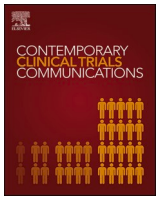
Contemporary Clinical Trials Communications 36 (2023) 101218

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

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



Monitoring and responding to signals of suicidal ideation in pragmatic clinical trials: Lessons from the GRACE trial for Chronic Sickle Cell Disease Pain

Eric S. Swirsky [a,*], Andrew D. Boyd [a], Carol Gu [a], Larisa A. Burke [a], Ardith Z. Doorenbos [a], Miriam O. Ezenwa [b], Mitchell R. Knisely [c], Jonathan W. Leigh [a], Hongjin Li [a], Molly W. Mandernach [b], Robert E. Molokie [a], Crystal L. Patil [a], Alana D. Steffen [a], Nirmish Shah [c], Victoria A. deMartelly [a], Karen L. Staman [d], Judith M. Schlaeger [a]

[a] University of Illinois Chicago, Chicago, IL, USA
[b] University of Florida, Gainesville, FL, USA
[c] Duke University, Durham, NC, USA
[d] Duke Clinical Research Institute, Durham, NC, USA

ARTICLE INFO

Keywords:
Depression
Patient-reported outcomes
Research ethics
Suicidal ideation
Suicidal monitoring
Pragmatic trial

ABSTRACT

Sickle cell disease (SCD) is a hemoglobin disorder and the most common genetic disorder that affects 100,000 Americans and millions worldwide. Adults living with SCD have pain so severe that it often requires opioids to keep it in control. Depression is a major global public health concern associated with an increased risk in chronic medical disorders, including in adults living with sickle cell disease (SCD). A strong relationship exists between suicidal ideation, suicide attempts, and depression. Researchers enrolling adults living with SCD in pragmatic clinical trials are obligated to design their methods to deliberately monitor and respond to symptoms related to depression and suicidal ideation. This will offer increased protection for their participants and help clinical investigators meet their fiduciary duties. This article presents a review of this sociotechnical milieu that highlights, analyzes, and offers recommendations to address ethical considerations in the development of protocols, procedures, and monitoring activities related to suicidality in depressed patients in a pragmatic clinical trial.

Key message

Suicidality should be monitored in pragmatic clinical trials that measure depression as an outcome. Free and remotely accessible digital resources are available for participants who struggle with suicidal ideation to decrease risk of harm. Prompt response to this condition is critical for participants to engage in treatment and for investigators to conduct research ethically.

1. Introduction

Sickle cell disease (SCD) is a chronic condition and the most lethal genetic blood disorder in the world [1]. Approximately 300 million people live with SCD globally, and 100,000 individuals of mainly Black or African American (86%) and Latino (8%) backgrounds have SCD in the United States [1,2]. Depression is the leading cause for suicidal self-directed violence and death by suicide [3], and a strong relationship exists between suicidal ideation, suicide attempts, and depression [4]. The prevalence of depression in patients with SCD is contested; however, evidence suggests that mild to severe depression is present in 24–30% of adults with SCD [5–8]. Among Black or African American people living with SCD, 29% indicated a previous episode of suicidal ideation and 8% have attempted suicide in their lifetime [9].

Our team is conducting a National Institutes of Health (NIH) HEAL (Helping to End Addiction Long Term) Initiative pragmatic trial evaluating the effects of guided relaxation and acupuncture for chronic SCD pain [10]. The Hybrid Effectiveness-implementation Trial of Guided Relaxation and Acupuncture for Chronic Sickle Cell Disease Pain (GRACE Trial) is one of the 27 Demonstration Projects that are part of the NIH Pragmatic Trials Collaboratory, the resource coordinating

* Corresponding author. University of Illinois Chicago, College of Applied Health Sciences, 1919 W. Taylor St. M/C 530, Chicago, IL, 60612, USA.
E-mail address: eswir@uic.edu (E.S. Swirsky).

https://doi.org/10.1016/j.conctc.2023.101218
Received 10 July 2023; Received in revised form 11 September 2023; Accepted 1 October 2023
Available online 5 October 2023

center for the Pragmatic and Implementation Studies for the Management of Pain (PRISM) to Reduce Opioid Prescribing Program that is part of the HEAL Initiative. The Demonstration Projects are pragmatic clinical trials (PCTs) that are embedded in healthcare systems and address problems of major public health significance. PCTs measure effectiveness (how well the intervention performs in the real-world), produce generalizable findings that can be applied routinely in clinical settings, and use typical patients and clinicians who may or may not be researchers. To this end, GRACE Trial methods include the electronic collection of patient-reported outcomes data, including data on pain, depression, and suicide. However, given that we, as researchers, are collecting data on potentially actionable mental health issues, we needed to: 1. *understand our responsibility to act*, 2. *define triggers for action*, 3. *examine responsibilities for action* [11], 4. *protect patient autonomy and privacy,* 5. *identify indirect and collateral participants,* 6. *mitigate the risk of bias,* and 7. *manage sociotechnical considerations of integrating research data into clinical practice.* The purpose of this article is to use GRACE as a case study to review and analyze the ethical considerations in the development of protocols, procedures, and monitoring activities related to suicidality in depressed patients.

1.1. GRACE trial setting

The GRACE Trial is in its implementation phase, where 336 adults with sickle cell disease and chronic pain will be retained at three healthcare systems: University of Illinois Hospital & Health Sciences System (UI Health), University of Florida Health (UF Health), and Duke University Health System (Duke). The GRACE Trial's primary aim is to determine the effectiveness of guided relaxation and acupuncture as compared to usual care on several patient-reported outcomes (PROs). The primary outcome is pain impact (composite measure of pain intensity, pain interference, and function) as measured by the PROMIS Pain Impact Scale. Secondary outcomes include: Pain, Enjoyment of Life, and General Activity (PEG); Global Satisfaction with Treatment (PGIC); sleep disturbance, fatigue, and constipation (PROMIS Sleep Disturbance, Fatigue, and Constipation); pain catastrophizing (Pain Catastrophizing); Substance Use (Taps 1); self-reported opioid use; other non-pharmacologic treatments; anxiety (GAD-7); and depression and suicidality (PHQ-9). Severe depression symptoms such as suicidal ideation will be assessed in patients using the PHQ-9. The PHQ-9 is a validated, self-report instrument used to score depression severity by inquiring about the presence and severity of depression, passive thoughts of death, and active ideas of self-harm [12]. The PHQ-9 is part of the HEAL Initiative Common Data Element (CDE) Program. All HEAL clinical pain studies are required to use the HEAL CDEs [13]. To decrease the burden on GRACE research participants, PROs are being collected remotely in REDCap via survey-embedded text messages [14,15]. Additionally, the study is collecting and analyzing population data at multiple timepoints for suicidal ideation to improve understanding of the risk of suicide for an individual at a given moment in time.

1.2. Defining issues and ethical analysis

1. Understanding our responsibility to act

Suicidality should be monitored in clinical trials that measure depression as a research outcome. By not monitoring suicidality, researchers may overlook an important unknown that has clinical and ethical implications. Free and remotely accessible digital resources are available for research participants that struggle with suicidal ideation. A prompt response is critical for risk mitigation and for clinical investigators with fiduciary duties as caregivers and researchers. Since the lifetime prevalence of depression in SCD is 24%–30%, monitoring and responding to participants with suicidal ideation offers an additional opportunity to ameliorate severe depressive symptoms [1,5].

Since this PCT aims to embed interventions for SCD patients with a high burden of chronic pain, and we are assessing depression and risk of suicidal ideation, there is an obligation to intervene with crisis interventions and mental health services when such duties arise [15] however, because data are collected remotely from participants who may be at higher risk for suicidal self-directed violence and death by suicide, we need to remotely monitor the responses. Therefore, we discussed remote monitoring with the NIH Pragmatic Trials Collaboratory Ethics Core for feedback and recommendations [11]. Since all GRACE Trial performance sites are part of the NIH "All of Us" Research Program [16] and are using the PHQ-9 instrument remotely, IRB-approved procedures were established for participants to be asked question 9 on suicidal ideation remotely. Also, the GRACE Trial team was informed that past studies have remotely screened participants for depression and suicidal ideation with the PHQ-9 through smartphones (over 10,000 people studied with the apps 'Health Monitor', 'Depression Monitor' and 'Mindful Moods') with no adverse events reported [17–19]. Therefore, the GRACE Team made a decision to remotely monitor, as follows: 1) when participants complete question 9 on suicidal ideation, (several days, more than half days, or nearly every day) a message pops up, for those who score 1, 2, or 3 points, that will direct them to the National Suicide Prevention Lifeline and Crisis Text Line (Fig. 1), but not if they score zero (not at all). We plan to monitor and summarize the occurrence of suicidal ideation and the digital delivery of crisis resources as well as other follow-up activities including any possible adverse events over the duration of the trial and will include these findings in a main effects article.

2. Determine triggers for action

There is evidence that a positive response to the PHQ-9 item 9 is predictive of risks of suicide attempts or deaths; however, only a small percentage of these patients may attempt or complete the act [20]. For example, Simon et al. [20] reported an increased cumulative risk of suicide death over a one-year period from .03% to 0.3% among patients reporting suicidal thoughts "nearly every day"; however, like many studies in this area, data specific to Black or African American and Latino populations was not reported. Coleman et al. reported evidence supporting use of the PHQ-9 as an indicator of suicide risk in racial and ethnic minority patients up to 90 days after suicidal ideation [21], but predictive ability 90 days after administration of most instruments is generally limited when applying standard regression analysis approaches [22]. Given historical disparities in access to health services and research, the generalizability of existing datasets to the population of interest in the GRACE Trial is unclear.

Like the GRACE Trial, other studies have addressed suicide risk management in remotely delivered behavioral studies [23,24] and developed triggers as catalysts for action. Belnap et al. [24] described an electronic, telephone-based suicide risk management protocol (SRMP) that offered comprehensive guidance to research personnel, enabling them to effectively triage clinical trial participants who may be at risk of self-harm. A clearly defined protocol for risk management is essential, not only for explanatory trials with dedicated research staff, but also for pragmatic trials where research is conducted as part of every-day care—including GRACE that uses REDCap for data collection and other trials conducted within the NIH Pragmatic Trials Collaboratory. We defined the trigger for action to be *those who score 1, 2, or 3 points on question 9 of the PHQ-9.*

3. Examine responsibilities for action

The intersection of clinical research and mental health can raise ethical quandaries regarding boundaries, duties, and the role of investigators and primary care clinicians working with populations at risk for suicide. Inclusion of health information technology (HIT) in research can interfere with equipoise and further blur the lines of ethical responsibility. Other NIH Collaboratory sponsored trials have

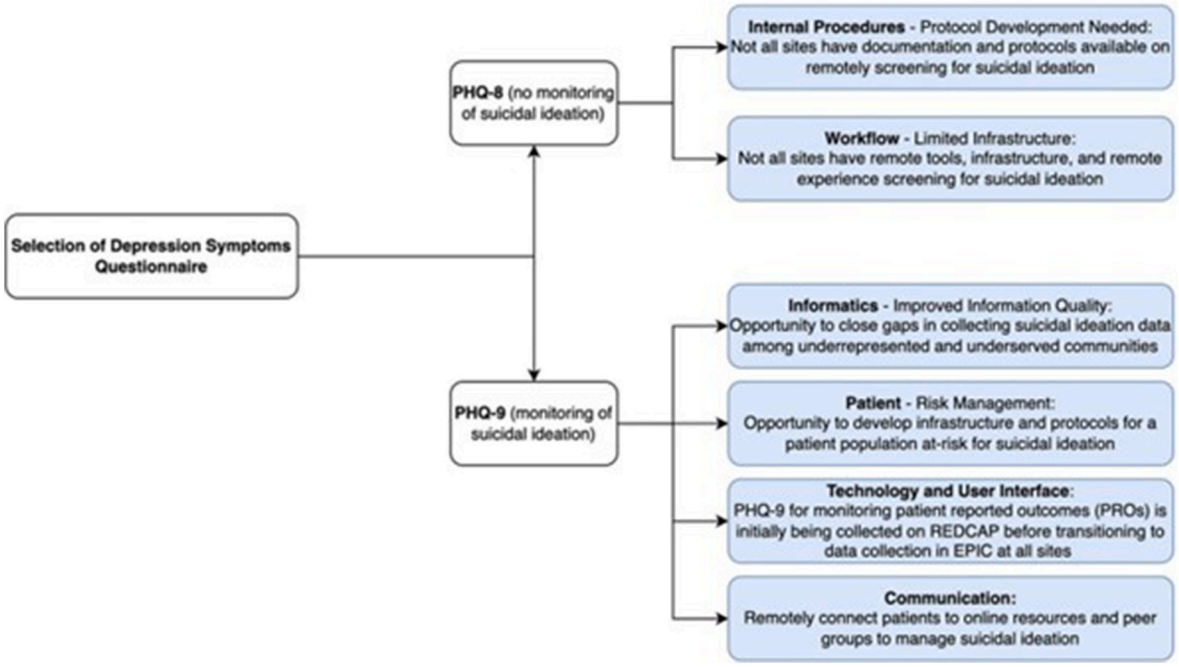


Fig. 1. Overview of socio-technical considerations for monitoring of suicidal ideation with the PHQ-9.

disseminated empiric observations of suicidal patient monitoring that may inform work in this area. The Suicide Prevention Outreach Trial (SPOT) studied the comparative effectiveness of two clinical interventions delivered primarily online to a largely non-Hispanic White study sample and observed no significant reduction in incidents of, and in some cases an increased risk of, self-harm when compared to usual care, suggesting that some interventions differ when delivered digitally rather than through traditional delivery methods [25]. Other investigations have employed rigorous telephonic monitoring of the PHQ-9 item 9 responses by study clinicians with varying evidence of effectiveness [26,27] and which raise questions regarding pragmatism of follow-up methods in PCTs designed to reflect real-life routine practice. There is evidence suggesting that among racial minorities, symptoms of depression are more frequently reported to family doctors than to mental health professionals [28,29]. Moreover, due to systematic racism, poor cultural competency, and underrepresentation in health research, interventions may require deliberately tailored and targeted methods for successful engagement of minority populations [30,31].

To address the needs of the GRACE Trial, the NIH Pragmatic Trials Collaboratory Ethics Core recommended that any participant indicating symptoms of suicidal ideation immediately be given information regarding an over-the-phone connection to the National Suicide Prevention Lifeline and text-based support from the Crisis Text Line (Fig. 2). In the GRACE Trial, when a signal of suicide ideation is detected, REDCap immediately digitally delivers the National Suicide Prevention Lifeline and text-based support from the Crisis Text Line to the participant. The protocol also calls for implementation of this sensitive PRO into the patient's medical record for review by primary care physicians. Successful implementation of electronic PROs into clinical practice requires a nuanced approach to meet a diversity of stakeholder needs, interests, and values throughout the sociotechnical system [24,32], discussed in section 7 below. For the duration of GRACE Trial, study team members will encourage patients to seek treatment of co-existing depression and/or anxiety, if indicated, and will inform the primary care providers and other relevant clinicians about any mental health symptoms, such as depression and anxiety, discovered during study assessments and will develop a collaborative plan, maximizing safety and efficacy of any prescribed medications.

4. Protect patient autonomy and privacy

The stigma surrounding depressive symptoms can prevent patients from openly seeking help and accessing treatment; transitioning to computerized questionnaires, which are nonreactive and nonjudgmental, can help combat this stigma [33]. Computerized questionnaires have lower rates of missing data and higher acceptability rates when compared to paper-questionnaires; however, since the PHQ-9 is only a quantitative assessment and does not provide a formal diagnosis of depression, this requires clinician input [34]. Supplementing the PHQ-9 with assessments by a qualified healthcare provider that seeks to understand the participant's perspectives can help personalize treatment when required, alleviate severe symptoms, and offer encouragement to seek help for their mental state [35].

The Common Rule guides researchers to protect populations through minimization of risk (nonmaleficence), maximizing benefits (beneficence), receiving voluntary informed consent prior to participation (autonomy), and the equitable distribution of benefits and risks (justice) [36]. The principle of autonomy obligates healthcare providers to respect decisions made by patients with capacity to make their own decisions. In a patient displaying suicidal ideation, autonomy conflicts with the principles of beneficence and non-maleficence. The tension between these principles is commonplace in healthcare as patients have the right to refuse care; however, autonomy may be impaired because a suicidal patient may not have capacity to act based on their values, preferences, and/or beliefs [36–38]. While ethics and law both recognize patient rights to confidentiality and self-determination, these rights are not absolute. This delicate balancing act creates numerous obligations for clinical investigators who decide if and when to act in response to a signal of behavioral or mental health distress. For example, some jurisdictions mandate that clinicians act to prevent a patient's suicide or imminent harm to third persons when their conduct involves a foreseeable zone of risk [38]. Ultimately, those involved in the clinical enterprise must consider their fiduciary responsibilities in managing patient safety, autonomy, and privacy along with their professional responsibility and clinical actionability of PRO data.

5. Identify indirect and collateral participants

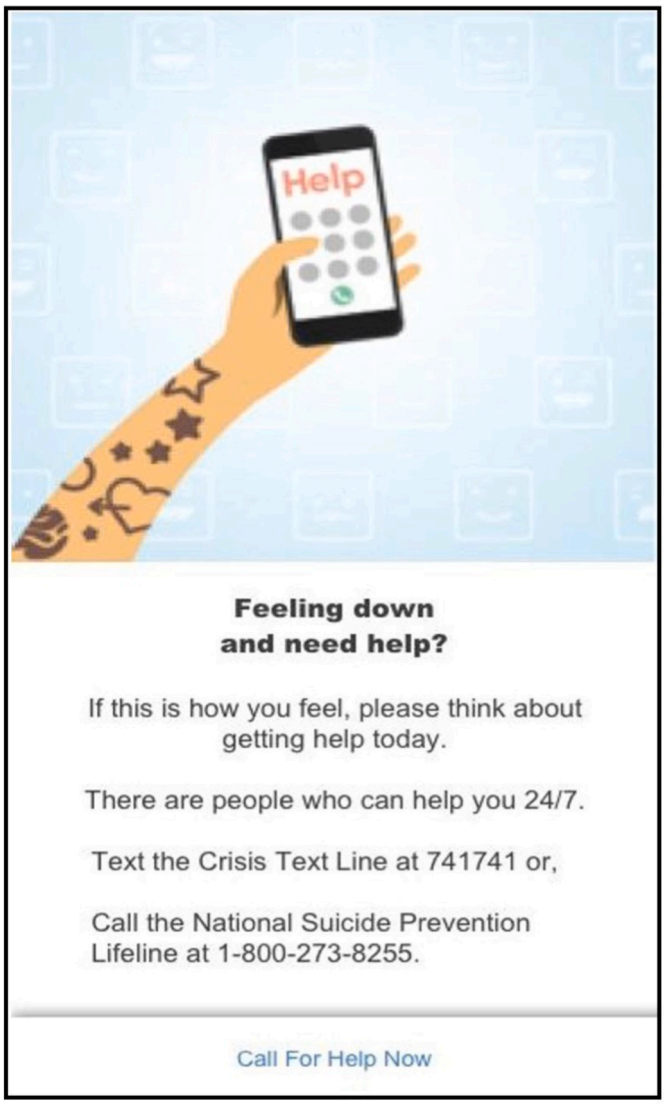


Fig. 2. National Suicide Prevention Lifeline and Crisis Text Line. Deaf and hard of hearing research participants can use the number 1-800-799-4889.

While IRBs are responsible for the protection of direct participants as described above, there are other affected stakeholders who should be considered. Indirect participants, for example, are those whose rights or welfare may be impacted by PCTs; in studies involving the use of PROs this could include clinical investigators, multidisciplinary care teams, clinical health informaticians, information technology (IT) professionals, regulatory and bioethics specialists, policymakers, and administrators [39]. The inclusion of indirect participants can mitigate barriers to implementation of PROs by convening stakeholders to address issues including multicomponent patient-centered pain management, system fragmentation, clinical integration of PROs, professional responsibilities, contractual obligations, training, reliable measurement, and maximizing utility of data for patient engagement and improved outcomes [40,41].

Additionally, PCTs may have a wider impact that affects other stakeholder communities, such as collateral participants [40]. Frameworks for incorporating collateral participant involvement into research and clinical care allow these individuals and institutions to act as drivers of change that contribute patient and community perspectives [42]. Identifying stakeholders who may be impacted by trial outcomes, such as patients, citizen scientists, community members, and organizations can contribute important public perspectives to the research process, including study design, cultural appropriateness, and relevance of outcome measures [39]. This approach promotes shared decision-making, fair representation, and development of future PCT methodologies [43–45]. Patient support networks such as families and primary care providers, could also be affected by the research, as there is a risk that a primary care physician will assume the researchers are managing behavioral and mental health risks. Thus, PCTs would be well-served to identify indirect and collateral participants engaging in discourse that incorporates patient and other stakeholder perspectives to broaden coordination in data collection, integration, and utilization.

For the GRACE Trial, our indirect and collateral participants are integral drivers of change. To inform our implementation blueprint [45], for our planning phase (UG3) we interviewed SCD patients, providers, and clinic staff to explore their perspectives on using guided relaxation and/or acupuncture for the management of chronic SCD pain. We learned that all were open to using these two CIH interventions that we are introducing into American healthcare for treating chronic SCD pain. Now in our implementation phase (UH3), we are conducting interviews of participants who completed the study interventions to explore facilitators, barriers, and solutions for integrating guided relaxation and acupuncture into the GRACE Trial's three healthcare systems [46].

6. Mitigate risk of bias

The NIH National Center for Complementary and Integrative Health (NCCIH) is partnering with the HEAL Initiative in co-leading strategies to reduce chronic pain in underrepresented minorities [47,48]. One of these approaches focuses on pragmatic trials that study CIH interventions with proven efficacy or effectiveness for integration into the American healthcare system [45], such as the GRACE Trial. Bias among healthcare providers regarding who is suitable to be recruited for a clinical trial contributes to disparities in health outcomes [49]. Offering patients with SCD enrollment in our pragmatic trial of two CIH interventions enables health equity research to be conducted. CIH therapies can then be implemented and integrated into the American healthcare system for the reduction of chronic pain in underrepresented minority populations, which is a crucial step in eliminating health disparities. Access barriers must also be overcome in the implementation of these CIH therapies into clinical practice, such as insurance coverage and costs, transportation, and limited information on CIH therapies [50,51].

Algorithms are often developed using datasets contributed by predominantly non-Hispanic White patients [50]; therefore, capturing symptoms of depression and suicidal ideations in Black and Hispanic communities is an important step to bridging the gap of missing data. The Fiscal Years 2023–2027 NIH-wide Strategic Plan for Diversity, Equity, and Inclusion (DEI) [51] intent is to make significant strides in collecting data from underrepresented and underserved individuals. Currently, there is little research on suicide risk due to the exclusion of individuals who are suicidal from these populations in most clinical studies [52]. In 2015, approximately 13.4% of randomized controlled trials in leading medical journals analyzed or reported outcomes by race or ethnicity [53]. Since participants in the GRACE Trial are predominantly Black and Hispanic, important opportunities, to collect more comprehensive mental health information and provide suicide prevention services to populations living with chronic SCD pain, present themselves.

Information gaps related to the depressive symptoms of ethnic and racial minorities may be reduced by monitoring suicidal ideation data collection. These disparities in mental healthcare can include gaps in not just access, treatment, and quality of care but also systemic bias that minimizes mental illness at the levels of the practice network, treatment organization, and community [54]. Additional data collection is a valuable step in the right direction to address this issue. While technology can help connect research participants struggling with suicidal

ideation to a crisis hotline or text line, the decision to reach out for help is ultimately up to the participant. The principle of autonomy indicates that patients have a right to refuse treatment if that is their choice; however, investigators may identify indirect and collateral participants to engage in discourse that incorporates patient perspectives and broadens coordination in data collection, integration, and utilization.

7. Manage sociotechnical considerations of integrating research data into clinical practice

Amid organizational cultures' workflows, information technologies, physical and technical infrastructures, processes, protocols, and regulations of each health system, several sociotechnical conditions emerged. Each of our three trial performance sites has a different infrastructure, experience with, and perspective on use of the PHQ instruments. Properly implemented and analyzed, PROs may serve as a basis for clinical decision-making; however, the lack of standardization for PRO implementation can lead to fragmentation of clinical interactions and data [55]. The Patient-Centered Outcomes Research Institute (PCORI) has promulgated integration recommendations, including ethicolegal system architecture, inclusion of PROs in clinical trials, and integrating PROs with EHRs; however, they are not consistently applied [56–58]. Additionally, issues of interoperability between EHR and stand-alone PRO systems must be addressed for successful implementation [41]. Assessing the challenges inherent with electronic PRO deployment requires an inclusive sociotechnical analysis that accounts for social systems, technical systems and infrastructures, and organizational environments, as depicted in Fig. 3 [59].

A fundamental concept in information ethics and law is that of fair representation, which includes how decision-makers make their activities known to others. Fair representation applies to the paradigm of informed consent and informs whether and how consent should be obtained in PCTs that leverage PROs and EHRs [60,61], and impacts study design such that PCTs are intended to yield actionable evidence through representative enrollment of direct participants and inclusion of indirect and collateral participants [40]. Investigators must consider how PROs will be represented within EHRs that structure information through fixed fields that can impede useability, and if data quality is influenced by response shifts or other biases [43,62]. Finally, fair representation of PROs and their contents requires precise, valid, and available reporting of trial outcomes; however, published studies regularly omit PRO-related hypotheses, data, or outcomes [63].

Sittig and Singh [64] offer a multi-dimensional framework to model interacting dimensions of complex HIT interventions that includes rules and regulations, policies and procedures, personnel, clinical workflows and communication, human-computer interaction, clinical content, hardware and software infrastructure, and measurement and monitoring. Applied to the GRACE PCT, sociotechnical issues become apparent, including inconsistencies in internal policies and procedures, issues affecting the deployment of PROs through EHRs; populations with diverse needs affected by social determinants of health, and differences in measuring and monitoring among screening tools, all of which impact clinical content and actionability of data.

The impact of these considerations should not be underestimated. For example, one study comparing the PHQ-8 to the PHQ-9 showed that they are equally useful in screening for major depressive disorder, while another study reported that the PHQ-9 might not be accurately screening for suicide [65,66]. Stakeholders would benefit from additional guidance exploring the ethical conduct of research in the assessment of suicidal ideation and the ethical obligations that arise when clinical researchers gain knowledge of this patient safety issue. This information is of crucial importance to clinical investigators for designing methods that support robust screening when working among populations at risk for depression and suicidal ideation.

2. Discussion and recommendations

The national agenda for EHR implementation has allowed clinical investigators to develop novel methods for collecting, organizing, and sharing patient data. Among these developments has been the collection of PROs to study relationships between interventions and outcomes experienced by patients. At the intersection of PROs and PCTs, there are ethical questions concerning boundaries and responsibilities, safety and confidentiality, and standards for identifying and reporting clinically actionable information that investigators should consider when designing their protocols. We offer seven recommendations, applied in the ethical analysis above, for monitoring and responding to suicidality in pragmatic clinical trials that measure depression as an outcome (Fig. 4). These recommendations are based upon our experience conducting research in the GRACE Trial and on the ethical work of the NIH

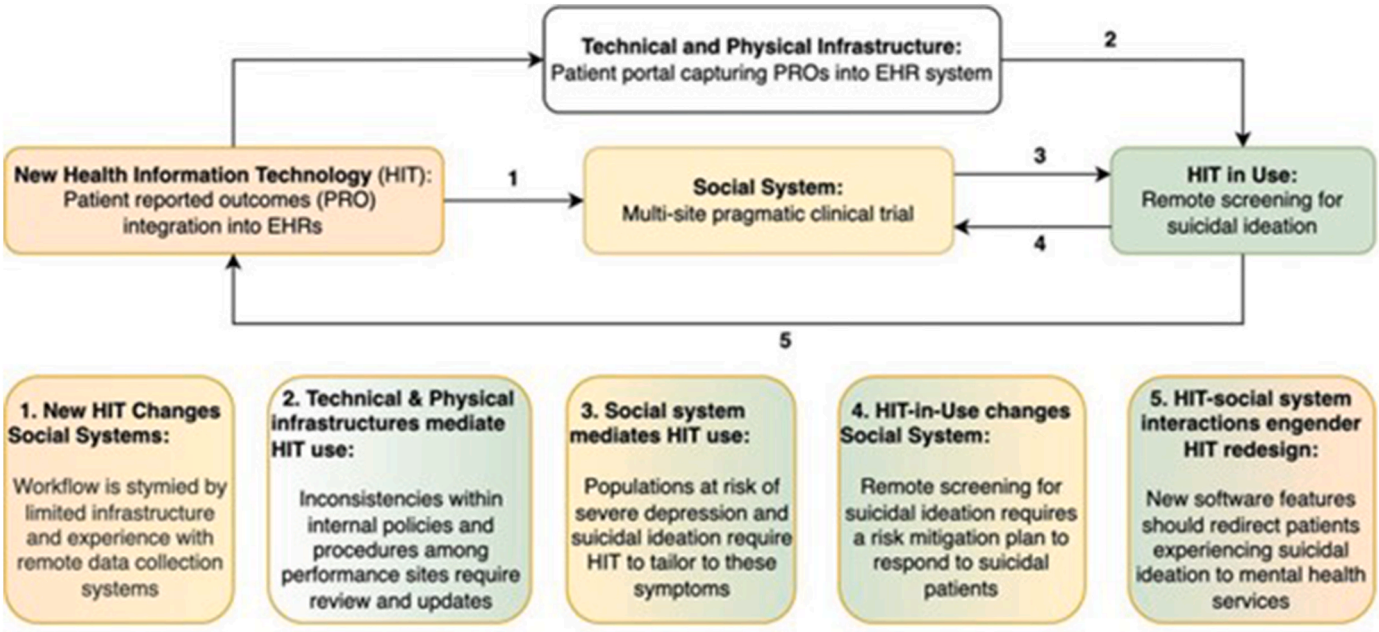


Fig. 3. Unintended consequences for new health information technology that remotely captures suicidal ideation symptoms.

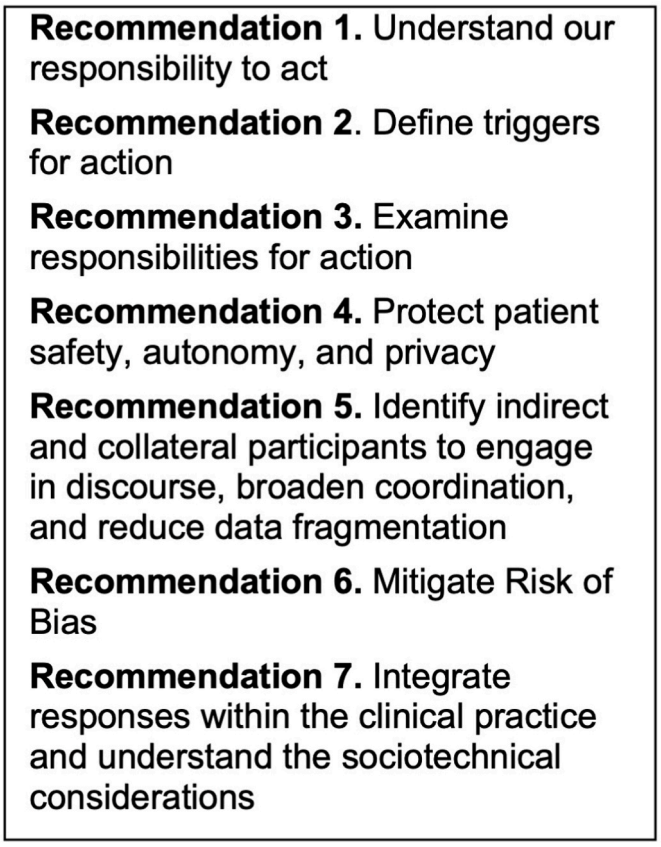


Fig. 4. Recommendations for monitoring and responding to suicidality in pragmatic clinical trials that measure depression as an outcome.

Pragmatic Trials Collaboratory Ethics and Regulatory Core [11].

Nearly one-third of registered clinical trials include a PRO measure [67]. Developments in HIT have ushered in numerous unresolved ethical dilemmas, many of which have been difficult to problematize due to dissonance between traditional values of medical practice with a new set of social and scientific interests that at times favor technological innovation over self-determination. HIT tends to draw attention away from human factors, impede provider-patient relationships, and limit clinical judgment; and there is uncertainty stemming from conflicting duties and priorities among clinical investigators and caregivers to act upon clinically relevant information [11,68,69]. Sociotechnical conceptual frameworks promote deliberate, inclusive decision-making and can serve to mitigate the occurrence of unintended consequences through critical and inclusive review of stakeholder values, rights, and duties. A trial design decision tool that could facilitate such a process is the PRECIS-2 (Pragmatic Explanatory Continuum Indicator Summary) tool, which is designed to attend to ethics and other decisions in the design of randomized trials by making judgments explicit to the trial team [70]. The PRECIS-2 conceptual model consists of nine domains intended to guide investigators' thinking about internal validity of their study design and the effects of design decisions on the applicability of results [70].

Through the lens of the PRECIS-2 model PCT investigators can attend to and possibly mitigate tensions that exist between adequate follow-up and assessment of depression and suicidal ideation, and collection of data from underserved populations, with the mandate for practical trial methods and aims. The GRACE Trial hybrid approach includes remote screening, digitally delivered resources, and desired inclusion of PRO data in the patient EHR for follow-up with primary care physicians. What works in different studies for different populations should continue to be a focus of inquiry as investigators consider pragmatic design and applicability of trial methods, and results on the real lives of target communities and populations. The PRECIS-2 tool is designed for this purpose, providing a standardized decision-making process and a basis for future research and communication of ethical challenges of PCT design [70]. The Pragmatic Trials Collaboratory continues to address areas of ethical inquiry with the dissemination of knowledge through *The Living Textbook* [71].

As structured representations of the patient voice, PRO data intersect core values of patient-centered care, patient and provider autonomy, and shared decision-making. PROs also have the potential to incorporate the participant narrative into clinical research and care. We offer this case example to promote implementation of PROs and improve the quality of data and patient/participant care particularly for those who struggle with suicidal ideation.

Funding

This work was supported within the National Institutes of Health (NIH) Pragmatic Trials Collaboratory through the NIH HEAL Initiative under award numbers UG3 AT011265, and UH3AT011265 administered by the National Center for Complementary and Integrative Health (NCCIH). The work received logistical and technical support from the PRISM Resource Coordinating Center under award number U24AT010961 from the NIH through the NIH HEAL Initiative. This work was also supported by Grant Number K24 AT011995 from National Center for Complementary and Integrative Health (NCCIH) and the National Institute of Neurological Disorders and Stroke (NINDS). The content is solely the responsibility of the authors and does not necessarily represent the official views of NCCIH, NINDS, or the NIH or its HEAL Initiative.

Author contributions

ESS, ADB, CG, LB, AZD, MOE, MRK, JWL, HL, MWM, REM, CLP, ADS, NS, VAd, KLS, JMS were responsible for the acquisition, interpretation, and drafting of the article. ESS, ADB, CG, CLP were responsible for the development and drafting of the figures. ESS, ADB, JMS, KLS critically revised the work for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work.

Data availability statement

N/A.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Data & Statistics on Sickle Cell Disease, CDC, Centers for Disease Control and Prevention, 2022. https://www.cdc.gov/ncbddd/sicklecell/data.html. (Accessed 18 June 2023).
[2] A.B. El Ariss, M. Younes, J. Matar, Z. Berjaoui, Prevalence of sickle cell trait in the southern suburbs of Beirut, Lebanon, Mediterr. J. Hematol. Infect. Dis. 8 (2016), 2016015, https://doi.org/10.4084/mjhid.2016.015.
[3] Major depression, national Institute of mental health (NIMH), n.d. https://www.nimh.nih.gov/health/statistics/major-depression. (Accessed 18 June 2023).
[4] U. Hiroeh, L. Appleby, P.B. Mortensen, G. Dunn, Death by homicide, suicide, and other unnatural causes in people with mental illness: a population-based study, Lancet 358 (2001) 2110–2112, https://doi.org/10.1016/S0140-6736(01)07216-6.
[5] S.P. Hasan, S. Hashmi, M. Alhassen, W. Lawson, O. Castro, Depression in sickle cell disease, J. Natl. Med. Assoc. 95 (2003) 533–537.
[6] J.L. Levenson, D.K. McClish, B.A. Dahman, V.E. Bovbjerg, V. de A. Citero, L. T. Penberthy, I.P. Aisiku, J.D. Roberts, S.D. Roseff, W.R. Smith, Depression and anxiety in adults with sickle cell disease: the PiSCES project, Psychosom. Med. 70 (2008) 192–196, https://doi.org/10.1097/PSY.0b013e31815ff5c5.

[7] M.M. Grant, K.M. Gil, M.Y. Floyd, M. Abrams, Depression and functioning in relation to health care use in sickle cell disease, Ann. Behav. Med. 22 (2000) 149–157, https://doi.org/10.1007/BF02895779.

[8] D. Oudin Doglioni, V. Chabasseur, F. Barbot, F. Galactéros, M.-C. Gay, Depression in adults with sickle cell disease: a systematic review of the methodological issues in assessing prevalence of depression, BMC Psychol. 9 (2021) 54, https://doi.org/10.1186/s40359-021-00543-4.

[9] C.L. Edwards, M. Green, C.C. Wellington, M. Muhammad, M. Wood, M. Feliu, L. Edwards, L. Hill, J.J. Sollers, C. Barksdale, E.L. Robinson, C.S. McDougald, M. Abrams, K.E. Whitfield, G. Byrd, B. Hubbard, M. Cola, L. DeCastro, J. McNeil, Depression, suicidal ideation, and attempts in Black patients with sickle cell disease, J. Natl. Med. Assoc. 101 (2009) 1090–1095, https://doi.org/10.1016/S0027-9684(15)31103-2.

[10] A.Z. Doorenbos, Y. Kato, Pragmatic clinical trials: increasing the rate of translating nursing research into practice †, Jpn. J. Nurs. Sci. 17 (2020) https://doi.org/10.1111/jjns.12350.

[11] J. Ali, S.R. Morain, P.P. O'Rourke, B. Wilfond, E.C. O'Brien, C.K. Zigler, K. L. Staman, K.P. Weinfurt, J. Sugarman, Responding to signals of mental and behavioral health risk in pragmatic clinical trials: ethical obligations in a healthcare ecosystem, Contemp. Clin. Trials 113 (2022), 106651, https://doi.org/10.1016/j.cct.2021.106651.

[12] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (2001) 606–613, https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

[13] L.D. Wandner, A.F. Domenichiello, J. Beierlein, L. Pogorzala, G. Aquino, A. Siddons, L. Porter, J. Atkinson, NIH pain consortium Institute and center representatives, NIH's helping to end addiction long-termSM initiative (NIH HEAL initiative) clinical pain management common data element Program, J. Pain 23 (2022) 370–378, https://doi.org/10.1016/j.jpain.2021.08.005.

[14] P.A. Harris, R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, L. McLeod, G. Delacqua, F. Delacqua, J. Kirby, S.N. Duda, The REDCap consortium: building an international community of software platform partners, J. Biomed. Inf. 95 (2019), 103208, https://doi.org/10.1016/j.jbi.2019.103208.

[15] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inf. 42 (2009) 377–381, https://doi.org/10.1016/j.jbi.2008.08.010.

[16] All of Us Research Program | National Institutes of Health (NIH), All of Us Research Program | NIH, 2020. https://allofus.nih.gov/future-health-begins-all-us. (Accessed 18 June 2023).

[17] N.F. BinDhim, E.M. Alanazi, H. Aljadhey, M.H. Basyouni, S.R. Kowalski, L.G. Pont, A.M. Shaman, L. Trevena, T.M. Alhawassi, Does a mobile phone depression-screening app motivate mobile phone users with high depressive symptoms to seek a health care professional's help? J. Med. Internet Res. 18 (2016) e156, https://doi.org/10.2196/jmir.5726.

[18] N.F. BinDhim, A.M. Shaman, L. Trevena, M.H. Basyouni, L.G. Pont, T. M. Alhawassi, Depression screening via a smartphone app: cross-country user characteristics and feasibility, J. Am. Med. Inf. Assoc. 22 (2015) 29–34, https://doi.org/10.1136/amiajnl-2014-002840.

[19] A. Vahabzadeh, N. Sahin, A. Kalali, Digital suicide prevention: can technology become a game-changer? Innov. Clin. Neurosci. 13 (2016) 16–20.

[20] G.E. Simon, C.M. Rutter, D. Peterson, M. Oliver, U. Whiteside, B. Operskalski, E. J. Ludman, Does Response on the PHQ-9 Depression Questionnaire Predict Subsequent Suicide Attempt or Suicide Death?, PS, vol. 64, 2013, pp. 1195–1202, https://doi.org/10.1176/appi.ps.201200587.

[21] K.J. Coleman, E. Johnson, B.K. Ahmedani, A. Beck, R.C. Rossom, S.M. Shortreed, G. E. Simon, Predicting suicide attempts for racial and ethnic groups of patients during routine clinical care, Suicide Life Threatening Behav. 49 (2019) 724–734, https://doi.org/10.1111/sltb.12454.

[22] J.C. Franklin, J.D. Ribeiro, K.R. Fox, K.H. Bentley, E.M. Kleiman, X. Huang, K. M. Musacchio, A.C. Jaroszewski, B.P. Chang, M.K. Nock, Risk factors for suicidal thoughts and behaviors: a meta-analysis of 50 years of research, Psychol. Bull. 143 (2017) 187–232, https://doi.org/10.1037/bul0000084.

[23] L. Sander, K. Gerhardinger, E. Bailey, J. Robinson, J. Lin, P. Cuijpers, C. Mühlmann, Suicide risk management in research on internet-based interventions for depression: a synthesis of the current state and recommendations for future research, J. Affect. Disord. 263 (2020) 676–683, https://doi.org/10.1016/j.jad.2019.11.045.

[24] B. Herbeck Belnap, H.C. Schulberg, F. He, S. Mazumdar, C.F. Reynolds, B. L. Rollman, Electronic protocol for suicide risk management in research participants, J. Psychosom. Res. 78 (2015) 340–345, https://doi.org/10.1016/j.jpsychores.2014.12.012.

[25] G.E. Simon, S.M. Shortreed, R.C. Rossom, A. Beck, G.N. Clarke, U. Whiteside, J. E. Richards, R.B. Penfold, J.M. Boggs, J. Smith, Effect of offering care management or online dialectical behavior therapy skills training vs usual care on self-harm among adult outpatients with suicidal ideation: a randomized clinical trial, JAMA 327 (2022) 630, https://doi.org/10.1001/jama.2022.0423.

[26] D. Zatzick, G. Jurkovich, P. Heagerty, J. Russo, D. Darnell, L. Parker, M.K. Roberts, R. Moodliar, A. Engstrom, J. Wang, E. Bulger, L. Whiteside, D. Nehra, L.A. Palinkas, K. Moloney, R. Maier, Stepped collaborative care targeting posttraumatic stress disorder symptoms and comorbidity for US trauma care systems: a randomized clinical trial, JAMA Surg 156 (2021) 430, https://doi.org/10.1001/jamasurg.2021.0131.

[27] A. Engstrom, K. Moloney, J. Nguyen, L. Parker, M. Roberts, R. Moodliar, J. Russo, J. Wang, H. Scheuer, D. Zatzick, A pragmatic clinical trial approach to assessing and monitoring suicidal ideation: results from A national US trauma care system study, Psychiatry 85 (2022) 13–29, https://doi.org/10.1080/00332747.2021.1991200.

[28] M. Alegría, P. Chatterji, K. Wells, Z. Cao, C. Chen, D. Takeuchi, J. Jackson, X.-L. Meng, Disparity in Depression Treatment Among Racial and Ethnic Minority Populations in the United States, PS, vol. 59, 2008, pp. 1264–1272, https://doi.org/10.1176/ps.2008.59.11.1264.

[29] K.B. Holden, L.D. Bradford, S.P. Hall, A.S. Belton, Prevalence and correlates of depressive symptoms and resiliency among African American women in a community-based primary health care center, J. Health Care Poor Underserved 24 (2014) 79–93, https://doi.org/10.1353/hpu.2014.0012.

[30] S.D. Brown, K. Lee, D.E. Schoffman, A.C. King, L.M. Crawley, M. Kiernan, Minority recruitment into clinical trials: experimental findings and practical implications, Contemp. Clin. Trials 33 (2012) 620–623, https://doi.org/10.1016/j.cct.2012.03.003.

[31] T. McCall, M. Threats, M. Pillai, A. Lakdawala, C.S. Bolton, Recommendations for design of a mobile application to support management of anxiety and depression among Black American women, Front. Digit. Health. 4 (2022), 1028408, https://doi.org/10.3389/fdgth.2022.1028408.

[32] S.V. Burton, A.L. Valenta, J. Starren, J. Abraham, T. Nelson, K. Kochendorfer, A. Hughes, B. Harris, A. Boyd, Examining perspectives on the adoption and use of computer-based patient-reported outcomes among clinicians and health professionals: a Q methodology study, J. Am. Med. Inf. Assoc. 29 (2022) 443–452, https://doi.org/10.1093/jamia/ocab257.

[33] H.S. Richardson, L. Belsky, The ancillary-care responsibilities of medical researchers. An ethical framework for thinking about the clinical care that researchers owe their subjects, Hastings Cent. Rep. 34 (2004) 25–33.

[34] S. Booth-Kewley, G.E. Larson, D.K. Miyoshi, Social desirability effects on computerized and paper-and-pencil questionnaires, Comput. Hum. Behav. 23 (2007) 463–477, https://doi.org/10.1016/j.chb.2004.10.020.

[35] J.E. Richards, U. Whiteside, E.J. Ludman, C. Pabiniak, B. Kirlin, R. Hidalgo, G. Simon, Understanding why patients may not report suicidal ideation at a health care visit prior to a suicide attempt: a qualitative study, Psychiatr. Serv. 70 (2019) 40–45, https://doi.org/10.1176/appi.ps.201800342.

[36] Office for human research protections (OHRP) 45 CFR 46, HHS.Gov, https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html, 2016. (Accessed 18 June 2023).

[37] J. Baruth, M. Lapid, Influence of psychiatric symptoms on decisional capacity in treatment refusal, AMA J. Ethics 19 (2017) 416–425, https://doi.org/10.1001/journalofethics.2017.19.5.ecas1-1705.

[38] M.K. Nock, E.M. Kleiman, M. Abraham, K.H. Bentley, D.A. Brent, R.J. Buonopane, F. Castro-Ramirez, C.B. Cha, W. Dempsey, J. Draper, C.R. Glenn, J. Harkavy-Friedman, M.R. Hollander, J.C. Huffman, H.I.S. Lee, A.J. Millner, D. Mou, J. Onnela, R.W. Picard, H.M. Quay, O. Rankin, S. Sewards, J. Torous, J. Wheelis, U. Whiteside, G. Siegel, A.E. Ordóñez, J.L. Pearson, Consensus statement on ethical & safety practices for conducting digital monitoring studies with people at risk of suicide and related behaviors, Psychiatr. Res. Clin. Pract. 3 (2021) 57–66, https://doi.org/10.1176/appi.prcp.20200029.

[39] D.C. Lavallee, K.E. Chenok, R.M. Love, C. Petersen, E. Holve, C.D. Segal, P. D. Franklin, Incorporating patient-reported outcomes into health care to engage patients and enhance care, Health Aff. 35 (2016) 575–582, https://doi.org/10.1377/hlthaff.2015.1362.

[40] J.B. Smalley, M.W. Merritt, S.M. Al-Khatib, D. McCall, K.L. Staman, C. Stepnowsky, Ethical responsibilities toward indirect and collateral participants in pragmatic clinical trials, Clin. Trials 12 (2015) 476–484, https://doi.org/10.1177/1740774515597698.

[41] E. Basch, C. Snyder, Overcoming barriers to integrating patient-reported outcomes in clinical practice and electronic health records, Ann. Oncol. 28 (2017) 2332–2333, https://doi.org/10.1093/annonc/mdx506.

[42] J. Carlton, T. Peasgood, S. Khan, R. Barber, J. Bostock, A.D. Keetharuth, An emerging framework for fully incorporating public involvement (PI) into patient-reported outcome measures (PROMs), J. Patient Rep. Outcomes 4 (2020) 4, https://doi.org/10.1186/s41687-019-0172-8.

[43] I.D. Hartog, D.L. Willems, W.B. Van Den Hout, M. Scherer-Rath, T.H. Oreel, J.P. S. Henriques, P.T. Nieuwkerk, H.W.M. Van Laarhoven, M.A.G. Sprangers, Influence of response shift and disposition on patient-reported outcomes may lead to suboptimal medical decisions: a medical ethics perspective, BMC Med. Ethics 20 (2019) 61, https://doi.org/10.1186/s12910-019-0397-3.

[44] R. Sawatzky, J.-Y. Kwon, R. Barclay, C. Chauhan, L. Frank, W.B. van den Hout, L. K. Nielsen, S. Nolte, M.A.G. Sprangers, Response Shift – in Sync Working Group, Implications of response shift for micro-, meso-, and macro-level healthcare decision-making using results of patient-reported outcome measures, Qual. Life Res. 30 (2021) 3343–3357, https://doi.org/10.1007/s11136-021-02766-9.

[45] M.R. Knisely, E. Rivera, V.A. deMartelly, A. Abdulkadir, A.Z. Doorenbos, M. O. Ezenwa, R.E. Molokie, H. Li, N. Shah, J.M. Schlaeger, C.L. Patil, Developing an implementation blueprint for the NIH HEAL initiative GRACE trial: perspectives on acupuncture and guided relaxation for Chronic Sickle Cell Disease Pain, J. Integr. Compl. Med. (2023), https://doi.org/10.1089/jicm.2022.0781 jicm.2022.0781.

[46] A.Z. Doorenbos, J.M. Schlaeger, V.A. deMartelly, L.A. Burke, A.D. Boyd, M. R. Knisely, J.W. Leigh, H. Li, M.W. Mandernach, R.E. Molokie, C.L. Patil, A. D. Steffen, N. Shah, M.O. Ezenwa, Hybrid effectiveness-implementation trial of guided relaxation and acupuncture for Chronic Sickle Cell Disease Pain (GRACE): a protocol, Contemp. Clin. Trials Commun. 32 (2023), 101076, https://doi.org/10.1016/j.conctc.2023.101076.

[47] NCCIH's role in the NIH HEAL initiative | NCCIH, n.d. https://www.nccih.nih.gov/grants/nccihs-role-in-the-nih-heal-initiative#:~:text=NCCIH%20is%20

playing%20a%20major,addiction%2C%20and%20enhancing%20. (Accessed 18 June 2023).
[48] HEAL initiative offers funding for clinical trial research on pain, NCCIH. (n.d.). https://www.nccih.nih.gov/research/blog/heal-initiative-offers-new-funding-options-for-clinical-trial-research-on-pain (accessed June 18, 2023).
[49] L.M. Dember, The potential for pragmatic trials to reduce racial and ethnic disparities in Kidney disease, JASN (J. Am. Soc. Nephrol.) 33 (2022) 1649–1651, https://doi.org/10.1681/ASN.2022030301.
[50] A.D. Boyd, R. Gonzalez-Guarda, K. Lawrence, C.L. Patil, M.O. Ezenwa, E. C. O'Brien, H. Paek, J.M. Braciszewski, O. Adeyemi, A.M. Cuthel, J.E. Darby, C. K. Zigler, P.M. Ho, K.R. Faurot, K. Staman, J.W. Leigh, D.L. Dailey, A. Cheville, G. Del Fiol, M.R. Knisely, K. Marsolo, R.L. Richesson, J.M. Schlaeger, Equity and bias in electronic health records data, Contemp. Clin. Trials 130 (2023), 107238, https://doi.org/10.1016/j.cct.2023.107238.
[51] NIH-wide strategic plan for diversity, equity, inclusion, and accessibility (DEIA) | national Institutes of health (NIH), n.d. https://www.nih.gov/about-nih/nih-wide-strategic-plan-diversity-equity-inclusion-accessibility-deia. (Accessed 18 June 2023).
[52] S.M. Goodday, A. Kormilitzin, N. Vaci, Q. Liu, A. Cipriani, T. Smith, A. Nevado-Holgado, Maximizing the use of social and behavioural information from secondary care mental health electronic health records, J. Biomed. Inf. 107 (2020), 103429, https://doi.org/10.1016/j.jbi.2020.103429.
[53] S.E. Geller, A.R. Koch, P. Roesch, A. Filut, E. Hallgren, M. Carnes, The more things change, the more they stay the same: a study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials, Acad. Med. 93 (2018) 630–635, https://doi.org/10.1097/ACM.0000000000002027.
[54] L.R. Snowden, Bias in mental health assessment and intervention: theory and evidence, Am. J. Publ. Health 93 (2003) 239–243, https://doi.org/10.2105/ajph.93.2.239.
[55] J. Lehmann, M. Rothmund, D. Riedl, G. Rumpold, V. Grote, M.J. Fischer, B. Holzner, Clinical outcome assessment in cancer rehabilitation and the central role of patient-reported outcomes, Cancers 14 (2021) 84, https://doi.org/10.3390/cancers14010084.
[56] Legal and ethical architecture for patient-centered outcomes research (PCOR) data ("Architecture") | HealthIT.gov, n.d. https://www.healthit.gov/topic/scientific-initiatives/pcor/legal-and-ethical-architecture-patient-centered-outcomes-research-pcor-data-architecture. (Accessed 18 June 2023).
[57] Users' guide to integrating patient-reported outcomes in electronic health records | PCORI, n.d. https://www.pcori.org/document/users-guide-integrating-patient-reported-outcomes-electronic-health-records. (Accessed 18 June 2023).
[58] M. Calvert, D. Kyte, R. Mercieca-Bebber, A. Slade, A.-W. Chan, M.T. King, the Spirit-Pro Group, A. Hunn, A. Bottomley, A. Regnault, A.-W. Chan, C. Ells, D. O'Connor, D. Revicki, D. Patrick, D. Altman, E. Basch, G. Velikova, G. Price, H. Draper, J. Blazeby, J. Scott, J. Coast, J. Norquist, J. Brown, K. Haywood, L. L. Johnson, L. Campbell, L. Frank, M. Von Hildebrand, M. Brundage, M. Palmer, P. Kluetz, R. Stephens, R.M. Golub, S. Mitchell, T. Groves, Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension, JAMA 319 (2018) 483, https://doi.org/10.1001/jama.2017.21903.
[59] M.I. Harrison, R. Koppel, S. Bar-Lev, Unintended consequences of information technologies in health care–an interactive sociotechnical analysis, J. Am. Med. Inf. Assoc. 14 (2007) 542–549, https://doi.org/10.1197/jamia.M2384.
[60] R.J. Severson, The Principles of Information Ethics, M.E. Sharpe, Armonk, N.Y, 1997.
[61] D. Whicher, E. Evans, Informed consent for PROs in EHR research: are additional requirements necessary? Am. J. Bioeth. 16 (2016) 63–65, https://doi.org/10.1080/15265161.2016.1145300.
[62] A. Asudeh, Z. Jin, H.V. Jagadish, Assessing and remedying coverage for a given dataset, in: 2019 IEEE 35th International Conference on Data Engineering (ICDE), IEEE, Macao, Macao, 2019, pp. 554–565, https://doi.org/10.1109/ICDE.2019.00056.
[63] M. Calvert, J. Blazeby, D.G. Altman, D.A. Revicki, D. Moher, M.D. Brundage, F. T. Consort Pro Group, Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension, JAMA 309 (2013) 814, https://doi.org/10.1001/jama.2013.879.
[64] D.F. Sittig, H. Singh, A new sociotechnical model for studying health information technology in complex adaptive healthcare systems, Qual. Saf. Health Care 19 (Suppl 3) (2010) i68–i74, https://doi.org/10.1136/qshc.2010.042085.
[65] I. Razykov, R.C. Ziegelstein, M.A. Whooley, B.D. Thombs, The PHQ-9 versus the PHQ-8 — is item 9 useful for assessing suicide risk in coronary artery disease patients? Data from the Heart and Soul Study, J. Psychosom. Res. 73 (2012) 163–168, https://doi.org/10.1016/j.jpsychores.2012.06.001.
[66] C. Shin, S.-H. Lee, K.-M. Han, H.-K. Yoon, C. Han, Comparison of the usefulness of the PHQ-8 and PHQ-9 for screening for major depressive disorder: analysis of psychiatric outpatient data, Psychiatry Investig 16 (2019) 300–305, https://doi.org/10.30773/pi.2019.02.01.
[67] E. Vodicka, K. Kim, E.B. Devine, A. Gnanasakthy, J.F. Scoggins, D.L. Patrick, Inclusion of patient-reported outcome measures in registered clinical trials: evidence from ClinicalTrials.gov, Contemp. Clin. Trials 43 (2015) 1–9, https://doi.org/10.1016/j.cct.2015.04.004, 2007-2013.
[68] J.S. Crites, C. Chuang, A. Dimmock, W. Hwang, B. Johannes, A. Paranjape, A. W. Wu, PROs in the balance: ethical implications of collecting patient reported outcome measures in the electronic health record, Am. J. Bioeth. 16 (2016) 67–68, https://doi.org/10.1080/15265161.2016.1146543.
[69] S.J. Reiser, Medicine and the Reign of Technology, Cambridge Univ. Press, Cambridge, 2004. Reprinted.
[70] K. Loudon, S. Treweek, F. Sullivan, P. Donnan, K.E. Thorpe, M. Zwarenstein, The PRECIS-2 tool: designing trials that are fit for purpose, BMJ 350 (2015), https://doi.org/10.1136/bmj.h2147 h2147–h2147.
[71] K. Weinfurt, A.F. Hernandez, L.H. Curtis, Rethinking clinical trials: a living Textbook of pragmatic clinical trials, n.d. https://rethinkingclinicaltrials.org/chapters/pragmatic-clinical-trial/what-is-a-pragmatic-clinical-trial/. (Accessed 9 July 2020).