telephone calls.	Suicidality was no exclusion criterion	Weekly screening by telephone. Safety protocol for
Sheeber et al., 2012	Regular feedback and weekly telephone calls by a "coach"	Suicidality was no exclusion criterion	Online crisis link, which alerted coaches and supervisors via an immediate text message.
Titov et al., 2015	Weekly telephone or email contact to a	PHQ-9 suicide item >2 or recent suicide attempt	No information given
Ünlü Ince et al., 2013	Weekly feedback email from the PI	BDI, MINI, cut-off not specified	Participants with a relatively high risk were advised to contact their GP or were referred to the online portal for suicide prevention (URL: http://www.
Williams et al., 2013	Unsupported	Suicidal ideation and history of suicidality assessed and excluded, not specified	113online.nl/) No information given

researchers' ethical obligation to fully inform individuals about all inclusion and exclusion criteria.

With regard to the benefits of inclusion, five researchers argued towards the strong association between suicidality and depression. Four researchers argued that given there is empirical evidence for the effectiveness of IBIs for individuals at risk of suicide, excluding these individuals is unethical. Furthermore, researchers argued that IBIs may be a treatment option for individuals who would not utilize face-to-face treatments. Hence, by excluding individuals at risk of suicide, researchers may prevent high-risk individuals from accessing treatment at all.

The researchers also mentioned some limitations to including individuals at risk of suicide. Six researchers claimed that IBIs cannot provide sufficient help for individuals in crisis. Possible direct iatrogenic effects of the intervention were not mentioned. However, one researcher argued that stand-alone IBIs would not provide sufficient care for individuals with higher levels of suicidality, and that such interventions should not be provided without an additional face-to-face treatment. Another concern about the inclusion of individuals experiencing suicidal thoughts was regarding studies where the participants were anonymous and the communication between researchers and individuals was asynchronous, which was believed to compromise the ability of researchers to monitor severe risk of suicide and provide help in a crisis.

All researchers who excluded individuals based on suicide risk reported that they were influenced by their ethics committee. Three researchers added an exclusion criterion concerning suicidality after the ethics committee rejected their initial application expressing concerns about the participants' safety. In other cases, researchers included suicide-related exclusion criteria in anticipation that they would otherwise not be granted ethical approval.

Other barriers to include individuals at risk of suicide in IBIs for depression were reported to be limited time and financial resources and a lack of experience in this field of research.

3.3. Safety procedures in case of suicidality

Ten researchers arranged procedures for responding to suicide risk. The level of comprehensiveness and detail in these protocols varied among the different research groups. While eight research teams followed a written step-by-step guideline (defined in a protocol), two research teams only verbally arranged their procedures.

Seven researchers collected contact details of their participants before randomization. The most common information collected was the telephone number of the participant or their general practitioner. In three studies, the researchers requested the current address or postcode of their participants.

All of the interviewed researchers offered some form of support to individuals at risk of suicide. Two different types of support could be identified. Direct support, provided by the research team itself, included a phone call with a member of the research team and one research group provided an extra module in the intervention designed specifically for individuals experiencing suicidal thoughts. Indirect support included written referral to external services (e.g. out- or inpatient settings, GP) and the provision of information material about where to seek help in a crisis (e.g. crisis hotline). Different forms of indirect support were most common and eight out of the thirteen studies did not provide any form of direct support.

3.4. Role of human support

Twelve researchers evaluated interventions that included an element of human support, which ranged from e-mail feedback to weekly telephone calls provided by members of the research team. Nine of the interviewed researchers reported ethical concerns about including individuals at risk of suicide in research on interventions that did not have an element of human support, as it would make monitoring and the provision of support more difficult.

All researchers agreed that the providers of human support (e-coaches) should have a psychological or medical background. However, the qualifications of the e-coaches varied (from students with a bachelor's degree to trained psychotherapists or psychiatrists). All e-coaches received some form of training in providing human support in internet interventions. Two thirds of the interviewed researchers integrated specific training elements for the management of suicidality.

All researchers agreed on the importance of supervision of e-coaches in order to ensure adequate management of suicidality. The extent of supervision varied, ranging from one session every three months to daily sessions. On average, supervision was provided to the e-coaches every second week. All supervisors were trained psychologists.

4. Discussion

This paper presents a comprehensive overview of current practices concerning the management of suicidality in trials of IBIs for depression by employing multiple methods including a review of literature, an online survey and follow-up interviews. Our sample consisted of researchers from eight different countries and three continents, representative to a broad range of international perspectives.

The identified studies differed concerning frequency of assessments, inclusion and exclusion criteria, safety procedures, and the qualifications of personnel providing support to participants.

Most studies either used single items of self-report scales like the PHQ-9 (Kroenke et al., 2001) or structured interviews like the MINI (Sheehan et al., 1998) to assess suicidal risk before randomization. Seventeen out of 24 reviewed studies excluded individuals based on the results of these instruments.

We identified several reasons for the exclusion of individuals at risk of suicide. Firstly, researchers reported that they did not always have sufficient resources to provide adequate monitoring of, and response to, individuals experiencing suicidal thoughts. Researchers reported they would include individuals at risk of suicide more often if adequate management procedures could be guaranteed. Researchers believed that some degree of human support in the intervention would allow for better monitoring of suicide risk compared to studies with no human guidance or support. Secondly, researchers who had excluded individuals with suicide thoughts reported that the ethics committees had influenced their decision. Some researchers figured that ethics committees lack experience in the field of internet intervention research and therefore impose overly cautious requirements when it comes to the management of suicidality in these trials. However, obstacles to conducting trials with suicidal participants are a general issue for international review boards (Sisti and Joffe, 2018).

Safety procedures for responding to suicide risk detected at baseline or that emerged during the course of the trial varied. Eight of the thirteen interviewed researchers followed written step-by-step guidelines and about half collected the contact details of the individuals or their general practitioner. All researchers provided some sort of direct or indirect support to individuals with suicide thoughts. None of the studies from the literature but one expert from the interviews incorporated a specific module on suicidality for individuals at risk of suicide in their trials. This is surprising because many individuals with depression experience suicide thoughts, and there is some evidence suggesting that IBIs can reduce the risk of suicide if modules that specifically target suicidal thoughts are included (De Jaegere et al., 2019; van Spijker et al., 2018, 2014). Therefore, content that specifically targets suicide thoughts is recommended to be included in IBIs for depression.

Suicidal ideation is a fluctuating phenomenon and might not be present at the baseline assessment but emerge after inclusion. Moreover, suicidal ideation might, for different reasons, simply not be reported in the assessments. Hence, even with the highest barriers to

Table 2

Checklist for managing participants with suicidal ideation in internet-based interventions for depression.

General recommendations					
Α	Include content that specifically targets suicidal ideation in the intervention.				
В	Include a questionnaire that measures the participants' level of suicidal ideation.				
С	Offer the same help options to participants with suicidal ideation, irrespectively of their allocation to the intervention or the control group.				
D	Encourage participants with severe suicidal ideation to access other forms of treatment whilst participating in the trial.				
Ε	Give instructions on how to develop a crisis plan to participants with moderate to severe suicide thoughts or develop an individual crisis plan together with the participant.				
F	If the intervention includes human support, then provide supervision to those members of the team in order to maintain their wellbeing and to ensure high-quality support to the participants.				
G	Include in the training manuals and safety protocols information regarding the identification and management procedures for individuals with different levels of suicidal ideation, including referral options and steps to take in an emergency.				
Rec	Recommendations for non-anonymous trials				
ц	Obtain the context information of participants and/or their CBs				

H Obtain the contact information of participants and/or their GPs.

inclusion, research on individuals with depression will most likely include some participants that experience some degree of suicidal ideation during the study period. While researching new forms of treatment such as IBIs always provides the opportunity to find better ways to help people in need, it also holds a potential risk of participation as well as the risk that individuals will not receive a potentially beneficial, already standardized treatment (Mishara and Weisstub, 2005). We therefore also recommend that studies that include participants with severe suicide thoughts encourage them to seek other forms or help while participating in the study. We believe that it is most important to the field of IBIs to expand the assessment and reporting of suicidal ideation and to establish a stronger degree of transparency regarding suicidality. This will help to bring us closer to defining evidence-based recommendations on which interventions work best for participants with suicidal ideation and how best to manage suicidal ideation in internet intervention trials. This would require the routinely inclusion of a specific measure of suicidal ideation (e.g. the Columbia-Suicide Severity Rating Scale (Posner et al., 2011) or the Beck Scale for Suicide Ideation (Beck et al., 1988) as a secondary outcome as recommended by the Lancet Psychiatry Commission (Holmes et al., 2018).

Some limitations need to be considered. First, our sample fully consists of researchers that are active in the field of IBIs. They might have a biased attitude towards treatment via the internet and the research field would benefit if the opinions of ethics committee board members, patients who used the interventions or policy stakeholders were also investigated. Second, our sample was over-represented by researchers who were examining interventions with an element of human support (e.g. written feedback), although an equal number of researchers who had examined interventions with no human support was invited to participate in this investigation. While guided IBI's can also rely on the regular communication between the participants and researcher to detect a high risk of suicide, unguided interventions are more dependent on assessments of suicide risk. The primary inclusion of researchers that have examined human support interventions reduces the representativeness of our sample and lead to a potential bias of our results regarding the role of human support on the management of suicidality. Lastly, in only 13 (54%) of the included studies an interview could be conducted with one of the authors, which might bias the results.

5. Conclusion

In conclusion, to the best of our knowledge, this is the first study to examine procedures to manage suicidality in research trials on IBIs for depression. The results show that the management procedures for participants with suicidal thoughts differ between studies and that the majority of studies exclude participants at risk of suicide. To exclude participants with suicide thoughts in IBI trials will limit the studies' external validity (Sisti and Joffe, 2018). However, concerns for the participants' safety, limited time and financial resources, a lack of experience of working with individuals with suicide thoughts together with concerns from ethical committees are also valid arguments as to why many researchers within the IBIs depression field have been hesitant to include participants with suicidal thoughts. Their concerns follow many other researchers within the mental health intervention field, where it has been common practice to exclude participants with suicide thoughts (Fisher et al., 2002).

We have listed a set of recommendations to increase participants' safety in Table 2. These recommendations are based on the results of this study and the viewpoints from the researchers that participated. We hope that these recommendations can be the first step to the development of a structured guideline to inform researchers, ethics committees and clinicians.

CRediT authorship contribution statement

Lasse Sander: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing - original draft, Writing review & editing. Katharina Gerhardinger: Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. Eleanor Bailey: Methodology, Writing - review & editing. Jo Robinson: Methodology, Writing - review & editing. Jiaxi Lin: Data curation, Methodology, Writing - review & editing. Pim Cuijpers: Data curation, Supervision, Writing - review & editing. Charlotte Mühlmann: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing - original draft, Writing review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

Acknowledgments

The article processing charge was funded by the German Research Foundation (DFG) and the University of Freiburg in the funding program Open Access Publishing.

References

- American Association of Suicidology, 2014. Depression and suicide risk [WWW Document]. URLhttps://www.suicidology.org/portals/14/docs/resources/ factsheets/2011/depressionsuicide2014.pdf (accessed 4.12.19).
- American Psychiatric Association, 2003. Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am. J. Psychiatry 160, 1–60.
- Barak, A., Klein, B., Proudfoot, J.G., 2009. Defining internet-supported therapeutic interventions. Ann. Behav. Med. 38, 4–17. https://doi.org/10.1007/s12160-009-9130-7.
- Baumeister, H., Reichler, L., Munzinger, M., Lin, J., 2014. The impact of guidance on internet-based mental health interventions - a systematic review. Internet Interv 1, 205–215. https://doi.org/10.1016/j.invent.2014.08.003.

Beck, A.T., Steer, R.A., Ranieri, W.F., 1988. Scale for suicide ideation: psychometric properties of a self-report version. J. Clin. Psychol. 44, 499–505.

- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571. https://doi.org/10.1001/ archpsyc.1961.01710120031004.
- Buntrock, C., Ebert, D., Lehr, D., Riper, H., Smit, F., Cuijpers, P., Berking, M., 2015. Effectiveness of a web-based cognitive behavioural intervention for subthreshold depression: pragmatic randomised controlled trial. Psychother. Psychosom. 84, 348–358. https://doi.org/10.1159/000438673.
- Carlbring, P., Hägglund, M., Luthström, A., Dahlin, M., Kadowaki, Å., Vernmark, K., Andersson, G., 2013. Internet-based behavioral activation and acceptance-based treatment for depression: a randomized controlled trial. J. Affect. Disord. 148, 331–337. https://doi.org/10.1016/j.jad.2012.12.020.
- Choi, I., Zou, J., Titov, N., Dear, B.F., Li, S., Johnston, L., Andrews, G., Hunt, C., 2012. Culturally attuned internet treatment for depression amongst Chinese Australians: a randomised controlled trial. J. Affect. Disord. 136, 459–468. https://doi.org/10. 1016/j.jad.2011.11.003.
- De Jaegere, E., van Landschoot, R., van Heeringen, K., van Spijker, B.A.J., Kerkhof, A.J.F.M., Mokkenstorm, J.K., Portzky, G., 2019. The online treatment of suicidal ideation: a randomised controlled trial of an unguided web-based intervention. Behav. Res. Ther. 119, 103406. https://doi.org/10.1016/J.BRAT.2019.05.003.
- DGPPN, 2015. S3-Leitlinie. Nationale Versorgungsleitlinie Unipolare Depression Langfassung. Ärztliches Zent. für Qual. der Medizin. https://doi.org/10.6101/AZQ/ 000266.
- Domhardt, M., Geßlein, H., von Rezori, R.E., Baumeister, H., 2019. Internet- and mobilebased interventions for anxiety disorders: a meta-analytic review of intervention components. Depress. Anxiety 36, 213–224. https://doi.org/10.1002/da.22860.
- Ebert, D.D., Lehr, D., Boß, L., Riper, H., Cuijpers, P., Andersson, G., Thiart, H., Heber, E., Berking, M., 2014. Efficacy of an internet-based problem-solving training for teachers: results of a randomized controlled trial. Scand. J. Work. Environ. Heal. 40, 582–596. https://doi.org/10.5271/sjweh.3449.
- Ebert, D.D., Van Daele, T., Nordgreen, T., Karekla, M., Compare, A., Zarbo, C., Brugnera, A., Øverland, S., Trebbi, G., Jensen, K.L., Kaehlke, F., Baumeister, H., 2018. Internetand mobile-mased psychological interventions: applications, efficacy, and potential for improving mental health. Eur. Psychol. 23, 167–187. https://doi.org/10.1027/ 1016-9040/a000318.
- Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J.L., Vos, T., Whiteford, H.A., 2013. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med 10, e1001547. https://doi.org/10.1371/journal.pmed.1001547.
- First, M., Williams, J., Karg, R., Spitzer, R., 2015. Structured Clinical Interview for DSM-5 - Research Version (SCID-5-RV). American Psychiatric Association, Arlington, VA. https://doi.org/10.1002/9781118625392.wbecp351.
- Fisher, C.B., Pearson, J.L., Kim, S., Reynolds, C.F., 2002. Ethical issues in including suicidal individuals in clinical research. IRB Ethics Hum. Res. 24, 9–14. https://doi.org/ 10.2307/3563804.
- Gega, L., Kenwright, M., Mataix-Cols, D., Cameron, R., Marks, I.M., 2005. Screening people with anxiety/depression for suitability for guided self-help. Cogn. Behav. Ther. 34, 16–21. https://doi.org/10.1080/16506070410015031.
- Geraedts, A.S., Kleiboer, A.M., Wiezer, N.M., van Mechelen, W., Cuijpers, P., 2014. Shortterm effects of a web-based guided self-help intervention for employees with depressive symptoms: randomized controlled trial. J. Med. Internet Res. 16, e121. https://doi.org/10.2196/jmir.3185.
- Gilbody, S., Littlewood, E., Hewitt, C., Brierley, G., Tharmanathan, P., Araya, R., Barkham, M., Bower, P., Cooper, C., Gask, L., Kessler, D., Lester, H., Lovell, K., Parry, G., Richards, D.A., Andersen, P., Brabyn, S., Knowles, S., Shepherd, C., Tallon, D., White, D., REEACT Team, 2015. Computerised cognitive behaviour therapy (CCBT) as treatment for depression in primary care (REEACT trial): large scale pragmatic randomised controlled trial. BMJ 351, h5627. https://doi.org/10.1136/bmj.h5627.
- Hallgren, M., Kraepelien, M., Öjehagen, A., Lindefors, N., Zeebari, Z., Kaldo, V., Forsell, Y., 2015. Physical exercise and internet-based cognitive-behavioural therapy in the treatment of depression: Randomised controlled trial. Br. J. Psychiatry 207, 227–234. https://doi.org/10.1192/bjp.bp.114.160101.
- Holmes, E.A., Ghaderi, A., Harmer, C.J., Ramchandani, P.G., Cuijpers, P., Morrison, A.P., Roiser, J.P., Bockting, C.L.H., O'Connor, R.C., Shafran, R., Moulds, M.L., Craske, M.G., 2018. The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. The Lancet Psychiatry 5, 237–286. https://doi.org/10.1016/ S2215-0366(17)30513-8.
- Hom, M.A., Podlogar, M.C., Stanley, I.H., Joiner, T.E., 2017. Ethical issues and practical challenges in suicide research: collaboration with institutional review boards. Crisis 38, 107–114. https://doi.org/10.1027/0227-5910/a000415.
- Imamura, K., Kawakami, N., Furukawa, T.A., Matsuyama, Y., Shimazu, A., Umanodan, R., Kawakami, S., Kasai, K., 2014. Effects of an Internet-based cognitive behavioral therapy (iCBT) program in Manga format on improving subthreshold depressive symptoms among healthy workers: a randomized controlled trial. PLoS One 9, e97167. https://doi.org/10.1371/journal.pone.0097167.
- Johansson, R., Ekbladh, S., Hebert, A., Lindström, M., Möller, S., Petitt, E., Poysti, S., Larsson, M.H., Rousseau, A., Carlbring, P., Cuijpers, P., Andersson, G., 2012a. Psychodynamic guided self-help for adult depression through the internet: a randomised controlled trial. PLoS One 7, e38021.
- Johansson, R., Sjöberg, E., Sjögren, M., Johnsson, E., Carlbring, P., Andersson, T., Rousseau, A., Andersson, G., 2012b. Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. PLoS One 7, e36905. https://doi.org/10.1371/journal.pone.0036905.
- Karyotaki, E., Ebert, D.D., Donkin, L., Riper, H., Twisk, J., Burger, S., Rozental, A., Lange, A., Williams, A.D., Zarski, A.C., Geraedts, A., van Straten, A., Kleiboer, A., Meyer, B., Ünlü Ince, B.B., Buntrock, C., Lehr, D., Snoek, F.J., Andrews, G., Andersson, G., Choi, I., Ruwaard, J., Klein, J.P., Newby, J.M., Schröder, J., Laferton, J.A.C., Van Bastelaar,

K., Imamura, K., Vernmark, K., Boß, L., Sheeber, L.B., Kivi, M., Berking, M., Titov, N., Carlbring, P., Johansson, R., Kenter, R., Perini, S., Moritz, S., Nobis, S., Berger, T., Kaldo, V., Forsell, Y., Lindefors, N., Kraepelien, M., Björkelund, C., Kawakami, N., Cuijpers, P., 2018. Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. Clin. Psychol. Rev. 63, 80–92. https://doi.org/10.1016/j.cpr.2018.06.007.

- Karyotaki, E., Riper, H., Twisk, J., Hoogendoorn, A., Kleiboer, A., Mira, A., Mackinnon, A., Meyer, B., Botella, C., Littlewood, E., Andersson, G., Christensen, H., Klein, J.P., Schröder, J., Bretón-López, J., Scheider, J., Griffiths, K., Farrer, L., Huibers, M.J.H., Phillips, R., Gilbody, S., Moritz, S., Berger, T., Pop, V., Spek, V., Cuijpers, P., 2017. Efficacy of self-guided internet-based cognitive behavioral therapy in the treatment of depressive symptoms: a meta-analysis of individual participant data. JAMA Psychiatry 74, 351–359. https://doi.org/10.1001/JAMAPSYCHIATRY.2017.0044.
- Kenter, R.M.F., Cuijpers, P., Beekman, A., Van Straten, A., Kenter, R.M.F., Cuijpers, P., Beekman, A., Van Straten, A., Maria, R., Kenter, F., Cuijpers, P., Beekman, A., Van Straten, A., Kenter, R.M.F., Cuijpers, P., Beekman, A., Van Straten, A., 2016. Effectiveness of a web-based guided self-help intervention for outpatients with a sepressive sisorder: Short-term results from a randomized controlled trial. J. Med. Internet Res. 18, e80. https://doi.org/10.2196/jmir.4861.
- Kivi, M., Eriksson, M.C.M., Hange, D., Petersson, E.L., Vernmark, K., Johansson, B., Björkelund, C., 2014. Internet-based therapy for mild to moderate depression in swedish primary care: Short term results from the PRIM-NET randomized controlled trial. Cogn. Behav. Ther. 43, 289–298. https://doi.org/10.1080/16506073.2014. 921834.
- Kleiboer, A., Donker, T., Seekles, W., van Straten, A., Riper, H., Cuijpers, P., 2015. A randomized controlled trial on the role of support in Internet-based problem solving therapy for depression and anxiety. Behav. Res. Ther. 72, 63–71. https://doi.org/10. 1016/J.BRAT.2015.06.013.
- Klein, J.P., Berger, T., Schröder, J., Späth, C., Meyer, B.B., Caspar, F., Lutz, W., Arndt, A., Greiner, W., Gräfe, V., Hautzinger, M., Fuhr, K., Rose, M., Nolte, S., Löwe, B., Anderssoni, G., Vettorazzi, E., Moritz, S., Hohagen, F., Schr'der, J., Sy'h, C., Meyer, B.B., Caspar, F., Lutz, W., Arndt, A., Greiner, W., Gr'fe, V., Hautzinger, M., Fuhr, K., Rose, M., Nolte, S., L'we, B., Andersson, G., Vettorazzi, E., Moritz, S., Hohagen, F., 2016. Effects of a psychological internet intervention in the treatment of mild to moderate depressive symptoms: results of the EVIDENT study, a randomized controlled trial. Psychother. Psychosom. 85, 218–228. https://doi.org/10.1159/ 000445355.
- Königbauer, J., Letsch, J., Doebler, P., Ebert, D., Baumeister, H., 2017. Internet- and mobile-based depression interventions for people with diagnosed depression: A systematic review and meta-analysis. J. Affect. Disord. 223, 28–40. https://doi.org/10. 1016/j.jad.2017.07.021.
- Kroenke, K, Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16, 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
- Lakeman, R., FitzGerald, M., 2009. The ethics of suicide research. Crisis 30, 13–19. https://doi.org/10.1027/0227-5910.30.1.13.
- Meuser, M., Nagel, U., 2009. The expert interview and changes in knowledge production. In: Bogner, A., Littig, B., Menz, W. (Eds.), Research Methods Series: Interviewing Experts. Palgrave Macmillan, UK, London.
- Meyer, B., Bierbrodt, J., Schröder, J., Berger, T., Beevers, C.G., Weiss, M., Jacob, G., Späth, C., Andersson, G., Lutz, W., Hautzinger, M., Löwe, B., Rose, M., Hohagen, F., Caspar, F., Greiner, W., Moritz, S., Klein, J.P., Schroder, J., Berger, T., Beevers, C.G., Weiss, M., Jacob, G., Spath, C., Andersson, G., Lutz, W., Hautzinger, M., Lowe, B., Rose, M., Hohagen, F., Caspar, F., Greiner, W., Moritz, S., Klein, J.P., 2015. Effects of an Internet intervention (Deprexis) on severe depression symptoms: Randomized controlled trial. Internet Interv 2, 48–59. https://doi.org/10.1016/j.invent.2014.12. 003.
- Mira, A., Bretón-López, J., García-Palacios, A., Quero, S., Baños, R.M., Botella, C., 2017. An Internet-based program for depressive symptoms using human and automated support: a randomized controlled trial. Neuropsychiatr. Dis. Treat. 13, 987–1006. https://doi.org/10.2147/NDT.S130994.
- Mishara, B.L., Weisstub, D.N., 2005. Ethical and legal issues in suicide research. Int. J. Law Psychiatry 28, 23–41. https://doi.org/10.1016/j.ijlp.2004.12.006.
- Moritz, S., Schilling, L., Hauschildt, M., Schröder, J., Treszl, A., 2012. A randomized controlled trial of internet-based therapy in depression. Behav. Res. Ther. 50, 513–521. https://doi.org/10.1016/j.brat.2012.04.006.
- National Institute for Health and Care (NICE), 2009. Depression in adults: recognition and management [WWW Document]. URLhttps://www.nice.org.uk/guidance/cg90 (accessed 11.1.18).
- Newby, J.M., Mackenzie, A., Williams, A.D., Mcintyre, K., Watts, S., Wong, N., Andrews, G., 2013. Internet cognitive behavioural therapy for mixed anxiety and depression: A randomized controlled trial and evidence of effectiveness in primary care. Psychol. Med. 43, 2635–2648. https://doi.org/10.1017/S0033291713000111.
- Nobis, S., Lehr, D., Ebert, D.D., Baumeister, H., Snoek, F., Riper, H., Berking, M., 2015. Efficacy of a web-based intervention with mobile phone support in treating depressive symptoms in adults with type 1 and type 2 diabetes: a randomized controlled trial. Diabetes Care 38, 776–783. https://doi.org/10.2337/dc14-1728.
- Oquendo, M.A., Stanley, B., Ellis, S.P., John Mann, J., 2004. Protection of human subjects in intervention research for suicidal behavior. Am J Psychiatry 161, 1558–1563.
- Pearson, J.L., Stanley, B., King, C.A., Fisher, C.B., 2001. Intervention research with persons at high risk for suicidality: safety and ethical considerations. J. Clin. Psychiatry 62 (Suppl 2), 17–26.
- Phillips, R., Schneider, J., Molosankwe, I., Leese, M., Foroushani, P.S., Grime, P., McCrone, P., Morriss, R., Thornicroft, G., 2014. Randomized controlled trial of computerized cognitive behavioural therapy for depressive symptoms: effectiveness and costs of a workplace intervention. Psychol. Med. 44, 741–752. https://doi.org/

L. Sander, et al.

10.1017/S0033291713001323.

- Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K. V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The columbia-suicide severity rating scale: initial validity and internal consistency findings from three multistic studies with adolescents and adults168, 1266–1277. https://doi.org/10. 1176/appi.ajp.2011.10111704.
- Raison, C.L., Woolwine, B.J., Demetrashvili, M.F., Borisov, A.S., Weinreib, R., Staab, J.P., Zajecka, J.M., Bruno, C.J., Henderson, M.A., Reinus, J.F., Evans, D.L., Asnis, G.M., Miller, A.H., 2007. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. Aliment. Pharmacol. Ther. 25, 1163–1174. https://doi.org/10.1111/j.1365-2036.2007.03316.x.
- Sander, L., Rausch, L., Baumeister, H., 2016. Effectiveness of internet-based interventions for the prevention of mental disorders: a systematic review. JMIR Ment. Heal. 3, e38. https://doi.org/10.2196/mental.6061.
- Sheeber, L.B., Seeley, J.R., Feil, E.G., Davis, B., Sorensen, E., Kosty, D.B., Lewinsohn, P.M., 2012. Development and pilot evaluation of an Internet-facilitated cognitive-behavioral intervention for maternal depression. J. Consult. Clin. Psychol. 80, 739–749. https://doi.org/10.1037/a0028820.
- Sheehan, D.V, Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59, 22–33.
- Silverman, M.M., 2006. The Language of Suicidology. Suicide Life-Threatening Behav. 36, 519–532. https://doi.org/10.1521/suli.2006.36.5.519.
- Sisti, D.A., Joffe, S., 2018. Implications of zero suicide for suicide prevention research. JAMA - J. Am. Med. Assoc. 320, 1633–1634. https://doi.org/10.1001/jama.2018. 13083.

Titov, N., Dear, B.F., Ali, S., Zou, J.B., Lorian, C.N., Johnston, L., Terides, M.D., Kayrouz,

R., Klein, B., Gandy, M., Fogliati, V.J., 2015. Clinical and cost-effectiveness of therapist-guided internet-delivered cognitive behavior therapy for older adults with symptoms of depression: a randomized controlled trial. Behav. Ther. 46, 193–205. https://doi.org/10.1016/j.beth.2014.09.008.

- Ünlü Ince, B., Cuijpers, P., Van'T Hof, E., Van Ballegooijen, W., Christensen, H., Riper, H., Ince, B., Cuijpers, P., van 't Hof, E., Van Ballegooijen, W., Christensen, H., Riper, H., 2013. Internet-based, culturally sensitive, problem-solving therapy for Turkish migrants with depression: randomized controlled trial. J. Med. Internet Res. 15, 248–262. https://doi.org/10.2196/jmir.2853.
- van Spijker, B.A.J., van Straten, A., Kerkhof, A.J.F.M., 2014. Effectiveness of online selfhelp for suicidal thoughts: Results of a randomised controlled trial. PLoS One 9, e90118. https://doi.org/10.1371/journal.pone.0090118.
- van Spijker, B.A.J., Werner-Seidler, A., Batterham, P.J., Mackinnon, A., Calear, A.L., Gosling, J.A., Reynolds, J., Kerkhof, A.J.F.M., Solomon, D., Shand, F., Christensen, H., 2018. Effectiveness of a web-based self-help program for suicidal thinking in an australian community sample: Randomized controlled trial. J. Med. Internet Res. 20, e15. https://doi.org/10.2196/jmir.8595.
- Wicks, P., Stamford, J., Grootenhuis, M.A., Haverman, L., Ahmed, S., 2014. Innovations in e-health. Qual. Life Res. 23, 195–203. https://doi.org/10.1007/s11136-013-0458-x.
- Williams, A.D., Blackwell, S.E., Mackenzie, A., Holmes, E.A., Andrews, G., 2013. Combining imagination and reason in the treatment of depression: A randomized controlled trial of internet-based cognitive-bias modification and internet-CBT for depression. J. Consult. Clin. Psychol. 81, 793. https://doi.org/10.1037/a0033247.
- Zimmerman, M., Chelminski, I., Posternak, M.A., 2005. Generalizability of antidepressant efficacy trials: Differences between depressed psychiatric outpatients who would or would not qualify for an efficacy trial. Am. J. Psychiatry 162, 1370–1372. https:// doi.org/10.1176/appi.ajp.162.7.1370.