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Do human subject safeguards matter to potential participants in psychiatric genetic research?

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ABSTRACT

Despite longstanding concerns about the adequacy of human research protections in mental illness investigations, minimal work has focused on the perspectives of key stakeholders regarding these safeguards. This investigation examined the perspectives of potential research participants regarding safeguards for psychiatric genetic research. Individuals with mental illness (n = 71), first-degree family members of individuals with mental illness (n = 54), and individuals with no personal or close family history of mental illness (n = 57) provided responses to items regarding perceptions of: 1) protectiveness of a range of research safeguards in genetic research on mental illness; 2) influence of these safeguards on research participation decision-making; and 3) importance of these safeguards depending on the nature of the research (i.e., *genetic* vs. *non-genetic* mental illness research; and genetic research on *mental illness* vs. *physical illness*). Potential research participants perceived existing safeguard procedures as generally protective. The three groups did not differ in their ratings of protectiveness, with the exception of the safeguard domain of "Informed Consent or Alternative Decision-Making Procedures," which was viewed as more protective by family members of people with mental illness than by individuals with mental illness or comparison participants. Safeguard procedures were perceived as strongly influential with respect to willingness to enroll in psychiatric genetic research. These findings suggest that the presence of safeguards positively influences enrollment decision-making by research volunteers and indicate that potential psychiatric genetic research participants find safeguards to be protective, underscoring the responsibility to implement safeguard practices conscientiously.

1. Introduction

Mental illnesses take an enormous global toll on individuals, families, and society. The World Health Organization ranks depression as the number one source of disability worldwide and estimates that 800,000 people die by suicide annually (World Health Organization, 2017). The need for improved evaluation and treatment of individuals with mental illness is acute and growing.

Psychiatric genetic research has the potential to identify genetic risk, pathophysiological mechanisms, and treatment targets (Hurd and O'Brien, 2018; Thapar, 2018; Yehuda and Flory, 2018; Zeier et al., 2018). The immense hope placed in psychiatric genetic research to alleviate global suffering is matched, however, by the enormous complexity of the brain and the concomitant difficulties in understanding brain-based disorders (Green et al., 2019; Liu et al., 2017; Sullivan et al., 2018).

Advances in psychiatric genetic research depend, in large part, on the informed and voluntary participation of many research volunteers who likely derive no direct personal benefit from their participation. In order to identify and replicate putative genetic markers and mechanisms of mental illness and to examine variation across populations in the presence and manifestation of symptoms, a number of different types of volunteers are needed—i.e., individuals with mental illness, family members of individuals with mental illness, and community comparison participants with neither a personal nor family history of mental illness.

To facilitate robust enrollment in psychiatric genetic research, the trust of potential participants in the investigators conducting these research endeavors, and in the institutions approving and overseeing them, is critical. The need to foster and maintain public trust is particularly salient for psychiatric research, which has arguably been more highly stigmatized and closely scrutinized compared to non-psychiatric medical research (Dunn et al., 2006; Michels, 1999). For instance, the 1998 report of the National Bioethics Advisory Commission ("Research Involving Persons with Mental Disorders that May Affect Decision-making Capacity") (National Bioethics Advisory C, 1998) made a series

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of recommendations specific to psychiatric research, intended to provide additional protections for research participants with mental illness. The recommendations included required independent assessments of participants' decision-making capacity for studies presenting greater than minimal risk and procedures for involving alternative (surrogate) decision makers when participants were deemed to lack capacity. However, such calls for more stringent regulations for studies involving people with psychiatric disorders met with strong criticism from the psychiatric research community (Carpenter and Conley, 1999; Charney, 1999; Roberts and Roberts, 1999) and other important stakeholders, including family members and advocates of people with mental illness (Public comments, 1998).

Such criticism was based upon ethically principled arguments (justice and fairness in the burdens and benefits of research; autonomy of individual participants), as well as empirical evidence on research-related decision-making abilities of individuals with mental disorders. These arguments proceeded, essentially, as follows: First, because mental illness, in and of itself, has not been shown to reliably predict decisional incapacity, the diagnosis of mental illness, in and of itself, is an insufficient basis for requiring additional research safeguards (Dubois et al., 2011; Dunn et al., 2006; Palmer et al., 2005). Second, such additional requirements would constrain psychiatric research unfairly, further limiting needed progress in alleviating the burdens of mental illness on patients, families, and society (Michels, 1999).

Despite concerns about the adequacy of human subject protections for studies enrolling individuals with mental illness, minimal work has focused on the perspectives of key stakeholders regarding research safeguards (Kim et al., 2004; McDonald et al., 2016; Roberts et al., 2004a, 2004b). In the context of psychiatric genetic research, even fewer investigations have assessed views of people living with mental disorders regarding research safeguards such as institutional review boards, confidentiality practices, informed consent procedures, surrogate decision-making, and community engagement (Erickson and Cho, 2013; Laegsgaard et al., 2009). Given the need for psychiatric genetic research to enroll not only individuals with mental disorders, but also their relatives and non-affected comparison participants, ascertaining the perspectives of these diverse groups could shed light on the perceived adequacy of research safeguards, as well as areas where stakeholders may hold divergent views.

The purpose of this study is to ascertain and compare the perspectives of three groups of potential research participants regarding human subject safeguards. This paper focuses specifically on perceptions of 1) protectiveness of a range of research safeguards when applied to genetic research on mental illness; 2) influence of these safeguards on research participation decision-making; and 3) importance of these safeguards depending on the nature of the research (i.e., *genetic* vs. *non-genetic* mental illness research; and genetic research on *mental illness* vs. *physical illness*). We hypothesized that potential participants would endorse the protectiveness of these safeguards overall and would express greater willingness to volunteer in research studies with these safeguards in place. We further hypothesized that safeguards would be identified as of greater importance in genetic investigations and investigations of mental disorders. With respect to group comparisons, we hypothesized that community comparison volunteers would endorse the importance of safeguards for genetic research to a greater degree than individuals living with mental illness and family members.

2. Methods

2.1. Participants and procedures

Potential volunteers in Milwaukee, WI and Albuquerque, NM were recruited through community advertisements (flyers posted in local organizations such as grocery stores, coffee shops, clinics, and community centers), clinician referrals from Medical College of Wisconsin (MCW) and University of New Mexico clinics, and postings on national organization websites (Craig's List, National Alliance for the Mentally Ill). Individuals were screened by telephone; those meeting inclusion criteria were asked to attend an in-person interview. At the in-person interview, participants completed an informed consent process, a genetic literacy assessment (REAL-G) (Erby et al., 2008), a self-administered illness checklist, a quality of life assessment (SF-12) (Ware et al., 1996), and the Brief Symptom Inventory 18 (BSI) (Derogatis, 1993), a validated instrument that evaluates psychiatric symptom severity.

Of 195 scheduled interviews with volunteers who met the screening criteria, 187 volunteers appeared for in-person interviews (96%). Only 5 of 187 volunteers did not complete the full survey interview.

Trained research staff conducted face-to-face interviews with individuals in three groups: individuals ≥18 years of age who self-reported that they were living with mental illness (e.g., schizophrenia or schizoaffective disorder, bipolar disorder, major depressive disorder, anxiety disorder, personality disorder; i.e., "MI" group), first-degree family members (by self-report) of individuals living with mental illness (i.e., "Family" group); and individuals with no self-reported personal or close family history of mental illness ("Community Comparison" group). The MI and Family groups were included given that they would be natural potential participants in psychiatric genetic research studies. The Community Comparison group was included in order to contrast the views of those with personal or family experience with mental illness with the views of those of individuals from the local community.

2.2. Ethics approval

This study was approved by institutional review boards (IRBs) at University of New Mexico, the Medical College of Wisconsin, and Stanford University. All participants were given background information about this minimal risk study and an opportunity to ask questions; volunteers provided their written consent in person. Data were confidentially encoded and analyzed with identifiers removed. Participants received a $50 gift card.

2.3. Survey instrument

The final survey contained 344 rating-scaled and open-ended items on legal, social and ethical issues concerning psychiatric genetic research. Interviews lasted approximately 2 h (Roberts et al., In press), with scheduled and as-needed breaks. For this analysis, we examined 26 items focusing on human subject safeguards. The first set of items queried participants regarding eleven safeguard procedures, which were selected based on extensive prior work and a review of the existing literature on safeguards (Roberts et al., 2004a, 2004b). Each procedure was described individually in a short paragraph (Appendix 1, items 1a-1b to 11a-11b). After each safeguard description, participants were asked two questions. The first question (i.e., "Protectiveness" [items 1a-11a]) asked, "How much does [**Safeguard Procedure X**] actually **protect** people who take part in genetic research about mental illness?" and was rated from 0 to 10 (0 = "Not protect at all; " 5 = "Somewhat protects; " 10 = "Very much protects"). The second question (i.e., "Influence on willingness" [items 1b–11b]) asked, "If you knew that a study [**included Safeguard Procedure X**], how would it influence **your willingness to participate** in a genetic research study about mental illness?" and was rated from 0 to 10 (0 = "Much LESS willing to participate; " 5 = "No influence; " 10 = "Much MORE willing to participate").

The second set of items consisted of two pairs of questions comparing perspectives on safeguards based on the nature of the research. Specifically, the first pair of items (Appendix 1, items 12 and 13) asked participants to rate the importance of having the eleven research safeguard procedures "to protect participants in studies that do **not** include gathering **genetic** information"; as well as "to protect participants in studies that **do** include gathering **genetic** information". Each of these items was rated from 0 to 10 (0 = "Not important at all; "

5 = "Somewhat important; " 10 = "Extremely important"). The second pair of items (Appendix 1, items 14 and 15) also asked participants to rate the importance of the eleven research safeguard procedures "to protect participants in **genetic** **research** on **physical** illness"; as well as "to protect participants in **genetic** **research** on **mental** illnesses". Each of these items was rated from 0 to 10 (0 = "Not important at all; " 5 = "Somewhat important; " 10 = "Extremely important").

2.4. Data analysis

Statistical analyses were performed using SPSS Statistics (version 24). Descriptive statistics were generated for sociodemographic characteristics. Differences among participant groups were assessed using Chi-square or analysis of variance (ANOVA) tests.

We created five conceptually-related safeguard composite measures from the eleven safeguard procedures (Appendix 2): "Research Review & Oversight Committees" (Composite 1); "Confidentiality Protection" (Composite 2); "Consent & Protection of Participants" (Composite 3); "Ethics Training for Researchers" (Composite 4); "Community Engagement" (Composite 5).

Perceived protectiveness of the safeguard procedures and influence of the safeguard procedures on willingness to participate were analyzed using analysis of variance (ANOVA) tests, assessing mean differences across groups. Repeated measures ANOVA was used to analyze mean differences within each participant group across the five composite measures. Perceived importance of the full set of safeguard procedures was analyzed using paired t-tests. Paired t-tests were also used to evaluate mean differences within each participant group for the paired items on *genetic* vs. *non-genetic* mental illness research and genetic research on *mental* vs. *physical* illness. Multivariate linear regression analysis, using generalized estimating equations, was performed to assess the association between the primary outcome (willingness to participate in research) with perceived protectiveness of safeguards, adjusting for potential confounders (i.e., gender, ethnicity, student, and employment status).

3. Results

3.1. Participant characteristics

Sociodemographic characteristics of participants are shown in Table 1. Slightly more than half of the participants were female (57.1%), and the majority were white (62.6%). The mean age of participants was 42.5 years (SD 13.4); the Comparison group was younger (mean 38.4 years, P value = 0.014). A smaller proportion of those with MI (32.4%) were married or partnered (P value = 0.045). Approximately half of the participants (51.6%) had a 2-year college degree or higher and a smaller proportion of those with MI were employed (36.6%, P value = 0.042). A greater proportion of those with MI (60.6%) reported their annual income as ≤ $20,000 ($P$ value < 0.001).

Overall, participants endorsed low-to-moderate levels of traditional religious values (mean = 4.4 out of 10). The Comparison group reported being less spiritual (6.4 out of 10) (P value = 0.019).

3.2. Perceived protectiveness of the safeguard procedures in genetic research about mental illness

Ratings of perceived protectiveness of the five safeguard procedure domains are listed in Table 2 in descending order of protectiveness as rated by the combined sample (overall repeated measures ANOVA P value < 0.001). In the combined sample, Research Review and Oversight Committees were rated highest in terms of perceived protectiveness (mean = 7.8 out of 10), while Community Engagement Procedures received only moderate protectiveness ratings (mean = 5.5 out of 10). When analyzed separately, each of the three participant groups provided the same overall order of ratings of the safeguard procedure domains (from most to least protective, all three repeated measures ANOVAs P values < 0.001), as did the combined sample.

The three stakeholder groups differed significantly in their views of the protectiveness of Informed Consent or Alternative Decision-Making Procedures. Specifically, compared to the MI and Comparison groups, the Family group rated this safeguard domain as more protective (means = 7.2 [MI]; 6.8 [Comparison]; and 7.9 [Family]; P value = 0.008). The stakeholder groups' protectiveness ratings did not differ significantly for the other four of the five safeguard procedure domains.

3.3. Influence of safeguard procedures on willingness to participate in genetic research about mental illness

Ratings of self-reported influence of the five safeguard procedure domains are listed in Table 3 in descending order of influence as rated by the combined sample (overall repeated measures ANOVA P value < 0.001). Across stakeholder groups, Research Review and Oversight Committees were rated highest in terms of influence on willingness to participate (mean = 7.8 out of 10), while Community Engagement Procedures received only moderate ratings of influence on willingness to participate (mean = 5.9 out of 10). Within each of the three stakeholder groups, the overall order of self-reported influence of the five safeguard procedure domains was consistent with the order within the combined sample (all three repeated measure ANOVAs P values < 0.001), with the exception that, within the Family group, the Confidentiality Practices domain was rated highest (mean = 7.9 out of 10), followed by Research Review and Oversight Committees (mean = 7.8 out of 10). The only safeguard domain that was rated significantly differently across the three stakeholder groups was Research Review and Oversight Committees (ANOVA P value = 0.010).

Results from multivariate regression analysis demonstrated an increasing relationship between the perceived protectiveness of safeguards and expressed willingness to participate in research procedures (regression coefficient = 0.64, P value < 0.001). We did not find a significant association between expressed willingness and the potential confounders.

3.4. Perceived importance of the full set of safeguard procedures in genetic research compared with non-genetic research about mental illness

The combined sample rated the importance of the full set of safeguard procedures (taken together) for protecting research participants more highly for *genetic* research about mental illness (mean = 9.0 out of 10) than for *non-genetic* research about mental illness (mean 8.2 out of 10; P value < 0.001). Similarly, when analyzed separately, each of the three stakeholder groups rated the importance of the full set of safeguard procedures more highly for *genetic* research about mental illness compared to *non-genetic* research about mental illness (MI and Comparison groups: P value = < 0.001: Family group: P value = 0.001).

3.5. Perceived importance of the full set of safeguard procedures in genetic research about mental illness compared with physical illness

The combined sample rated the importance of the full set of safeguard procedures for protecting research participants more highly for genetic research on *mental illness* (mean = 9.2 out of 10) than for genetic research on *physical illness* (mean 8.9 out of 10; P value < 0.001). Again, each of the three stakeholder groups rated the importance of the full set of safeguard procedures more highly for genetic research on *mental illness* than for genetic research on *physical illness* (MI group: P value = 0.016; Family group: P value = 0.017; Comparison group: P value = 0.027).

Table 1
Sociodemographic characteristics of 3 stakeholder groups (n = 182).

	Individuals living with mental illness (n = 71)	Family members of individuals living with mental illness (n = 54)	Community comparison volunteers (n = 57)	Overall (n = 182)	*P* value
Age[a]					**.014**
Mean years (SD)	43.6 (11.2)	45.5 (15.5)	38.4 (13.2)	42.5 (13.4)	
Gender (%, n)[d]					.867
Female	57.7 (41)	59.3 (32)	54.4 (31)	57.1 (104)	
Male	42.3 (30)	40.7 (22)	45.6 (26)	42.9 (78)	
Race/Ethnicity (%, n)[d]					.384
Other	32.4 (23)	44.4 (24)	36.8 (21)	37.4 (68)	
White	67.6 (48)	55.6 (30)	63.2 (36)	62.6 (114)	
Married or Partnered (%, n)[d]					**.045**
Yes	32.4 (23)	53.7 (29)	52.6 (30)	43.4 (79)]	
Education (%, n) [d]					.063
2 year college degree or higher	42.3 (30)	51.9 (28)	63.2 (36)	51.6 (94)	
Occupational Status (%, n)[b, d]					**.042**
Employed	36.6 (26)	59.3 (32)	47.4 (27)	46.7 (85)	
Estimated Annual ($) Income (%, n)[c, d]					< **.001**
$20,000 or less	60.6 (43)	25.9 (14)	21.1 (12)	37.0 (69)	
$20,001 to $40,000	15.5 (11)	27.8 (15)	29.8 (17)	23.6 (43)	
$40,001 to $60,000	16.9 (12)	20.4 (11)	22.8 (13)	19.8 (36)	
Over $60,000	5.6 (4)	25.9 (14)	22.8 (13)	17.0 (31)	

[a] *P* values correspond to ANOVA tests.
[b] Respondents were asked to check all that apply.
[c] 3 participants (1.6%) left this section blank.
[d] *P* values correspond to Chi-square tests.

4. Discussion

The advancement of psychiatric genetic research heavily depends on the enrollment and participation of both individuals with mental disorders and their family members, as well as non-affected comparison participants. While such requisites could be viewed as an additional challenge, the participatory process may involve families and thus issues related to protection (e.g. alternative decision making, safeguarding of personal information, privacy) could be more nuanced. A better understanding the perspectives of these diverse groups could shed light on the perceived adequacy of research safeguards, as well as areas where stakeholders may hold divergent views. Despite the reliance of research oversight and regulatory bodies on a range of safeguards designed to protect human participants, very little is known about how potential research volunteers view the protectiveness of these safeguard practices. Moreover, to what extent the presence of such safeguards influences research enrollment choices remains largely unstudied.

To our knowledge, this is the first study to describe and compare the perspectives of individuals living with mental illness, family members of individuals living with mental illness, and community comparison volunteers regarding the perceived protectiveness of a range of research

Table 2
Perceived protectiveness of safeguard procedures in genetic research about mental illness by 3 stakeholder groups.

Perceived Protectiveness of safeguard procedures	Individuals living with mental illness (n = 71)		Family members of individuals living with mental illness (n = 54)		Community Comparison Volunteers (n = 57)		Overall (N = 182)		*P* value[a]
	mean	sd	mean	sd	mean	sd	mean	sd	
Research Review & Oversight Committees	7.9	1.6	7.9	1.4	7.6	1.6	7.8	1.5	.521
Confidentiality Practices	7.8	1.7	7.9	1.6	7.5	2.0	7.7	1.8	.525
Informed Consent or Alternative Decision-Making Procedures	7.2	1.9	7.9	1.6	6.8	2.1	7.3	1.9	**.008**
Ethics Training for Researchers	6.4	2.8	6.3	2.3	6.1	2.5	6.3	2.5	.622
Community Engagement Procedures	5.3	3.2	5.8	2.8	5.6	2.3	5.5	2.8	.593
P value[b]	< .001		< .001		< .001		< .001		

[a] P values correspond to ANOVA tests.
[b] *P* values correspond to Repeated Measures ANOVA Tests.
Participants were asked, e.g.,
"How much does an **Institutional Review Board's** review and approval of a study actually **protect** people who take part in genetic research about mental illness?"
"0 = Not protect at all; 5 = Somewhat protects; 10 = Very much protects".
Specific safeguard items comprising each domain (see Appendix 1).
Research Review & Oversight Committees: Items 1, 2, 3, 4, and 7.
Informed Consent OR Alternative Decision-Making Procedures: Items 5 and 6.
Confidentiality Practices: Items 9 and 11.
Community Engagement: Item 8.
Ethics Training for Researchers: Item 10.

Table 3
Self-reported influence of safeguard procedures on willingness to participate in genetic research about mental illness by 3 stakeholder groups.

Influence of safeguard procedure on willingness to participate

	Individuals living with mental illness (n = 71)		Family members of individuals living with mental illness (n = 54)		Community Comparison Volunteers (n = 57)		Overall (N = 182)		*P* value[a]
	mean	sd	mean	sd	mean	sd	mean	sd	
Research Review & Oversight Committees	8.2	1.4	7.8	1.5	7.4	1.5	7.8	1.5	**.010**
Confidentiality Practices	8.0	1.7	7.9	1.6	7.5	1.8	7.8	1.7	.166
Informed Consent or Alternative Decision-Making Procedures	7.3	2.0	7.7	1.8	7.0	1.8	7.3	1.9	.170
Ethics Training for Researchers	7.0	2.3	6.4	2.1	6.2	2.1	6.6	2.2	.103
Community Engagement Procedures	6.0	2.7	6.1	2.2	5.7	2.0	5.9	2.4	.681
P value[b]	< .001		< .001		< .001		< .001		

a P values correspond to ANOVA tests.
b P values correspond to Repeated Measures ANOVA Tests.
Participants were asked, e.g.,
"If you know that a study was approved by an **Institutional Review Board,** how would it influence **your willingness to participate** in a genetic research study about mental illness?"
"0 = Much LESS willing to participate; 5 = No influence; 10 = Much MORE willing to participate".
Specific safeguard items comprising each domain (see Appendix 1).
Research Review & Oversight Committees: Items 1, 2, 3, 4, and 7.
Informed Consent OR Alternative Decision-Making Procedures: Items 5 and 6.
Confidentiality Practices: Items 9 and 11.
Community Engagement: Item 8.
Ethics Training for Researchers: Item 10.

safeguard procedures, as well as the degree of influence these safeguards would have on their participation decisions. Other novel aspects of this study were the comparisons of stakeholders' views of safeguards in relation to the nature of the research.

The potential research participants in this investigation viewed systematic review and oversight procedures (e.g., IRB, DSMB, conflict of interest) and confidentiality practices as relatively more protective, when compared to ethics training for researchers or community engagement. This pattern of findings may reflect greater trust in organized bodies, which imply independent oversight, as compared to trust in the individual researcher. Prior work by Roberts and colleagues (Roberts et al., 2004a), in which individuals with schizophrenia (n = 60) and psychiatrists (n = 69) were asked to rate the protectiveness of confidentiality protections, IRBs, DSMBs, informed consent, and alternative decision makers, found that the first four safeguards were rated as more protective than alternative decision makers, which is consistent with our findings. The somewhat lower support for community engagement procedures could be explained by the relative underutilization of these safeguard practices by researchers (Roberts, 2013; Roberts et al., 2015) or the lack of familiarity by potential participants with the concept and language of "community engagement" as a safeguard. It is possible that some participants may not have understood that community-engaged research can be conducted with people who share a label, identity, or lived experience (e.g., serious mental illness) and that factors describing community participatory research in the survey instrument (i.e., ethnicity, cultural group, geography) could have limited participants' interpretation or understanding of what community research could look like. The finding of somewhat lower support for community engagement procedures motivates the need to further examine whether potential research participants understand the purpose and intent of community participatory research.

Despite these differences, research participants perceived existing safeguard procedures as generally protective. For all but one of the domains, the three groups did not differ in their ratings of protectiveness, suggesting general agreement across stakeholder groups. Of note, the safeguard domain of "Informed Consent or Alternative Decision-Making Procedures" was viewed as more protective by family members of people with mental illness than by ill individuals or comparison participants. This result is perhaps unsurprising, as family members are those who would be called on to serve as alternative decision makers, and would thus be inclined to view such a role in a favorably protective light. Furthermore, this difference in the protectiveness ratings for consent or alternative decision-making procedures between groups was of medium effect size (Cohen's $d = 0.36$), indicating that further work is needed to explore the ways in which stakeholder perspectives may diverge. For example, in the Roberts et al. study mentioned above (2004a), participants with schizophrenia, but not psychiatrists—another key stakeholder group—rated alternative decision makers as less protective than four other safeguards. Furthermore, the majority of research on alternative decision makers has focused on dementia research (Black et al., 2013; Dunn et al., 2011, 2013; Kim et al., 2009; Overton et al., 2013), so additional work is needed to deepen our understanding of alternative decision-making procedures as safeguards in mental illness research.

Beyond viewing safeguards as generally protective, the participants in our study rated the procedures as strongly influential with respect to their willingness to enroll in a psychiatric genetic research study. These findings are consistent with prior empirical work suggesting that individuals with and without a history of mental illness reported positive attitudes toward genetic research (Laegsgaard et al., 2009; Roberts and Kim, 2017). As mentioned before, the three groups did not differ statistically from one another in their views regarding the influence of these safeguard procedures. Moreover, irrespective of group, individuals felt that they were more likely to participate in the research projects that had safeguards they more strongly perceived as protective. This pattern of results offers a highly relevant implication for all stakeholders involved in psychiatric genetic research. Fostering awareness of safeguards may positively influence potential volunteers to enroll in genetic studies, but this finding also reinforces the professional obligations of investigators to ensure that safeguards are implemented robustly in order to fulfill the public trust broadly and the expectations of study volunteers.

In addition, irrespective of stakeholder group, our participants on the whole highly supported the importance of the full set of safeguard procedures to protect participants in both genetic and non-genetic mental illness research. Of note, all three groups more strongly endorsed the importance of safeguards in genetic research on mental illness. This finding may signify thoughtfulness and a sensitivity to the unique kinds of information collected in genetic research, although further work is needed. Support was high for the importance of safeguards for genetic research on both mental and physical illness, and all three groups supported safeguarding genetic research on mental disorders moreso than genetic research on physical disorders. Taken together with the finding regarding safeguards for genetic vs. non-genetic research on mental illness, these results suggest that both genetic research and mental illness research may be viewed in a different light than non-genetic research and physical illness research – and, importantly, that the combination (psychiatric genetic research) may be somewhat stigmatized. Thus, for investigators and IRBs, it is worth carefully ensuring that safeguards of psychiatric genetic studies are appropriately attuned to participants' concerns. This said, singling out psychiatric research, or psychiatric genetic research specifically (and we would suggest unfairly), for additional safeguards (e.g., independent capacity assessment) does not have direct support based on the present findings.

Limitations of this study include its reliance on self-reported data and the relatively limited geographic diversity of the study sample. The use of in-person interviews may have led to social desirability bias when participants were questioned about their perspectives. Social desirability bias, though difficult to measure in this instance, may have impacted the interviewees in multiple ways; interviewees may have desired to appear agreeable to the interviewer in the particular setting of our study (i.e. an academic medical center) and may have provided more favorable responses than they might have otherwise. In addition, as in any survey, the structure of the survey, the specific topics we chose to focus on, the juxtaposition of topics or categories across questions, the wording of the items, and the anchors used in the rating scales may have contributed to bias. For instance, by contrasting mental illness with physical illness, and genetic research with research in general, we may have inadvertently enhanced participants' tendency to draw distinctions that they may not have made otherwise had the interviews been less structured.

Another limitation of this study is that some safeguards (e.g., alternative decision makers) may be more complex than we were able to convey in the brief explanatory paragraphs used. In addition, despite attempts to word items and questions clearly, it is impossible to know whether participants were answering from their own perspective or from a more detached, "other people" perspective. In light of these limitations, any inferences drawn from these findings should be viewed with caution. Nevertheless, the structure of the interview allowed us to cover a broad range of topics related to ethical issues in psychiatric genetics, and to evaluate for differences in perspectives about different types of research and research safeguards that respondents may not have consciously considered or spontaneously discussed in another interview format. Finally, we did not directly assess actual research behavior (i.e., revealed preferences) of participants. Given that our respondents *were* research participants in this interview study, their responses might also be more heavily weighted toward willingness to participate in other forms of research.

Despite these limitations, these findings suggest that the presence of safeguards influences research enrollment decisions by potential volunteers and provides reassurance that those most directly affected by research practice, participants themselves, find the safeguards to be protective. The results of this investigation should help refute the notion–not uncommonly held by the research community–that ethical oversight potentially threatens the acceleration of scientific discovery. Rather, these results demonstrate that ethical oversight likely positively enables participation, which is essential for sustaining scientific advancement. Our findings, moreover, do not directly support arguments for additional safeguards specifically targeting mental illness research.

Advancing science to alleviate the suffering of people living with mental disorders and their loved ones and to lessen the burdens associated with mental disorders felt across our world depends on the generosity of research volunteers. The findings of our study suggest that human subject safeguards are favorably viewed by potential participants and underscore the importance of the conscientious implementation of these safeguard procedures by members of the research community.

Disclosures and acknowledgements

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Appendix 1. Items Describing Safeguard Procedures

1. Before a research study is started, a committee of people carefully discusses the research study to decide whether it is safe and worthwhile to conduct the study. This committee is made up of doctors and researchers from the institution where the research is conducted, and the committee also includes other people who live in the community but who do not work for the institution where the research is conducted. None of the members have any close personal or professional relationship with the researchers. The committee is called an **Institutional Review Board.** The **board** reviews all the details of the study and decides whether or not it is acceptable to do the study. The **Institutional Review Board** also decides how the study should be conducted so that the people who participate are kept as safe as possible while they are in the study. Researchers are required to do what the board says to do.
   A. How much does an **Institutional Review Board's review and approval** of a study actually **protect people** who take part in genetic research about mental illness?
   B. If you know that a study was approved by an **Institutional Review Board**, how would it influence **your willingness to participate** in a genetic research study about mental illness?
2. Another type of procedure designed to protect people in research is when an **Institutional Review Board examines or audits** a researcher's records while the study is in progress to make sure that the study is being conducted properly and safely.
   A. How much does an **Institutional Review Board's reviewing a researcher's records** during the study actually **protect people** who take part in genetic research about mental illness?
   B. If you knew that an **Institutional Review Board** might review the records of a research study, how would it influence **your willingness to participate** in a genetic research study about mental illness?
3. A second kind of committee also watches over a research study while it is being performed. The committee is called a **Data Safety and Monitoring Board.** It is made up of researchers and doctors not involved with the study in any other way. The **monitoring board** is informed

about any progress or lack of progress in the study and if any people are harmed as a result of being in the study. The **monitoring board** will stop the study if the study appears to be placing research participates at too much risk of being harmed. **A Data Safety and Monitoring Board** will also stop a study before it is over IF the data from the study show that the research participants will either definitely be helped or definitely not be helped by the treatment being studied.

A. How much does a **Data Safety and Monitoring Board** actually **protect people** who take part in genetic research about mental illness?
B. If you know that a study was being monitored by a **Data Safety and Monitoring Board**, how would it influence **your willingness to participate** in a genetic research study about mental illness?

4. Researchers are required to report to the **Institutional Review Board** and the **Data Safety and Monitoring Board** any events that have negative or adverse effects on the participants. This is called **"adverse event reporting."** Both **boards** decide whether the **adverse events** show that the risks to people in the study have become too great. In some situations, the study procedures may need to be changed or the study stopped completely.
   A. How much does having researchers **reporting adverse events** to monitoring boards actually **protect people** who take part in genetic research about mental illness?
   B. If you knew that, before a study started, researchers would **report any adverse events** in the study to the monitoring boards, how would it influence **your willingness to participate** in a genetic research study about mental illness?
5. Still another procedure is conducted before a person begins participating in a study. Before a person agrees to participate in a study, the researchers sit down and talk carefully to each person who volunteers to participate. They explain the purpose of the study, what he or she will be asked to do in the study, and about the risks and benefits of participating in the study. The researchers also answer any questions the person might have before deciding whether or not to participate in the study. Finally, the researchers ask the research participants to read a document called an "informed consent statement" that describes the study, the study's risks and benefits and other aspects of the study. If the person agrees to participate in the study, the researchers ask the person to sign the "informed consent statement" to show that they understand what will happen in the study and that they agree to participate. The procedure is called gaining **the informed consent** of people to participate in a research study. For example, we explained our study today to you and asked you to read and sign an informed consent statement before we began this interview.
   A. How much does having researchers' gain the **informed consent** of research participants actually **protect people** who take part in genetic research about mental illness?
   B. If you knew that, before a study started, researchers would ask for your informed consent by talking with you carefully about the study, how would it influence **your willingness to participate** in a genetic research study about mental illness?
6. Sometimes mentally ill people who might take part in research have symptoms that make it difficult for them to make a careful decision about whether or **not** to participate in a study. In these situations, the mentally ill person may select a family member to make the decisions about research participation. The family member is called an **alternative decision maker**, and it is his or her job to make the choices about research for the ill person. This includes deciding whether or not the person will participate in the research and deciding whether to continue or stop after the research starts. In situations where an alternative decision-maker decides to give permission for their family member to participate in a research study, the person participating is also asked to give their permission to participate as well.
   A. How much does being able to select an **alternative decision maker** actually **protect** those mentally ill people who take part in genetic research about mental illness.
   B. If you knew that researchers would use an **alternative decision maker** for any people who needed one, how would it influence **your willingness to participate** in a genetic research study about mental illness?
7. A third kind of committee called a **Conflict of Interest Committee** includes researchers and community members who are not related to the research study. **Conflict of Interest Committees** try to make sure that researchers are **not** influenced by making personal money or getting other personal advantages when conducting their research.

For example, researchers may own stock in the company that makes the drug that is being tested in the researcher's study, or the drug company may pay the researcher directly for each research volunteer recruited. Or the researcher may be paid consulting fees or speaking fees by the company which makes the drug that is being tested in the researcher's study. These kinds of situations and others are called financial "conflicts of interest." Similar situations may exist in almost any kind of medical research study, including studies about genetics and mental illnesses.

Conflicts of interest must be reported by researchers to a **Conflict of Interest Committee**. The committee is responsible for determining whether or not researchers with conflict of interest can conduct the research safely and without bias; OR, if the committee believes the conflict is too great, they can prevent or stop the study from being conducted or they can request the researcher sell his or her stock or stop getting fees or payments; OR, the committee can decide that, when a researcher has a conflict of interest, that an independent person outside the study must monitor the study and the researcher to make sure the study is conducted safely and without bias.

A. How much does a **Conflict of Interest Committee** reviewing the researcher's situation actually **protect people** who take part in genetic research bout mental illness?
B. If you knew that a **Conflict of Interest Committee** was watching over a study, how would it influence **your willingness to participate** in a genetic research study about mental illness?

8. Another procedure is called doing "**community participatory research.**" It gives people in the community where the research is conducted some say in how the research is conducted. Some research focuses on people of a certain ethnic or cultural group or on people who live in a specific geographic area. Researchers have meetings with community members from such groups of people to talk with them about the research before it is conducted, as well as sometimes while the research is going on and after the research is concluded to help interpret the meaning of the study data and results. Researchers find out what people in the community think about the risks and benefits of the study and about how community members think that the study should be conducted and results interpreted. Researchers try do what the community members think is best in conducting the study.
   A. How much does having **meetings with community members** before studies are conducted actually **protect people** who take part in genetic research about mental illness?
   B. If you knew that researchers had **meetings with members of your community** about a study, how would it influence **your willingness to**

participate in a genetic research study about mental illness?

9. To protect the privacy of people participating in research, some studies store information about participants' DNA and genes using only **code numbers** instated of using the person's names.
   A. How much does storing information using **code numbers** rather than names actually **protect people** who take part in genetic research about mental illness?
   B. If you knew that a study would store information using a **code number** rather than your name, how would it influence **your willingness to participate** in a genetic research study about mental illness?
10. Researchers are required to take a **training course** that takes a few hours to complete every 3 years to learn about the ethics of conducting research with people as research participants. The course is usually conducted on the internet by reading the course materials and then answering test questions. The training is not conducted face-to-face with an instructor. The course is designed to help researchers treat volunteers safely and with respect.
   A. How much does having researchers take such a **training course** actually **protect people** who take part in genetic research about mental illness?
   B. If you knew that all the researchers involved in your study had taken such a **course**, how would it influence **your willingness to participate** in a genetic research study about mental illness?
11. Researchers can apply to the U.S. government to receive a **Certificate of Confidentiality.** The certificate is an **extra layer** of confidentiality protection that is designed to ensure that study information can never be revealed even under extreme situations such as when the police or district attorney or a court requests to see the data because a research participant is suspected of a crime such as using illegal drugs. However, courts have not yet decided whether such a certificate protects researchers from having a disclose data about research participants when it is requested by people defending themselves in criminal cases.
   A. How much does having a **Certificate of Confidentiality** actually **protect people** who take part in genetic research about mental illness?
   B. If you knew that a study had a **Certificate of Confidentiality**, how would it influence **your willingness to participate** in a genetic research study about mental illness?

Please think in general about the **11 research procedures** that I just described in the previous questions. Recall that these procedures are designed to help protect people who participate in research.

12. How important is it to have all these procedures to protect participants in studies that do **not** include gathering **genetic** information?
13. How important is it to have all these procedures to protect participants in studies that **do** include gathering **genetic** information?
14. How important is it to have all these procedures to protect participants in **genetic research** on **physical** illness?
15. How important is it to have all these procedures to protect participants in **genetic research** on **mental** illness?

Appendix 2
Five Composite Measures of Safeguard Procedures

Composite 1: Research Review & Oversight Committees	- Institutional Review Board's review and approval - Institutional Review Board's reviewing research records - Data Safety and Monitoring Board - Reporting adverse events to Institutional Review Board and Data Safety and Monitoring Board - Conflict of Interest Committee
Composite 2: Consent & Protection of Participants	- Informed consent of research participants - Alternative decision maker
Composite 3: Confidentiality Protections	- Code numbers - Certificate of Confidentiality
Composite 4: Community Engagement	- Meeting with community members
Composite 5: Ethics Training for Researchers	- Training courses for researchers

References

Black, B.S., Wechsler, M., Fogarty, L., 2013. Decision making for participation in dementia research. Am. J. Geriatr. Psychiatry 21 (4), 355–363.

Carpenter, W.T., Conley, R.R., 1999. Sense and nonsense: an essay on schizophrenia research ethics. Schizophr. Res. 35 (3), 219–225.

Charney, D.S., 1999. The National Bioethics Advisory Commission report: the response of the psychiatric research community is critical to restoring public trust. Arch. Gen. Psychiatr. 56 (8), 699–700.

Derogatis, L.R., 1993. BSI Brief Symptom Inventory: Administration, Scoring, and Procedure Manual, fourth ed. National Computer Systems, Minneapolis, MN.

Dubois, J., Bante, H., Hadley, W.B., 2011. Ethics in psychiatric research: a review of 25 Years of NIH-funded empirical research projects. AJOB Prim. Res. 2 (4), 5–17.

Dunn, L.B., Candilis, P.J., Roberts, L.W., 2006. Emerging empirical evidence on the ethics of schizophrenia research. Schizophr. Bull. 32 (1), 47–68.

Dunn, L.B., Hoop, J.G., Misra, S., Fisher, S.R., Roberts, L.W., 2011. A feeling that you're helping": proxy decision making for Alzheimer's research. Narrat. Inq. Bioeth. 1 (2), 107–122.

Dunn, L.B., Fisher, S.R., Hantke, M., Appelbaum, P.S., Dohan, D., Young, J.P., Roberts, L.W., 2013. Thinking about it for somebody else": alzheimer's disease research and proxy decision makers' translation of ethical principles into practice. Am. J. Geriatr. Psychiatry 21, 337–345.

Erby, L.H., Roter, D., Larson, S., Cho, J., 2008. The rapid estimate of adult literacy in genetics (REAL-G): a means to assess literacy deficits in the context of genetics. Am. J. Med. Genet. 146A (2), 174–181.

Erickson, J.A., Cho, M.K., 2013. Interest, rationale, and potential clinical applications of genetic testing for mood disorders: a survey of stakeholders. J. Affect. Disord. 145 (2), 240–245.

Green, T., Flash, S., Reiss, A.L., 2019. Sex differences in psychiatric disorders: what we can learn from sex chromosome aneuploidies. Neuropsychopharmacology 44 (1), 9–21.

Hurd, Y.L., O'Brien, C.P., 2018. Molecular genetics and new medication strategies for opioid addiction. Am. J. Psychiatry 175 (10), 935–942.

Kim, S.Y., Millard, R.W., Nisbet, P., Cox, C., Caine, E.D., 2004. Potential research participants' views regarding researcher and institutional financial conflicts of interest. J. Med. Ethics 30 (1), 73–79.

Kim, S.Y., Kim, H.M., Langa, K.M., Karlawish, J.H., Knopman, D.S., Appelbaum, P.S., 2009. Surrogate consent for dementia research: a national survey of older Americans. Neurology 72 (2), 149–155.

Laegsgaard, M.M., Kristensen, A.S., Mors, O., 2009. Potential consumers' attitudes toward psychiatric genetic research and testing and factors influencing their intentions to test. Genet. Test. Mol. Biomark. 13 (1), 57–65.

Liu, X., Li, Z., Fan, C., Zhang, D., Chen, J., 2017. Genetics implicate common mechanisms in autism and schizophrenia: synaptic activity and immunity. J. Med. Genet. 54 (8), 511–520.

McDonald, K.E., Conroy, N.E., Kim, C.I., LoBraico, E.J., Prather, E.M., Olick, R.S., 2016. Is safety in the eye of the beholder? Safeguards in research with adults with intellectual disability. J. Empir. Res. Hum. Res. Ethics 11 (5), 424–438.
Michels, R., 1999. Are research ethics bad for our mental health? N. Engl. J. Med. 340 (18), 1427–1430.
National Bioethics Advisory, C., 1998. Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity. National Bioethics Advisory Commission, Rockville, MD.
Overton, E., Appelbaum, P.S., Fisher, S.R., Dohan, D., Roberts, L.W., Dunn, L.B., 2013. Alternative decision-makers' perspectives on assent and dissent for dementia research. Am. J. Geriatr. Psychiatry 21 (4), 346–354.
Palmer, B.W., Dunn, L.B., Appelbaum, P.S., Mudaliar, S., Thal, L., Henry, R., Golshan, S., Jeste, D.V., 2005. Assessment of capacity to consent to research among older persons with schizophrenia, Alzheimer disease, or diabetes mellitus: comparison of a 3-item questionnaire with a comprehensive standardized capacity instrument. Arch. Gen. Psychiatr. 62 (7), 726–733.
Public comments, 1998. National Bioethics Advisory Commission. https://bioethicsarchive.georgetown.edu/nbac.
Roberts, L.W. (Ed.), 2013. Community-Based Participatory Research for Improved Mental Healthcare: A Manual for Clinicians and Researchers. Springer, New York.
Roberts, L.W., Kim, J.P., 2017. Receptiveness to participation in genetic research: a pilot study comparing views of people with depression, diabetes, or no illness. J. Psychiatr. Res. 94, 156–162.
Roberts, L.W., Roberts, B., 1999. Psychiatric research ethics: an overview of evolving guidelines and current ethical dilemmas in the study of mental illness. Biol. Psychiatry 46 (8), 1025–1038.
Roberts, L.W., Dunn, L.B., Kim, J.P., Rostami, M., (in press). Perspectives of psychiatric investigators and IRB chairs regarding benefits of psychiatric genetics research. J. Psychiatr. Res..
Roberts, L.W., Hammond, K.A., Warner, T.D., Lewis, R., 2004a. Influence of ethical safeguards on research participation: comparison of perspectives of people with schizophrenia and psychiatrists. Am. J. Psychiatry 161 (12), 2309–2311.
Roberts, L.W., Warner, T.D., Anderson, C.T., Smithpeter, M.V., Rogers, M.K., 2004b. Schizophrenia research participants' responses to protocol safeguards: recruitment, consent, and debriefing. Schizophr. Res. 67 (2–3), 283–291.
Roberts, L.W., Reicherter, D., Adelsheim, S., Joshi, S.V. (Eds.), 2015. Partnerships for Mental Health: Narratives of Community and Academic Collaboration. Springer, New York.
Sullivan, P.F., Agrawal, A., Bulik, C.M., Andreassen, O.A., Borglum, A.D., Breen, G., Cichon, S., Edenberg, H.J., Faraone, S.V., Gelernter, J., Mathews, C.A., Nievergelt, C.M., Smoller, J.W., O'Donovan, M.C., Psychiatric Genomics, C., 2018. Psychiatric genomics: an update and an agenda. Am. J. Psychiatry 175 (1), 15–27.
Thapar, A., 2018. Discoveries on the genetics of ADHD in the 21st century: New findings and their implications. Am. J. Psychiatry 175 (10), 943–950.
Ware Jr., J., Kosinski, M., Keller, S.D., 1996. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med. Care 34 (3), 220–233.
World Health Organization, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization, Licence CC BY-NC-SA 3.0 IGO., Geneva.
Yehuda, R., Flory, J.D., 2018. Considering the genetic and epigenetic signature of early adversity within a biopsychosocial framework. Am. J. Psychiatry 175 (6), 491–492.
Zeier, Z., Carpenter, L.L., Kalin, N.H., Rodriguez, C.I., McDonald, W.M., Widge, A.S., Nemeroff, C.B., 2018. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. Am. J. Psychiatry 175 (9), 873–886.