Challenges and Strategies for the Recruitment of Patients With Schizophrenia in a Research Setting

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Abstract

Background: With numerous potentially novel targets and pharmacodynamic biomarkers for schizophrenia entering late-stage testing, the next decade will bring an urgent need for well-conducted clinical trials. A critically important step for the successful execution of clinical research trials is timely and appropriate recruitment of participants. Patients with schizophrenia can be especially challenging to recruit because of the disability inherent in psychotic spectrum disorders. Research on how best to recruit for clinical trials is understudied. Clearly defining a model for recruitment procedures would be valuable for researchers and, by extension, the patient populations that may benefit from the insight gained by future clinical research.

Methods: This article aims to offer suggestions for recruitment based on years of experience at the Columbia Schizophrenia Research Clinic (CSRC), a hub for clinical trials focusing on the etiology and treatment of various psychotic disorders.

Results: The present report provides practical, step-by-step recommendations for implementing the highly effective CSRC recruitment model, including the benefits of 2 recruitment initiatives that were instituted in 2018: hiring a dedicated recruiter and targeted chart reviews at affiliated clinics. Other topics discussed include our umbrella protocol and database, advertising, and tips for collaborating with external sites.

Conclusions: Despite ongoing complications from coronavirus disease 2019, these strategies have been successful, increasing the rate of both consents and study enrollments by approximately 40% and enabling the CSRC to conduct multiple studies simultaneously.

Keywords: Challenges, strategies, recruitment, research, schizophrenia

INTRODUCTION

Schizophrenia is a heterogenous, major mental illness that affects approximately 1% of the population worldwide. It has a complex etiology.

Even with the best available treatments, only 10% to 20% of patients with schizophrenia recover fully (Jaaskelainen et al., 2013; Taylor and Jauhar, 2019). In particular, both cognitive deficits (Green et al., 2012, 2015) and negative symptoms (Kantrowitz, 2017, 2021a) typically persist, despite the best available psychiatric treatments. Although significantly effective against psychotic symptoms such as delusions and hallucinations, current US Food and Drug Administration-approved treatments for schizophrenia have limited efficacy against cognitive deficits and negative symptoms.
Several novel-mechanism, non–dopamine type 2 receptor–targeting compounds (Gomes and Grace, 2021), including serotonergic (Kantrowitz, 2020; Davidson et al., 2022; Sehatpour et al., 2022), non-D2R dopaminergic (Abi-Dargham et al., 2022), glutamatergic (de la Garrigue et al., 2020; Fleischhacker et al., 2021; Goh et al., 2021; Murthy et al., 2021), trace amine-associated receptor 1 (Koblan et al., 2020; Kantrowitz, 2021b), and muscarinic (Brannan et al., 2021) compounds, are under active investigation. Given the breadth of options, there is optimism for a near-term potentially “game-changing” treatment for partially or fully treatment-resistant schizophrenia, including specific treatments for persistent negative symptoms or cognitive deficits. Nevertheless, given the historical difficulty of phase 3 success and the rising number of placebo effects, this optimism is tempered by caution. Thus, the combination of unmet needs in schizophrenia coupled with the growing number of potentially viable targets speak to the need to conduct high-quality interventional research in schizophrenia. Many factors contribute to the success or failure of clinical research, but a key and understudied issue is timely and accurate identification and enrolment of appropriate participants. The Columbia Schizophrenia Research Clinic (CSRC), a joint venture of the New York State Psychiatric Institute (NYSPI) and the Columbia University Department of Psychiatry, has more than a decade of experience in federal, foundation, and privately funded research and in seeing investigator-initiated, biomarker-driven clinical trials from conception to publication (Jaroskog et al., 2015; Girgis et al., 2016, 2018, 2019; Kantrowitz et al., 2016, 2019, 2020a, 2020b; Javitt et al., 2018; Clelland et al., 2020; Sehatpour et al., 2022). The CSRC is also a referral base for Columbia faculty studies (Lee et al., 2018; Sehatpour et al., 2020) and a site for phase 2/3 industry-sponsored, multicenter studies (Bugarski-Kirola et al., 2016, 2017; ClinicalTrials.gov, NCT02717195, 2019, NCT03503318, 2022; Brunette et al., 2020). Accordingly, we have a need to enroll participants with varied symptomatology, including those with prominent negative symptoms (Bugarski-Kirola et al., 2017), persistent auditory hallucinations (Kantrowitz et al., 2019), and cognitive impairments (de la Garrigue et al., 2020), as well as those in an acute exacerbation (ClinicalTrials.gov, NCT03503318) or a first episode (Abi-Dargham et al., 2022). The present report describes the evidence-based recruitment model we have used for recruitment at the CSRC, focusing on recommendations for implementing 2 recruitment initiatives—hiring a dedicated recruiter and targeted chart reviews at affiliated clinics—both of which have been particularly successful. The effect of these interventions is illustrated in Figure 1, which shows the mean number of participants newly screened, providing consent, and enrolled in the 3 years before and after these interventions were instituted.
at first, and then transitioned to full time depending on the number of new, recruited participants. An ideal recruiter should be outgoing, self-motivated, optimistic, persistent, and excited about the role. Similar to a baseball player’s batting average, for which failing 7 out of 10 times still leads to an excellent .300 batting average, a good recruiter should be prepared for but not disheartened by failure. Many if not most encounters will not result in immediate success, and a good recruiter can carefully balance perseverance in building new relationships with clinics and interested participants without veering into coercion of a vulnerable population.

Although we prefer prior experience in clinical research, psychiatry, or psychology, we have also had success with master’s level personnel who have experience in other medical fields. Their background can be established through formal education or prior employment experience. For those with less direct experience with people who have psychosis, being a quick learner is essential because the role requires familiarity with the most common symptoms, course, and severity of schizophrenia. This background knowledge will help the recruiter accurately relay important information to potential study participants with varying degrees of disease severity, potential referral sources, and the medical personnel conducting the trial. The recruiter’s education regarding psychiatric diseases can be facilitated by providing allocated time for the recruiter to shadow interviews and self-study. Regardless of background, recruiters should know their limitations and seek guidance from their supervisor or principal investigator (PI), especially when safety concerns or questions arise. Additionally, having the technical skills necessary to create informational material for patients and for recruitment in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA); Adobe Creative Cloud (San Jose, CA, USA); or other, similar programs is important.

The recruiter’s job description and responsibilities should be made clear from the beginning. The research center should provide recruiters with instructional information about how to contact and obtain consent from potential participants, determine their eligibility, and schedule them for their first appointment. Recruiters must be trained on how to ask questions that lead to clear answers, how to use those answers to anticipate eligibility for present and future studies, and how best to approach patients with schizophrenia. The research center should perform an internal assessment of areas where current recruitment efforts are lacking, and the new hire should be offered an opportunity to contribute to improvements in those areas. The goals of the recruitment position, such as expanding the research participant database and retaining current participants through follow-up, should be discussed. Expanding the research participant database can occur through both recruiting new participants and developing partnerships with other inpatient/outpatient providers. The recruiter will be responsible for documenting all important meetings, participant encounters, and recruitment efforts. Training on CITI, the Health Insurance Portability and Accountability Act (HIPAA), and protected health information (PHI) are also essential early requirements.

When a potential participant signs consent, the main point of contact shifts to a research assistant. We maintain this division of labor to stress the recruiter’s focus on recruitment but understand that this relative firewall from the rest of the clinic staff can be isolating, especially because a large part of the recruiter’s day is spent conducting solitary activities, such as making phone calls and reviewing charts. Thus, we include recruiters in scheduled team meetings and situate them near the rest of the group to maintain a sense of connection. Moreover, our recruiter is prepared to continue to act as an available liaison between the study participants and the research personnel, building on the rapport developed during the initial contacts.

Finally, recruiters should be forward-thinking and able to determine which potential participants are the best fit for a particular study, especially when the center is conducting multiple studies simultaneously. Recruiter should, therefore, have the foresight to know which participants should be considered for upcoming trials.

**UMBRELLA (SCREENING) PROTOCOL**

We use an institutional review board (IRB)-approved “umbrella protocol,” which covers permission to collect PHI, conduct in-person and telephone screenings, and review medical records at affiliated clinics under our IRB jurisdiction (see “Chart Reviews at Collaborating Recruitment Sites”). This protocol includes an approved phone script (Figure 2) as well as general and study-specific advertisements and brochures for external clinicians and potential participants (see the section “Advertising”). We conduct screening for all CSRC trials under this umbrella, allowing for a systematic assessment of eligibility for trials while alleviating the need to reinvent the wheel for every new study. The screening protocol includes a waiver of written documentation of consent to conduct a phone interview or chart review. For participants who progress to in-person consent, written documentation of consent should be obtained. We also request and document permission to reconnect for the next 3 years, allowing for rescreening for subsequent trials. Thus, although the focus of chart reviews and 1-on-1 interviews is on the determination of eligibility for active studies, the umbrella protocol allows for easy documentation of currently noneligible potentials for consideration for a subsequent study.

**WHERE AND HOW TO FIND POTENTIAL RESEARCH PARTICIPANTS**

As schizophrenia studies vary in their enrollment criteria and restrictions, to ensure access to a wide range of symptom severity, age, and demographics (Loughland et al., 2004), recruitment from a variety of sources is crucial. Additionally, although an individual study’s enrollment criteria are an inherent limitation, having a wide-ranging recruitment base with higher- and lower-functioning potential participants minimizes a disconnect between trial and real-world populations (Kennedy-Martin et al., 2015), potentially reducing the presence of a less severe clinical trial population (Lally et al., 2018; Freudenthal et al., 2021; Taipale et al., 2022).

As further described in the sections “Chart Reviews at Collaborating Recruitment Sites” and “Advertising,” we have increasingly relied on established connections with our affiliated clinics and our umbrella protocol database for participants. With permission, other schizophrenia research groups at the institute with nonoverlapping eligibility criteria (eg, medicated vs medication-free or with those conducting brief noninterventional assessments) can also be a source of potential participants for cross-referrals.

For new sources, the researchers should consider recruiting from local outpatient psychiatry clinics, emergency departments, assertive community treatment teams, personalized recovery-oriented services teams, assisted living facilities, and mental health charities. Recruiters should also seek online
Screening Consent Form will be read and verbal consent will be obtained before the phone screen is conducted.

**Indicate date of consent:**
If not interested in research at this time, participant will be asked if it is ok to contact them in the future for other research.

**If yes, Indicate date of consent for future contact:**
Once verbal consent is obtained, a listed of standardized questions will be asked to assess initial eligibility.

Phone screen questions are listed below:

**What is your name?**

**Source (where did we find this patient?):**
- "If source is unknown, ask “How did you hear about us?"

**What is the best number to reach you at?:**

**What is your e-mail (if you have an e-mail?):**

**How old are you?:**

**What is your date of birth?**

**How tall are you?:**

**How much do you weigh?:**

**What is your diagnosis and when were you diagnosed:**

**Are you currently receiving psychiatric treatment if yes, from where?**
- "If yes, indicate name of clinic or clinician if known"

**How many times have you been hospitalized for psychiatric care in your lifetime?**
- "Write down dates of each hospitalization and clinic if known"

**Have you ever attempted suicide in your lifetime?**
- "Write down date(s) of attempt(s) if known"

**Do you ever have suicidal thoughts or ideas?**
- "If yes, ask how often, and ask if any they have plan or intent to commit suicide"

**What psychiatric medication are you currently taking?**

**For all medications please ask:**
- "When were you first prescribed?"
- "How many milligrams are you taking now?"
- "Has the dose ever been lowered or raised (if yes, take down all dates of dose changes)"
- "Indicate how long patient has been on a stable dose of their antipsychotic medications"

**Have you ever taken Clozapine?**
- "If yes, indicate dates and dosage if known"

**Do you have any other major medical problems?**

**Have you ever had a major head injury?**

**Have you ever had electroshock therapy?**
- "If yes, indicate dates and number of sessions if possible"

**Have you ever been violent or been in trouble with the law for violence?**

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*Figure 2. Excerpt of our institutional review board–approved phone screen.*

 listings of local mental health providers as a starting point for new sources.

Connecting with a new external site is among the biggest challenges for a recruiter. We suggest the development of a written script or template for "cold-calling" or emails that consists of a brief message explaining what the clinic is looking for and has to offer as incentives followed by a suggestion for setting a meeting or conference call. Unsolicited contact attempts are worthwhile, but our primary success in connecting with a new collaborating site has been on previously established relationships. The recruiters need to keep excellent documentation regarding their efforts and connections made. We recommend maintaining a spreadsheet that documents whom the facility contacted and when, the method of contact for each attempt, and the outcome of the contact.

When a dialogue has been established between the recruiter and the potential research participant or collaboration site, we recommend starting with an introductory meeting.
associate agreement [BAA] or IRB approval for targeted chart review, meetings with individual clinicians to review their list, or presentations to patient groups). The research team should be prepared for research hesitancy or even skepticism from external sites that are not affiliated with a research institution. In this case, it is important to review the unmet needs in schizophrenia and emphasize that without participants, treatments for schizophrenia cannot advance. Ethics and IRB supervision should also be emphasized, along with being receptive to the questions and needs of the external site.

**CHART REVIEWS AT COLLABORATING SITES**

Getting approved to conduct chart reviews at collaborating sites can be critical in the rapid recruitment of research potentials. NYSPI has a joint mission both to conduct research and to provide clinical care for the Washington Heights catchment area. NYSPI oversees an inpatient unit; 2 large adult outpatient clinics with approximately 500 clients with schizophrenia spectrum disorder; and a local OnTrackNY clinic, which is a treatment center dedicated to first-episode schizophrenia (Bello et al., 2017; Humensky et al., 2020). Through Columbia University, we are also affiliated with the New York-Presbyterian Comprehensive Psychiatric Emergency Program (CPEP). Before 2018, we would schedule periodic time at our affiliated clinics or CPEP staff meetings and present new studies to the assembled clinicians, but this methodology was rarely fruitful. Until recently, we assumed that this failure was because of a lack of interest on the part of the clinicians and potential participants and instead focused our efforts on advertisements in free periodicals available at public transportation hubs. Although the periodicals were free, the advertising was expensive and increasingly unreliable, especially as several periodicals ceased publication.

Consistent with evidence-based recommendations (Pfaff et al., 2019; Bardach et al., 2021), we obtained IRB approval and began reviewing the medical records of all patients with broadly defined schizophrenia spectrum disorder at our affiliated clinics in 2018. This intervention was closely followed by our hiring of a dedicated recruiter. The combination of interventions has led to an exponential increase in recruitment (see Figure 1).

The umbrella consent IRB approval covers chart review and sharing of PHI for NYSPI-affiliated sites. For external sites, we obtain approval through their local IRB or a BAA for sites without an established connection with an IRB. After receiving approval, we request a list of active patients with schizophrenia spectrum disorder, and then carefully review and document all these charts at the clinic (see the section “Umbrella Protocol Database”). We repeat this process every 1 to 2 years, and it generally takes a few months of several afternoons a week. This process enables us to accurately identify potential participants for both active and future studies and send targeted e-mails to clinicians requesting permission to contact a specific patient for a specific study. We generally ask the clinician to contact the potential participant first to provide an introduction. This targeted approach minimizes the burden for busy clinicians (Allan et al., 2021), eliminating the need to review their caseload and recall the details of various protocols. With the institution of targeted chart reviews, we have found that despite our prior assumptions, most clinicians are happy to facilitate research.

Appointments to perform chart reviews should be made in advance at the convenience of the external site. Patient charts can often be lengthy and include both important and irrelevant information. Using a preapproved, HIPAA-compliant chart review form can help recruiters quickly find the answers to questions that will determine the eligibility of each potential participant for research studies. Recruiters should discuss how chart review will be tracked and compiled with the collaborating site. Recruiting from the CPEP brings unique challenges—namely, a commitment to send staff frequently to review the board for potentially eligible participants. Although the level of potentially exclusionary co-morbidities is high in the CPEP, it is a good source for acutely exacerbated or relapse prevention studies.

**MAINTAINING A RELATIONSHIP WITH COLLABORATING SITES**

Once a potential participant is identified at an affiliated site, successful enrollment is highly dependent on coordination with the individual’s treatment team, which consists of clinicians with varied degrees and experience, many of whom are overworked and have varying individual interest in research. As recently reviewed (Bucci et al., 2015), there are multiple potential barriers to successfully engaging treatment teams, such as time constraints, potential disruptions to the treatment relationship, lack of reward or recognition for the clinician, lack of engagement in the research question, clinician discomfort with promoting research, and satisfaction with current treatment. Until recently, we had assumed that these were insurmountable obstacles. Similar to the evidence-based recommendations (Bucci et al., 2015; Allan et al., 2021), we have adopted a flexible approach to communicating with individual clinicians and realized that different strategies are needed on a clinic-by-clinic and clinician-by-clinician basis.

Regular communication is key to developing lasting relationships with external sites. Whereas we previously limited onsite presence to periodic high-level presentations by the PI when new studies were approved, we now have our recruiter regularly engage the clinicians with targeted e-mails or calls along with more causal in-person meetings when feasible, which have the added benefit of making the recruiter a familiar face. We are also in regular contact with the clinic director, ensuring that things are running smoothly and that any emergent concerns are promptly addressed. The treatment team is aware that PIs are available for questions and to address medical concerns when necessary.

Furthermore, although we are careful not to blur the lines between research and clinical activities, we offer to provide IRB-approved study brochures or study summaries for both the clinician and new and existing potential participants, enabling us to introduce research early in their treatment relationship (Treweek et al., 2018) (see the section “Advertising”). We also offer to provide the clinical team with clinically relevant outcomes (Furimsky et al., 2008), such as reading evaluations, cognitive tests, and clinical status updates at the beginning and end of research participation, along with updates on any clinically significant changes.

To minimize the burden placed on collaborating sites, we request any chart reviews or other tasks that are time intensive up front and offer to conduct time-consuming activities ourselves, when allowable. We also regularly update collaborating sites on the enrollment of their patients and the well-being of those patients throughout the study, particularly on any emergent issues. Treatment teams generally appreciate the extra set of eyes on their patients.
ADVERTISING

Although we have recently had more success with targeted chart reviews, advertising has played a major role in our research center's recruitment efforts. All advertising materials, including study summaries and brochures, are approved by the IRB before reaching the public, and the umbrella protocol acts as a central repository for most advertisements.

In particular, concise, 1-page study summaries or brochures for hard-out or e-mails to busy clinicians at our affiliated sites are useful to facilitate a discussion with their patients. The study summary should be aesthetically pleasing and contain a brief overview of the study followed by brief sections on risks, enrollment criteria, procedures, compensation, and the clinic's or recruiter's contact information. The recruiter can also design patient-friendly versions of study summaries as patients may want more information or the opportunity to think for a few days before deciding on participation.

Recruiters can also display advertising material in local clinics, public transportation sites, and shopping areas. Additionally, they may want to use internet resources, such as Craigslist, Reddit, ClinicalTrials.gov, RecruitMe.com, and social media sites (e.g., Facebook, Instagram), an evidence-based, cost-effective intervention (Darmawan et al., 2020). We have also used media-based (internet, newspaper, radio, and television) advertising, but this approach is generally cost prohibitive for non-industry-sponsored studies.

We also use online, "targeted" recruitment platforms when offered through industry-sponsored, multicenter clinical trials, but we have not sought to budget for them on their own as we find the algorithm-driven process both cost prohibitive and less effective than our recruiter. We have found that although these platforms produce a high volume of referrals, they are rarely specific enough to justify the cost. For example, over a recent 2.5-month period, we received 50 referrals from 1 platform. Only 4 of these referrals appeared eligible on a phone screen, and 3 were no-shows to their scheduled consent visit. Only 1 out of 50 of those referred provided consent and enrolled.

UMBRELLA PROTOCOL DATABASE

An electronic spreadsheet is an integral part of the process of keeping track of participants over time and is especially useful for reviewing the data set of participants to determine the number of potentially eligible candidates for each study. We record important patient and research information that corresponds to relevant inclusion and exclusion criteria, such as demographics, medications, medical and psychiatric history, duration of illness, and prior hospitalizations. Specific nuances regarding each participant, such as clinician names and contacts, can be crucial for maintaining a good relationship with participants and external sites and for tracking successful collaborations. The spreadsheet should document the date and outcomes of all contacts, if any special permissions must be obtained before contact, and any qualities that may render them ineligible for certain research studies. In some cases, organizing the spreadsheet by placing potentially eligible participants into designated sections corresponding to each of the clinic's active and upcoming studies can be helpful.

Most participants should be contacted for updated information every few months unless they indicate that they are no longer interested in participating in the research or exhibit dangerous or inappropriate behavior. Such participants are placed on the do-not-contact list or referred to acute care. Recruiters should confirm that there is an unexpired umbrella consent on file for potential participants before reaching out to them and be sure to contact participants for a reconsent before its expiration. Recruiters must familiarize themselves with the information from the spreadsheet on the individual before contacting participants; this saves time for both parties. The research center will benefit from the connections and rapport the recruiter builds with participants. Based on information obtained from the spreadsheet or the memory of senior staff members, some potential participants can be discussed during recruitment meetings if there are specific studies in mind for them.

RAPID AND ACCURATE DETERMINATION OF ELIGIBILITY/INELIGIBILITY FOR POTENTIAL RESEARCH PARTICIPANTS

Based on the protocol for each study, a table should be created that differentiates inclusion and exclusion criteria for each study. This table should include the psychiatric diagnosis and severity, age, medications, duration of illness, number of hospitalizations, and any other important information needed to determine eligibility for a specific study.

Recruiters should have this information readily available and should be able to quickly search for enrollment criteria as needed. It is not necessary to memorize eligibility criteria for each study, but having some method by which the recruiter can determine eligibility other than the protocols themselves, which can be quite lengthy, is highly advised.

ENSURING THE ONGOING PRODUCTIVITY OF RECRUITMENT EFFORTS

At the CSRC, we periodically audit and evaluate the effectiveness of recruitment efforts. A weekly interdisciplinary among between the recruitment staff, the PI, and the clinical coordinator helps maintain open and consistent communication while mitigating the risk of mistakes and oversights. This meeting should include a discussion of how the list of potential participants is prioritized and which participants have been chosen for each particular research study. The meetings should also cover protocols, recruitment efforts, prioritization, and enrollment difficulties of the research center's ongoing clinical trials. Weekly recruitment meetings are also an ideal time to discuss the status of chart review updates and any potential participants the chart review identifies as well as determine whether it is appropriate to ask the clinician for permission to contact the patient regarding research. The recruiters should be offered semiannual or quarterly performance reviews to help them improve their work as well as be recognized for their efforts. Positive feedback and recognition help reduce turnover for the recruitment position.

CONCLUSIONS

In the present report, we have outlined the evidence-based recruitment strategies in use at the CSRC, adding to the limited literature on recruitment strategies for studies for people with schizophrenia. We acknowledge that some of our methodology and strategies are uniquely suited for use at our well-funded academic medical center in a densely populated metropolitan center. Hiring a full- or part-time recruiter may not be desirable or feasible for smaller research groups, although the qualities described are potentially translatable to any staff member involved in recruitment.
Noting these caveats, we have had the most success with “targeted” recruitment through chart reviews at our collaborating sites conducted by a dedicated recruiter, but we continue to advertise for most studies. Both targeted recruitment and advertising have advantages, but the higher volume and predetermined specificity for “targeted” recruitment balance the self-motivation and potentially higher interest in “help-seeking” (Rietdijk et al., 2012; Fusar-Poli et al., 2016) responses to advertisements.

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**Statement of Interest**

There are no known conflicts that are directly relevant to this work. J.T.K. reports having received consulting payments within the last 24 months from Alphasights, Medscape, Putnam, techspert.io, Health Monitor, Third Bridge, MEDACorp, Parexel, Trinity, Globaldata, GKA, Clarivate, GroupH, ECRI Institute, ExpertConnect, Schlesinger Group, Acel Health, Slingshot, Anthem, Guidepoint, L.E.K., SmartAnalyst, First Thought, Wedbush, Jefferies, Otsuka, Vox Neuro, and Reckner. He has served on the MedInCell Psychiatry, Merck, Leal, and Karuna Advisory Boards. He has conducted clinical research supported by the NIMH, Sunovion, Roche, Alkermes, Cerevance, Click, Neurocrine, Corcept, Takeda, Taisho, Boehringer Ingelheim, and Teva within the past 24 months. He owns a small number of shares of common stock from GlaxoSmithKline. The other authors report no known conflicts.

**References**

Abi-Dargham A, et al; TRANSCENDS Group (2022) Dopamine D1R receptor stimulation as a mechanistic pro-cognitive target for schizophrenia. Schizophr Bull 48:199–210.

Allan S, McLeod H, Bradstreet S, Bell I, Whitehill H, Wilson-Kay A, Clark A, Matrunola C, Morton E, Farhall J, Gleeson J, Gumley A (2021) Perspectives of trial staff on the barriers to recruitment in a digital intervention for psychosis and how to work around them: qualitative study within a trial. JMIR Hum Factors 8:e24055.

Bardach NS, Lam R, Jasik CB (2021) Assessment of automated clinical trial recruitment and enrolment using patient-facing technology. BMJ Health Care Inform 28:e100076.

Bello I, Lee R, Malinovsky I, Watkins L, Nossel I, Smith T, Ngo H, Birnbaum M, Marino L, Sederer LI, Radiag M, Gu G, Essock S, Dixon LB (2017) OnTrackNY: the development of a coordinated specialty care program for individuals experiencing early psychosis. Psychiatr Serv 68:318–320.

Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A (2021) Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. N Engl J Med 384:717–726.

Brunette MF, Correll CU, O’Malley SS, McDonnell D, DiPetrillo L, Jiang Y, Simmons A, Silverman BL, Citrome L, Green AI (2020) Olanzapine plus samidorphan (ALKS 3831) in schizophrenia and comorbid alcohol use disorder: a phase 2, randomized clinical trial. J Clin Psychiatry 81:19m12786.

Bucci S, Butcher I, Hartley S, Neil ST, Mulligan J, Haddock G (2015) Barriers and facilitators to recruitment in mental health services: care coordinators’ expectations and experience of referring to a psychosis research trial. Psychol Psychother 88:335–350.

Bugarski-Kirola D, Iwata N, Sameljak S, Reid C, Blaettler T, Millar L, Marques TR, Garibaldi G, Kapur S (2016) Efficacy and safety of adjunctive bitopertin versus placebo in patients with suboptimally controlled symptoms of schizophrenia treated with antipsychotics: results from three phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre studies in the SearchLyte clinical trial programme. Lancet Psychiatry 3:1115–1128.

Bugarski-Kirola D, Blaettler T, Arango C, Fleischhacker WW, Garibaldi G, Wang A, Dixon M, Bressan RA, Nasrallah H, Lawrie S, Napieralski J, Ochi-Lohmann T, Reid C, Marder SR (2017) Bitopertin in negative symptoms of schizophrenia-results from the phase III FlashLyte and DayLyte studies. Biol Psychiatry 82:8–16.

Clelland CL, Kantrowitz JT, Choo T, Clelland JD, Lieberman JA (2020) Adjunctive sapropterin dihydrochloride treatment in schizophrenia: a positive proof-of-concept, rater-blind, randomized, multivitamin-controlled study. Schizophr Res 218:321–323.

ClinicalTrials.gov (NCT02717195) (2019) Effect of Lu AF35700 in patients with treatment-resistant schizophrenia (DayBreak). https://www.clinicaltrials.gov/ct2/show/NCT02717195. Accessed 14 September 2022.

ClinicalTrials.gov (NCT03503318) (2018) Study to evaluate TV-46000 as maintenance treatment in adult and adolescent participants with schizophrenia (RISE). https://clinicaltrials.gov/ct2/show/NCT03503318. Accessed 14 September 2022.

Darmawan I, Bakker C, Brockman TA, Patten CA, Eder M (2020) The role of social media in enhancing clinical trial recruitment: scoping review. J Med Internet Res 22:e22810.

Davidson M, Saoud J, Staner C, Noel N, Werner S, Lurhinger E, Walling D, Weiser M, Harvey PD, Strauss GP, Lurhinger R (2022) Efficacy and safety of roluperonide for the treatment of negative symptoms of schizophrenia. Schizophr Bull 48:609–619.

de la Garrigue N, et al. (2020) Grant report on d-serine augmentation of neuroplasticity-based auditory learning in schizophrenia (dagger). J Psychiatr Brain Sci 6:e200018.

Fleischhacker WW, Podhorna J, Groschl M, Hake S, Zhao Y, Huang S, Keefe RSE, Desch M, Brenner R, Walling DP, Mantero-Atienza E, Nakagome K, Pollentier S (2021) Efficacy and safety of the novel glycine transporter inhibitor BI 425809 once daily in patients with schizophrenia: a double-blind, randomised, placebo-controlled phase 2 study. J Psychiatr Brain Sci 5:2200018.

Fusar-Poli P, Schultze-Lutter F, Cappucciati M, Rutigliano G, Bonoldi I, Stahl D, Borgwardt S, Riecher-Rossler A, Addington J, Perkins DO, Woods SW, McGlashan T, Lee J, Klosterkotter J, Yung AR, McGuire P (2016) The dark side of the moon: meta-analytical
Rietdijk J, Klaassen R, Ising H, Dragt S, Nieman DH, van de Kamp J, Cuijpers P, Linszen D, van der Gaag M (2012) Detection of people at risk of developing a first psychosis: comparison of two recruitment strategies. Acta Psychiatr Scand 126:21–30.

Rutherford BR, Pott E, Tandler JM, Wall MM, Roose SP, Lieberman JA (2014) Placebo response in antipsychotic clinical trials: a meta-analysis. JAMA Psychiatry 71:1409–1421.

Sehatpour P, Avissar M, Kantrowitz JT, Corcoran CM, De Baun HM, Patel GH, Girgis RR, Brucato G, Lopez-Calderon J, Silipo G, Dias E, Martinez A, Javitt DC (2020) Deficits in pre-attentive processing of spatial location and negative symptoms in subjects at clinical high risk for schizophrenia. Front Psychiatry 11:629144.

Sehatpour P, Javitt DC, De Baun HM, Carlson M, Beloborodova A, Margolin DH, Carlton MBL, Brice NL, Kantrowitz JT (2022) Mismatch negativity as an index of target engagement for excitation/inhibition-based treatment development: a double-blind, placebo-controlled, randomized, single-dose cross-over study of the serotonin type-3 receptor antagonist CVN058. Neuropsychopharmacology 47:711–718.

Taipale H, Schneider-Thoma J, Pinzón-Espinosa J, Radua J, Efthimiou O, Vinkers CH, Mittendorfer-Rutz E, Cardoner N, Pintor L, Tanskanen A, Tomlinson A, Fusar-Poli P, Cipriani A, Vieta E, Leucht S, Tiihonen J, Luykx JJ (2022) Representation and outcomes of individuals with schizophrenia seen in everyday practice who are ineligible for randomized clinical trials. JAMA Psychiatry 79:210–218.

Taylor M, Jauhar S (2019) Are we getting any better at staying better? The long view on relapse and recovery in first episode nonaffective psychosis and schizophrenia. Ther Adv Psychopharmacol 9:2045125319870033.

Treweek S, Fitzkethy M, Cook J, Fraser C, Mitchell E, Sullivan F, Jackson C, Taskila TK, Gardner H (2018) Strategies to improve recruitment to randomised trials. Cochrane Database Syst Rev 2:MR000013.