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Informed consent and ethical reporting of research in clinical trials involving participants with psychotic disorders

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ABSTRACT

Informed consent is critical for protecting vulnerable individuals interested in research participation, like those with psychotic disorders (e.g. schizophrenia, schizoaffective disorder, schizophreniform disorder, etc.). Individuals with psychotic disorders may have fluctuating capacity to consent and capacity assessment prior to research participation can help determine decisional status. However, there is little research on how, or if, these assessments are conducted in clinical research. A systematic review of randomized medication or device trials that specifically recruited individuals with psychotic disorders to understand the use and reporting of capacity assessment to consent was conducted. A total of 646 articles were reviewed using a developed questionnaire on ethical reporting of consent practices and capacity assessment. Less than 10% (n = 34; 5.3%) of the studies reported an assessment of capacity to provide informed consent and less than half of those used a standardized assessment. Sixty-four (9.9%) of the articles reported capacity to provide informed consent in the study's inclusion and exclusion criteria. Additionally, 66 (10.2%) of the articles did not provide a statement about institutional review board (IRB) approval; and given the large number of medication and device trials, one out of five articles (n = 134; 20.7%) reported no statement about potential conflicts of interest. Future research should continue to examine these issues and to better understand the benefits and challenges of research participation with psychotic individuals and their decisional capacity in this context.

1. Introduction

Informed consent is an essential element in the ethical protection of human subjects in biomedical research. Yet there is a gap between the theory of informed consent and its implementation in clinical practice and research [1,2]. In research, gaps in informed consent may include participants' understanding of relevant research-related information that affects their ability to provide informed consent. Capacity in research has been discussed by several authors [3–6] and generally includes the ability of an individual to make and communicate a decision after understanding and appreciating the goals of research and its potential impact [7]. However, there are many limitations in capacity to consent that stem from a wide variety of factors. This includes legal precedents, such as age or being declared incompetent through judicial means. Medical conditions also interfere with cognitive processes. Dementia [8], developmental disabilities [9], and serious mental illness [10] all correlate with high rates of impaired capacity. Those hospitalized in inpatient settings, often recruited for research purposes, may also have diminished capacity to consent, with research suggesting 34–45% of individuals lacking capacity [11]. For these participants, researchers cannot simply assume decisional capacity to provide informed consent [12]; it must be assessed and evaluated.

Psychotic disorders are a group of mental illnesses characterized by disorganized thoughts, hallucinations and/or delusions [13]. People with psychotic disorders experience a disconnect from the reality experienced by others. Specific psychotic disorders also come with other cognitive and psychological features, like flat affect and avolition with schizophrenia and the depressive or manic episodes of schizoaffective disorder. Symptoms are often unstable, with waxing and waning of severity across the lifespan. While not explicitly identified as a group protected by additional regulations like children and prisoners [14], people with psychotic disorders are often considered vulnerable for research participation because of their changing capacity status [15]. Their symptoms often fluctuate, creating periods where they lack capacity and periods where they experience no significant impairment or might present with narrow thought distortions that do not interfere with capacity [11]. Enrollment in clinical trials, while important to improving the health of this population, can have significant adverse

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consequences. This was seen in the case of Dan Markingson, a young man who participated in a psychiatric research study at the University of Minnesota that aimed to compare three atypical antipsychotic medications. Mr. Markingson was recruited from an inpatient psychiatric unit where he was experiencing acute psychosis [16]. This participant committed suicide while on study and ethical concerns surrounding his recruitment, informed consent, and decisional capacity remain.

Elliott and Lamkin recommend a moratorium on the recruitment of individuals on inpatient psychiatric units [17], but symptoms of psychotic disorders may fluctuate and often do not require psychiatric hospitalization. Ending recruitment from these settings may protect vulnerable individuals but a blanket exclusion of persons with psychotic disorders would be unjustified and unethical. In their meta-analysis on decisional competency of schizophrenic patients in clinical trials, Hostiuc et al. [18] found decreased levels on four elements of decision-making as measured by the MacArthur Competence Assessment Tool (MacCAT-CR): understanding, appreciation, and reasoning around research participation. They argued, however, that schizophrenic patients should be considered competent unless deemed otherwise. In their study of consent capacity for people with schizophrenia, Appelbaum notes that capacity to provide informed consent varied substantially when using an assessment measure, as "standard deviations in the schizophrenic group were large, and there was a good deal of overlap with the non-ill subjects" [19]. This is to say that many of the patients with schizophrenia scored as well as control subjects and were found to have capacity to consent to research participation. Because of this variability and the necessity to protect this vulnerable population, standardized assessments of capacity are recommended for these participants [19].

Capacity should be addressed in the development of research proposals and when enrolling psychiatric populations in research studies [20]. Due to the high variability of results when conducting unstructured assessments [21], standardized assessments have been recommended to create more consistent, reliable assessments of capacity [22]. Combining assessments with clinical judgment may provide a higher level of confidence about an individual participant's capacity; but, questions remain on best approaches and how to safeguard psychotic patients while still affording them the opportunity to participate in research.

Multiple reviews have examined capacity and capacity assessment for participants in clinical research [22–24]. However, the process of capacity assessment for informed consent, especially how it is conducted and by whom, and also how it is reported for patients with psychotic disorders remains largely unexplored. For the purpose of this review, we used the definition of "consent capacity" provided by the National Institutes of Health, that reflects a specific capacity and is described as "an adult's ability to understand information relevant to making an informed, voluntary decision to participate in research." [25] Thus, we conducted a systematic review of medicine and device clinical trials with participants diagnosed with psychiatric disorders to understand capacity assessment in clinical research and how it is reported in the scientific literature. Additionally, because there are other important procedural aspects to clinical trials, including IRB approval and potential conflicts of interest associated with funding sources, we secondarily report these incidental findings.

2. Methods

The review followed the PRISMA principles for systematic reviews [26]. Articles were identified using searches of three databases, including Pubmed, PsycINFO and Embase. The search focused on studies of participants with a psychiatric disorder with psychotic features (e.g., schizophrenia, schizoaffective disorder, a mood disorder with psychotic features) who were participating in testing a medication or device in a randomized control trial (RCT). Table 1 presents the search terms used for each of the databases.

Table 1
Search terms and strategy.

Search terms
Psycinfo searches
(su(psychosis) OR su(schizoph*) OR su(schizoaffect*) OR su(psychosis) OR su (psychoses*) OR su(hallucinat*) OR su(delusion*)) AND su(clinical drug trials) OR su(clinical trial) OR su(medication trial) OR su(drug trial) OR su(device trial) OR su(randomized controlled trial) NOT pediatric NOT systematic review
Results: 2127
EMBASE search
'controlled clinical trial'/exp. OR 'medication trial' OR 'drug trial' OR 'device trial'
AND
'psychosis'/exp. OR 'schizophrenia'/exp. OR 'hallucination'/exp. OR 'delusion'/exp. OR 'schizophren*' OR 'schizoaffect*' OR 'psychoses' OR 'psychotic*'
NOT pediatric
NOT retrospective study
Results: 3778
PubMed search
"Schizophrenia"[Mesh] AND ("2007/04/03"[PDAT]: "2017/03/30"[PDAT] AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms]) Filter: Clinicial Trial
Results: 2262

2.1. Inclusion and exclusion criteria

Studies were included if the: 1) study design was an RCT, 2) participants with psychiatric diagnoses with psychotic symptoms were enrolled (although not all participants needed to have psychotic disorders), 3) studies were published from 2007 to 2017 in peer-reviewed scientific journals and available in the English language, and 4) participants were adults. Articles were excluded if they 1) did not specifically recruit participants with psychotic disorders, 2) were not randomized, 3) had no recruited control group, or 4) were a secondary analysis of previously published research or publicly available datasets. Randomized clinical trials of medications and devices were the focus of the review because they tend to involve higher risk than psychosocial interventions and observational studies. We also excluded review articles, letters-to-the editor, clinical guidelines or other non-data-based articles.

2.2. Procedures

All articles were downloaded to a reference management software program for review in which all duplicates were removed and abstracts screened for inclusion in the analysis. Each article was reviewed and coded using a questionnaire developed by the authors that evaluated research reporting and informed consent capacity assessment in each article (see Appendix A for an example of the coding form and explanations of coding procedures). Following review and coding of the first 20 articles, the final coding questionnaire was adjusted after consultation among the authors. In addition, inter-rater reliability of coding procedures was assessed by the first author (GW) and a research assistant with a Cohen's kappa statistic ($k = 0.926$).

After development of the final coding questionnaire, all coding was conducted using REDCap [27] and then exported to SPSS [28] for data management and analytics. Descriptive statistics were generated, and chi-square tests were conducted to determine the effects of year of publication on select outcomes.

3. Results

The initial search strategy returned 8155 articles, narrowed to 646 articles (See PRISMA flow chart diagram; Fig. 1) based on the inclusion and exclusion criteria.

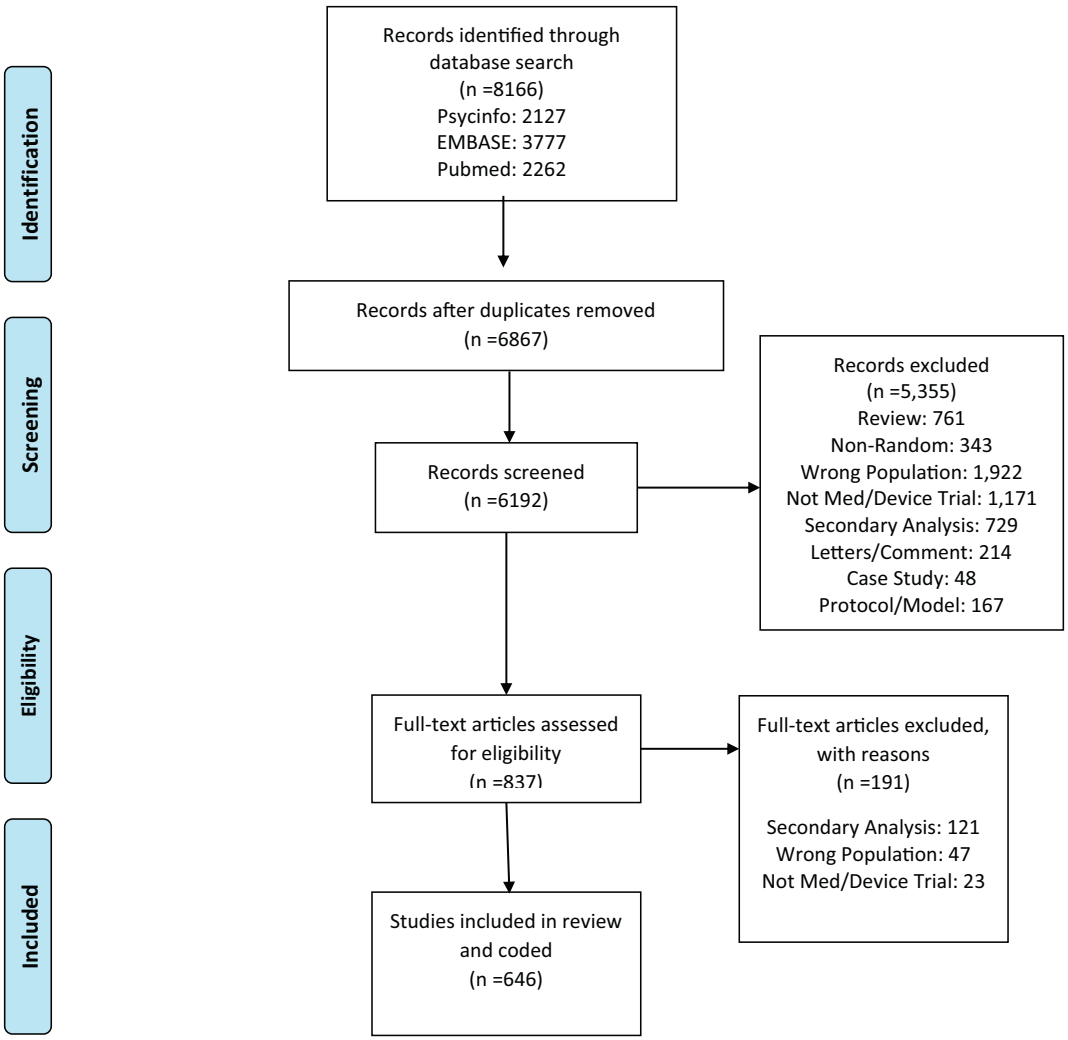

Fig. 1. PRISMA flow diagram.

3.1. Article demographics

A total of 97,288 participants with psychotic disorders participated in the 646 reviewed medication and device trials. Most of the studies only recruited patients with psychotic disorders (95.8%). A small percent of studies included individuals with other psychiatric disorders (0.8%) or healthy participants (4.4%) as controls. The most common psychiatric diagnoses among participants in these trials was schizophrenia. Most of the reviewed articles (n = 460, 71.2%) were from journals that focused on general psychiatry journals and 101 (15.6%) from journals focused on psychosis and psychotic disorders specifically. Medication trials made up the overwhelming majority of articles (n = 595; 92.1%), mostly antipsychotic medications (e.g. risperidone, olanzapine, clozapine, paliperidone) and medications/devices for treatment of symptoms, side effects and smoking cessation (e.g. repetitive transcranial magnetic stimulation, nicotine patches, metformin, simvastatin).

More than a quarter of studies were conducted wholly or in part in the United States (n = 187; 28.9%). All combined, the majority of studies were conducted outside the United States in a variety of countries, including Asia, Europe, and the Middle East, among others (see Table 2). About 20% (n = 127, 19.7%) of the studies did not state where data collection took place. Slightly over 30% of studies reported funding by governmental agencies, 47% by pharmaceutical companies and 16% by private foundations; many reported funding from multiple funding sources, agencies and mechanisms (See Table 2 for a more thorough breakdown of countries of data collection, study populations and funding sources).

3.2. Responsible reporting of research

A majority of the articles (80.3%) reported the country of data collection and more than three-quarters (76.6%) reported the country in which IRB approval was obtained. A number of studies did not report where data collection took place (N = 127) or where IRB approval was obtained (N = 151). Ten percent (10.2%) of the articles had no information about whether the study received approval from an IRB, ethics or research board review; and, an additional 5% did not state whether informed consent was obtained from participants.

Participants were recruited from a variety of settings, including inpatient (22.4%), outpatient (35.8%) or both (14.9%), while more than a third of articles (35.8%) did not report any information about whether participants recruited for the study were inpatient at the time of recruitment. Though most of the studies were large, randomized controlled medication and device trials with multiple funders, 20.7% did not include any statement about potential conflicts of interest that the authors or study staff may have had. This number decreased significantly from 2008 onwards ($\chi^2 \leq 0.001$, df = 10). Interestingly, 14.8% of the 303 studies that reported funding by pharmaceutical companies had no statement of potential conflicts of interest or financial disclosure information by the authors.

Table 2
Information on study articles.

Country of data collection[a]										
USA	Iran	India	China	Russia	Taiwan	Korea	Canada	Japan	Ukraine	Romania
187	45	44	41	39	34	31	29	27	27	25
Germany	Israel	South Africa	Italy	Spain	Australia	UK	Czech Republic	France	Other	Not Stated
23	23	20	20	20	17	16	15	15	132	127
Psychotic disorders enrolled[a]										
Schizophrenia		Schizoaffective		Schizophreniform		Bipolar Disorder w/Psychotic Features			Other	
625 (96.7%)		204 (31.6%)		55 (8.5%)		10 (1.5%)			43(6.7%)	
Site(s) of recruitment										
Inpatient			Outpatient & General Public			Both			Not Stated	
145 (22.4%)			174 (26.9)			96 (14.9%)			231 (35.8%)	
Research funding source[a]										
Hospital or Health System		Government		Pharmaceutical Company		Private or Non-Profit Funding		University		Source Not Stated
17 (2.6%)		195 (30.2%)		303 (46.9%)		105 (16.3%)		74 (11.5%)		93 (14.4%)

[a] Articles could fit more than one category so totals will exceed 646/100%.

3.3. Capacity Assessment

All studies recruited individuals with psychotic disorders; however, only a small percentage (N = 64; 9.9%) listed capacity or ability to provide informed consent as part of the study's inclusion or exclusion criteria. Thirty-four studies reported using a capacity assessment; of these, twenty-two did not mention capacity in their inclusion or exclusion criteria (Table 3). Of the 34 that identified the use of a capacity assessment, only four reported excluding potential participants because of their lack of capacity to provide informed consent. Only two of the four studies that excluded participants who lacked the capacity to consent reported the number of participants who were excluded for this reason. Ninety-eight (15.2%) articles mentioned the involvement of family in the consent process, with the family acting either as a surrogate for consent or requiring family consent as well as individual consent. None of the studies that discussed family involvement in the consent process discussed any other capacity assessment or how the decision was made to involve family in an individual's consent to participate in the study.

Sixteen of the thirty-four studies that reported capacity assessment used a standardized capacity assessment of some kind; the rest used researcher or provider judgment of capacity to provide research consent. The following assessments were used: the MacCAT-CR [29] (n = 4), the Evaluation of the Capacity to Sign Consent by DeRenzo [30] (n = 5), Wirshing's capacity assessment method [31] (n = 1), and standardized quizzes of unknown origin (n = 4). Two articles reported that study-specific procedures were developed to test ability to provide informed consent, but these procedures were not described. Eleven of the articles reported non-standardized assessment by research staff and the remaining six did not report how capacity was assessed, only that an assessment took place.

Of the small number of studies that used capacity assessments, one was a device trial and the rest were medicine trials. These studies recruited from inpatient (3), outpatient (12), both (9) or didn't state the status of recruited participants (10). Sixteen studies took place in the United States, nine did not state where they took place and the remainder were conducted in the following countries: Taiwan (n = 2), United States and the United Kingdom (n = 1), India (n = 1), Russia (n = 1), Iran (n = 1), Finland (n = 1), Israel (n = 1), and Australia (n = 1). These studies were spread across the ten-year time span, with no significant relationship found between use of capacity assessments and year of publication ($\chi^2 = 0.245$, df = 10).

Table 3
Illustrative quotes from reviewed studies on capacity assessment and inclusion and exclusion criteria.

Capacity assessment
"Participant's ability to provide valid informed consent was documented using validated study-specific procedures."
"Patient's competence to consent was determined by his/her own psychiatrist."
"All subjects were screened for the ability to provide informed consent"
Inclusion and exclusion criteria
"Patients were included in the study if they met the following criteria: understood the nature of the study and signed an informed consent document."
"All newly hospitalized patients with schizophrenia and an acute exacerbation of their psychosis and demonstrating deterioration in self-care or social function were screened"
"[Participants were excluded if they were] unable to provide consent or involuntarily committed to psychiatric hospitalization."
"[Participants were excluded if they had] cognitive impairment or symptom severity that precluded an ability to provide a generally coherent narrative or to provide informed consent."

4. Discussion

Vulnerable populations have the right to participate in research and often additional safeguards are necessary to protect them from potential harm. This is especially true when those with a mental illness participate in clinical trials where adverse events or other psychological, physical, and emotional risks might exist. Despite its importance in clinical research, information on the capacity of participants with psychotic disorders to participate in research or assessment of their capacity to participate was not well represented in our analysis of the literature. Few articles explicitly include capacity to give informed consent in their inclusion or exclusion criteria, despite the studies all directly recruiting patients with psychotic disorders. Fewer still had information about the way that capacity to consent to research participation was assessed and these trends were not concentrated in earlier time periods or specific countries.

Though there have been standardized assessments of capacity to provide informed consent since at least 2001 [29], these assessments were not, as we had hypothesized, described as a fundamental part of the reviewed clinical trials research for individuals with psychotic disorders. Like the use of many standardized assessment tools, significant variation was found when examining their use in research, but, overall, few articles reported the use of any kind of assessment of capacity to consent to research participation, much less a standardized capacity assessment. The information that is available from the studies in our analysis raises many questions on the recruitment of vulnerable participants with psychotic disorders and how to achieve ethical best practices. For example, we don't know how capacity assessment was viewed by principal investigators in the various studies that we reviewed or whether it was something required by the designated IRBs since a large majority of studies occurred outside the United States. Qualitative research would help to understand the nuances of capacity assessment with psychotic patients and the research team's role in such

assessments in both the developed and developing world.

People with psychotic disorders may or may not have capacity to consent to research participation and allowing an individual with impaired capacity to consent to participate in research is ethically problematic and, in some jurisdictions, illegal. This population may experience intense psychological symptoms as well as high rates of medical comorbidities and socioeconomic marginalization. They may also be particularly susceptible to the negative side effects of research, especially if they do not understand the procedures, risks and benefits and why they are participating in the research. We agree with Appelbaum who argued that research with psychiatric patients continues to raise several normative bioethical questions, particularly on how one balances the risks and potential benefits to this population whose decisional capacity might wax and wane [19]. We still are not clear on what level of capacity is acceptable that also corresponds to the level of study risk. Psychiatric patients should be afforded the opportunity to receive the potential benefits that might come from their study participation, but negative consequences can be exacerbated by their lack of resources and comorbid medical conditions, which may be more likely in those with more severe symptoms and decreased capacity [32,33]. Finally, the studies we examined were higher risk than non-clinical observational trials, all with the potential for major medical side effects and possibly even death. Thus, the lack of information about capacity to provide informed consent for research participation raises questions about why this information was not reported. If we are uncertain about whether consent at the beginning of the participant's research process was conducted, it creates further concerns on the overall scientific conduct of the study.

4.1. Voluntariness of participants

There are important ethical considerations in addition to consent capacity when conducting research with patients with psychotic disorders. For example, the ability to voluntarily agree to participate, refuse participation, or withdraw from the trial is an important consideration since novel psychiatric treatment is often linked to clinical trial participation. Voluntariness is an essential element of being informed; participants must freely decide whether the research supports their interests and goals. Although the ability to autonomously agree or refuse participation is part of the informed consent process, the focus of this paper was capacity to consent, and therefore specific information about voluntariness, refusal, and drop-out was not collected. However, more research is needed on voluntariness of psychotic patients to enroll in research. We don't know the types of constraints that might affect voluntariness among the psychiatric population, particularly those with psychosis. Research on specific individual, surrogate, situational, and clinician-researcher characteristics and their influence on voluntariness need to be explored [34].

As outlined by Nelson, Robert and Merz [35], the dual relationship as provider and clinical researcher and the promise of medical or psychiatric care can have a coercive effect on participants, especially those with questionable capacity. This can make initial refusal and withdrawal from a study more difficult and financially fraught for participants. If, for example, patients with psychotic disorders transfer their psychiatric care to that given during study participation, or participation is the only way they can receive care due to economic concerns, they may not feel able to refuse participation or leave the trial that they joined. Further work is necessary to understand if individuals with psychotic disorders, regardless of capacity, believe that they can voluntarily withdraw from clinical research without jeopardizing clinical care or relationships with providers.

4.2. Incidental issues

Finally, although it was not the initial purpose of this study, the authors were concerned by the lack of information in many studies around reporting conflicts of interest, the location of data collection, and IRB approval. These details are both useful for understanding the context of studies and whether the studies have followed ethical guidelines for research. As many of the articles were from scientific journals that focus on psychotropic trials and biopsychological measurement, there may be different standards and requirements in these trials than in other disciplines or journals that make location of data collection and IRB approval standard. Similarly, conflicts of interest may be less worrisome in certain countries or not required reporting by all journals. The number of articles that lacked statements about conflicts of interest decreased after 2009 but there were articles up to 2017 that did not have any statements on conflicts of interests, financial or otherwise. Finally, IRB or some form of ethics review is a cornerstone of research ethics and participant protections; any studies—especially in the United States and European Union countries—without ethics review is worrisome. Even if approval was gained but simply not reported, academic journals and their publishers have an ethical responsibility to ensure that information about studies is present in articles such that readers can determine if the contained research met ethical requirements with appropriate oversight.

4.3. Limitations

This systematic review has several limitations, most prominently that it is a retrospective review of the published literature and may not adequately reflect the way that research was conducted in the studies that we analyzed. Researchers may have considered consent capacity to be separate from their inclusion or exclusion criteria, which often focuses on medical and socio-demographic characteristics of the population. Because some studies included consent capacity in the inclusion or exclusion criteria and others did not, there remains some confusion on how consent capacity should be reported and in what context. Author guidelines and other journal constraints may not always call for reporting the information that we looked for and coded, including information about conflicts of interest, IRB approval, and data collection location. All research, however, should report ethical approval. It is possible that guidelines on capacity to consent were used by researchers when conducting these studies but were simply not reported in the articles. Additionally, some articles may have placed information such as informed consent capacity screening in a separate location, such as a published protocol. Nevertheless, many studies in our review did not include capacity to consent to research in their inclusion or exclusion criteria; it was also not clear how or if study staff assesses consent capacity.

The recruitment of individuals from inpatient psychiatric settings without capacity assessment is of concern, as these individuals may experience acute symptom exacerbations during their treatment. Further work is necessary to better understand how capacity to consent to research participation is assessed in medical and device clinical trials, as well as whether there are consistent, ethical policies that protect the psychiatric population as they engage in clinical trials research.

We propose several recommendations for researchers and scientific journals based on the results of this systematic review. First, capacity to provide informed consent or the use of surrogate consent should be listed as an inclusion or exclusion criteria for every study of individuals with psychotic disorders, especially high-risk studies like randomized medication and device trials. Second, we need broader dialogue within the research community on the reliability and validity of standardized capacity assessments and their generalizability across individuals, situations, and settings. Finally, scientific journals and peer-reviewers should require that articles include information about ethical approvals (IRB or similar ethical review). Moreover, researchers should clearly provide information about where the study took place, where the ethics review was conducted, and the process for obtaining informed consent for the overall protection of patients with a psychotic disorder who

participate in clinical research.

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Appendix A. Selected coding questionnaire

Variables	Notes on coding
Names of Authors	
Journal Title	
Year of Publication	
Was journal focused on general psychiatry/psychology, individuals with psychotic disorders or neither?	Based on the title of the journal
Medication or Device Trial	
Number of Participants	
Psychotic disorder diagnoses of participants in trial	
Status of patients when recruited to study?	Categories were inpatient, outpatient, both or not stated
Funding agencies, mechanisms and sources	
Countries of data collection and IRB approval?	If either was not explicitly stated, context clues in article were used (e.g. "Study was approved by University of Queensland and conducted at a local hospital") but authors affiliations were deemed insufficient to know locations
Was IRB, ethical review board, hospital review or other review process stated to be acquired?	
Was informed consent stated to be gained from participants in study?	"Participants were recruited" and other variations on this phrase were not considered adequate to be considered acknowledgement of informed consent
Was surrogate or family involvement in the informed consent process described?	
Was capacity to consent to research participation stated in the inclusion or exclusion criteria?	The statement "patients were willing to provide informed consent" was not considered adequate as it does not pertain to capacity
Was a capacity assessment used during the study? If so, what?	
Does the article state any participants were excluded due to impaired capacity to consent? If so, how many?	
Is there a statement about potential conflicts of interest? If so, with what groups or agencies?	

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