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Issues and Perspectives in Designing Clinical Trials for Negative Symptoms in Schizophrenia: Consensus Statements

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Review

Issues and perspectives in designing clinical trials for negative symptoms in schizophrenia

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ABSTRACT

A number of pharmacological agents for treating negative symptoms in schizophrenia are currently in development. Unresolved questions regarding the design of clinical trials in this area were discussed at an international meeting in Florence, Italy in April 2012. Participants included representatives from academia, the pharmaceutical industry, and the European Medicines Agency (EMA). Prior to the meeting, participants submitted key questions for debate and discussion. Responses to the questions guided the discussion during the meeting. The group reached agreement on a number of issues: (1) study subjects should be under the age of 65; (2) subjects should be excluded for symptoms of depression that do not overlap with negative symptoms; (3) functional measures should not be required as a co-primary in negative symptom trials; (4) information from informants should be included for ratings when available; (5) Phase 2 negative symptom trials should be 12 weeks and 26 weeks is preferred for Phase 3 trials; (6) prior to entry into a negative symptom study, subjects should demonstrate clinical stability for a period of 4 to 6 months by collection of retrospective information; and (7) prior to entry, the stability of negative and positive symptoms should be confirmed prospectively for four weeks or longer. The participants could not reach agreement on whether predominant or prominent negative symptoms should be required for study subjects.

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1. Introduction

Given their relationship to functioning and their importance for successful rehabilitation (Fenton and McGlashan, 1994; Rabinowitz et al., 2012) negative symptoms in schizophrenia are an important target for

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drug development. Negative symptoms are relatively common (Bobes et al., 2010) with one recent study finding that 57.6% of stable outpatients patients treated with second generation antipsychotics had at least one negative symptom. With the exception of amisulpride (Leucht et al., 2002) in some European countries, there are no pharmacological agents approved for the treatment of negative symptoms. As this is a relatively new therapeutic area, there are a number of unresolved questions regarding the design of clinical trials in this field. Although some of these issues have been discussed in previous publications (Kirkpatrick et al., 2006; Marder et al., 2011), a further review of methodological issues is warranted for a number of reasons: (1) considerable data have recently become available from negative symptom trials; (2) methodological issues had not been discussed in an international forum; and (3) regulatory agencies have been considering new guidelines for trials in schizophrenia.

NEWMEDS (Novel Methods leading to NeW MEdications in Depression and Schizophrenia), an academic industry collaboration funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU) by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union, sponsored a one day workshop on April 19, 2012 in Florence, Italy titled "Challenges, Issues, and Perspectives in Designing and Conducting Studies of Negative Symptoms in Schizophrenia". The goal of the workshop was to initiate a broad discussion of critical issues in designing clinical trials. International representatives from academia, the pharmaceutical industry, and the European Medicines Agency (EMA), a regulatory body attended. Prior to the meeting, participants submitted key questions for debate and discussion. The proposed questions focused on issues such as the selection criteria for trial participants; trial designs for medications that would be added to an antipsychotic as a co-medication and for "broad spectrum" medications that would treat both psychotic and negative symptoms; the duration of clinical trials; appropriate instruments for measuring negative symptoms and other measures that should be included in negative symptom trials. The questions were initially addressed in a survey that was administered to the meeting participants. The meeting agenda included all of the items from the survey that elicited differences of opinion. Advocates for different positions were selected from the survey and were asked to present their views at the meeting using supporting data. The survey was repeated following the meeting to determine whether the discussions had changed the opinions of participants. The goal of the meeting was not to reach a consensus on each issue that was discussed. Rather, the meeting focused on characterizing different positions that could be reconciled as new findings emerged from ongoing trials.

During the meeting, Jonathan Rabinowitz presented findings from the NEWMEDS data base of 29 placebo-controlled studies with second generation antipsychotics in schizophrenia which focused on the characteristics of individuals both at baseline and endpoint who would satisfy different inclusion and exclusion criteria for trials on negative symptoms. Stephen Marder presented an update on recent negative symptom trials that have reported results and other trials that had been registered at clinicaltrials.gov. Details from these presentations are included elsewhere in this special issue. For each issue discussed at the meeting, participants were selected to present contrasting views. This was followed by an open discussion. These discussions are summarized in this paper. Papers by David Daniel and Philip Harvey on clinical endpoints related to negative symptoms are also included in this special issue.

2. Issues not discussed

In addition to topics of disagreement, the pre-meeting survey identified a number of issues on which there was a consensus or a near consensus in the group. These are listed below and are not considered further.

1. Subjects entered into negative symptom trials should have no fewer than two negative symptoms and at least one should be rated as moderate or greater.
2. Subjects with notable extrapyramidal side effects from antipsychotic medications should be excluded.
3. Scales measuring the extrapyramidal syndromes should be included in negative symptom trials.
4. Subjects prescribed first and/or second-generation antipsychotics should be included in negative symptom trials of co-prescribed medication (that is, medication that is added to an antipsychotic) for negative symptoms.
5. Negative symptom trials should include an assessment battery to measure cognition.
6. Ratings for negative symptoms should include a single global score.
7. Ratings for negative symptoms should include global scores for major domains such as expressiveness and apathy/asociality.
8. Subjects currently treated with clozapine should not be excluded in negative symptom trials of co-medication.

3. Issues discussed

3.1. Issue 1. Should there be an upper age limit for subjects included in negative symptom trials?

3.1.1. Background

Schizophrenia trials from academia and industry commonly recruit subjects with a mean age in the late 30's or 40's and with 10–15 or more years of established schizophrenia, frequently with substantial disability. For example, subjects in the NIMH (National Institute of Mental Health) CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial had a mean age of 40.6 years and an average of more than 14 years of illness (Lieberman et al., 2005). Such subjects are often referred to these trials because they are not satisfied with their current treatment due to side effects or inadequate efficacy. Since many of these individuals have responded poorly to multiple trials, they may be likely to show a relatively poor response to newer agents. Further, there is some evidence that, in its early stages, the schizophrenic illness is more likely to show a good response that in its later stages. For example, subjects in the EUFEST (European First Episode Schizophrenia Trial) (Kahn et al., 2008) were in a first episode and had a mean age of 26 years. These subjects had a higher response rate than the sample in the CATIE study. As suggested above, this phenomenon might be an artifact of the more heterogeneous patient samples available early in the illness. This contrasts with long-term trials where the subjects who are recruited may be more likely to be characterized by persistent, relatively resistant illness. In addition, there is the possibility that chronic treatment with pharmacologic agents (e.g. dopamine receptor antagonists) might alter the potential response to newly introduced treatments (Samaha et al., 2007).

Although well-designed epidemiologic studies are lacking, it is possible that negative symptoms increase with illness chronicity but are already present in the early phase illness, thereby making the discussion regarding stage of the disease in recruiting for studies on negative symptoms less relevant. Nevertheless a recent longitudinal study reported that although symptomatic dimensions are highly variable during the course of the illness, after the first episode the negative dimension was the most consistent and stable over time accounting for 24% of the variance at baseline and 26% at 4 weeks (Rapado-Castro et al., 2010). Perhaps it is the duration of the negative symptoms rather than the age of the patient that is the crucial issue. Whether an agent would be effective as a prophylaxis against the development of negative symptoms is another issue to be considered once effective agents are available.

3.1.2. Meeting discussion

Meeting participants agreed that it was intuitive to expect that a negative symptom compound would have a larger impact on patients who are younger and earlier in their illness. Moreover, some view schizophrenia as a progressive illness which would suggest that the

best opportunities for changing the course of the illness would occur early in the illness. It is also plausible that confounds such as long-term drug effects may make subjects less responsive. In addition, subjects who are receiving disability benefits may have less motivation to engage in community activities. There was agreement, however, that there were no data to support this theory. The studies of amisulpride (Boyer et al., 1995; Moller, 2001), for example, did not show a differential effect between age groups.

3.1.3. Group recommendation

There was a consensus that patients in Phase 2 proof-of-concept studies should be under the age of 65 years. Nevertheless, even if there is such an age cut-off, regulatory bodies may require evidence of an effect or a lack of an effect in subjects who are older than the cut-off. The inclusion of substantial numbers of subjects early in their illness may be helpful in clarifying if there are age effects. There was also agreement that it may be useful to stratify patients according to age in large Phase 3 trials.

3.2. Issue 2. Should the study population consist only of subjects who have predominant negative symptoms? Alternatively, should subjects be included who have prominent negative symptoms even if these symptoms are not predominant?

3.2.1. Background

Negative symptoms usually occur in the presence of other symptoms of schizophrenia, particularly psychotic symptoms. For many subjects, these other symptoms are relatively mild and well controlled by currently available antipsychotic medicines and negative symptoms can then be viewed as *predominant*. Other subjects may have a substantial burden from psychotic symptoms including hallucinations and delusions. These individuals can also have a substantial burden from negative symptoms which can then be considered *prominent*, but not necessarily *predominant*. Different definitions for both prominent and predominant negative symptoms have been described in the literature (Alphs et al., 2007; Stauffer et al., 2012).

One argument for limiting negative symptom trials to subjects with predominant negative symptoms is based on the concern that negative symptoms may be secondary to positive symptoms. For example, patients who are suspicious may be less likely to engage in social interactions and individuals who are distracted by auditory hallucinations may be less able to engage in community activities. If a medication for negative symptoms led to improvement in both positive and negative symptoms it would be difficult to conclude that the agent was actually treating the negative symptoms.

The EMA – which was represented at the meeting – has adopted this position and currently requires studies involving co-medication for negative symptoms to be conducted in patients with predominant negative symptoms. The argument that subjects can be enrolled with prominent negative symptoms, even if they are not predominant, is partly based on concerns that subjects with predominant negative symptoms are a small minority and difficult to recruit. Adding the inclusion criterion that patients should have only minimal levels of positive symptoms could make these studies very difficult to carry out.

3.2.2. Discussion

There were differences of opinion among meeting participants. Some argued that patients with predominant negative symptoms represent a distinct subtype of stable schizophrenia patients. Treatments for negative symptoms should be developed for this group which is reasonably common although results in this subgroup may not be generalizable. Others viewed positive and negative symptoms as independent psychopathological dimensions. If positive symptoms remain stable and unchanged by the compound being studied, and negative symptoms improve, then it could be concluded that the agent is active for treating negative symptoms. If a subset of patients were to experience a significant improvement in both positive and negative symptoms, it would be difficult to conclude that the effect was specific to negative symptoms and not mediated through an effect on positive symptoms.

Resolving this issue complicated by a lack of agreement regarding the level of positive symptoms that would be permitted if negative symptoms were to be considered predominant. There was general agreement in the group that patients with severe or acute positive symptoms could be considered unstable. Moreover, scores on a rating scale may not reflect the personal burden that patients experience from particular symptoms. That is, patients may be able to function in the community with even mild or moderate auditory hallucinations. However, mild or moderate negative symptoms may have very substantial effects on functional outcomes.

3.2.3. Group recommendations

The meeting participants had a range of opinions on this issue before and after the meeting. The post-meeting survey asked participants if they believed that only subjects with predominant negative symptoms should be included. Ten individuals replied that they somewhat or strongly agreed with this statement and 11 replied that they somewhat or strongly disagreed. When participants were asked if patients with moderate or moderately severe positive symptoms should be excluded, 11 disagreed and 8 agreed. An alternative approach for an exploratory study is to stratify the population into “predominant” versus “prominent” based on the severity of positive symptoms. If the effect is observed in the population with “prominent” symptoms only, then this could raise a concern that the effect is nonspecific.

There was broad agreement that for Phase 2 studies, patients with predominant negative symptoms would be preferable in view of the lower heterogeneity of the population. There would be benefits for broadening the criteria for Phase 3 studies. Alternatively, both populations could be studied in parallel to allow conclusions on the generalizability of the benefit on negative symptoms.

3.3. Issue 3. Should subjects with depression be excluded?

3.3.1. Background

Negative symptoms and symptoms of depression can be difficult to separate in schizophrenia populations (Kirkpatrick et al., 1994; Gozdzik-Zelazny et al., 2011). This is, in part, due to the significant phenomenological overlap between the syndromes. For example, decreased expressiveness, anhedonia and apathy can be prominent in both conditions. If patients with substantial depressive features are incorrectly included in negative symptom trials, these individuals may not respond to an agent that is effective for negative symptoms but not depression.

On the other hand, if a cut-off score on an instrument such as the Hamilton Depression Rating Scale (HDRS) was used, this might exclude subjects who had highly representative negative symptoms such as psychomotor retardation, apathy, and anhedonia. This may exclude subjects who are very appropriate for a negative symptom trial.

3.3.2. Discussion

The meeting participants agreed that in principle subjects with depression should be excluded from negative symptom trials. However, there was also agreement that the two conditions could be distinguished by a number of characteristics. For example, sad mood is not common in negative symptom patients. In addition, patients with negative symptoms do not usually describe their symptoms as causing personal suffering. Anhedonia in schizophrenia is associated with a reduced ability to anticipate reward (Gold et al., 2012).

3.3.3. Group recommendations

Patients should not be excluded from negative symptom trials on the basis of a cut-off score on the Hamilton Depression Rating Scale

(HDRS) (Hamilton, 1967) or similar scales. They should be excluded for the presence of a selection of depressive symptoms that do not overlap with negative symptoms. Patients with the co-diagnosis of a Major Depressive Episode should be excluded. An alternative to be considered is a cut-off score on an instrument such as the Calgary Depression Rating Scale which better differentiates depressive symptoms from negative symptoms (Addington et al., 1990).

3.4. Issue 4. Should a functional measure be included in negative symptom trials? Should this measure be a co-primary required for drug registration?

3.4.1. Background

There is an expectation that improvement in negative symptoms will at some point result in improvement in community functioning and quality of life. However, it is unclear if these improvements will occur in a trial with a relatively brief duration such as 12 weeks. Moreover, salient outcomes such as securing a job, attending school, or having better social relationships may require opportunities that cannot be controlled during a trial. In addition such outcomes are highly dependent on regionally diverse socioeconomic background variables. This issue of actual functioning versus someone's capability to function was addressed in the NIMH MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative which focused on the development of drugs to enhance cognition in schizophrenia (Green et al., 2008). MATRICS participants recommended two types of functional measures for trials: (1) A functional capacity instrument that measured an individual's performance on a functionally meaningful task even if the person was not engaged in the activity in their everyday life; and (2) an interview-based scale that involves an interview of a patient or someone close to the patient regarding the patient's ability to carry out tasks in daily life. However, while these tasks may be appropriate for monitoring improvement in cognition, they were not developed for measuring the functional impact of negative symptoms. For example, the commonly used UPSA (UCSD Performance-Based Skills Assessment) (Patterson et al., 2001) utilizes tasks that are associated with cognitive functions. They do not measure motivation and social interest which are likely to be associated with negative symptoms.

If a functional measure were to be considered a co-primary parameter in negative symptom trials, this would mean that the results would need to show a statistically significant improvement in both negative symptoms and the functional measure for drug approval. An alternative would be to consider the functional measure as a key secondary measure. In this case, the study would not need to be powered for the secondary measure. If the study demonstrated a statistically significant effect on the primary measure, but not on the secondary measure, this would not invalidate the study findings. However, it would be important for the key secondary to move in the same direction as the primary symptom measure. Moreover, a positive outcome on a key secondary measure could be mentioned in labeling for a drug.

3.4.2. Discussion

Requiring improvement in both negative symptoms and a functional measure would be difficult in the context of most clinical trials. The expectation that a drug administered only during a brief trial will result in improvements in difficult to achieve outcomes such as work is unrealistic and context dependent. Moreover, compared to changes in neuropsychological tests, clinically relevant changes in negative symptoms are more easily recognized by clinicians.

There was also discussion of the importance of eventually demonstrating a link between improving negative symptoms and improving functional outcomes. This area should be aided by the development of instruments that measure outcomes such as the readiness to work. This will be particularly important for influencing payers as well as regulators — particularly in the European Union.

3.4.3. Group recommendations

Representatives from both the FDA (United States Food and Drug Administration) and the EMA have previously expressed the opinion that negative symptoms have sufficient face validity that improvement in these symptoms would suffice for supporting the effectiveness of a drug. Meeting participants agreed with this view and also agreed that functional measures, including functional capacity measures or real world functioning measures, should be included in negative symptom trials as key secondary measures.

The participants also agreed that Phase 3 trials should explore the effects of negative symptom agents on different aspects of community functioning.

3.5. Issue 5. Should information from informants be included in all negative symptom trials?

3.5.1. Background

Negative symptom scales frequently permit the inclusion of information from informants. This can be particularly valuable when patients are poor reporters of their internal experiences and actual behaviors. On the other hand, informants are not available for all study subjects and informants vary in the quality and reliability of their observations. Including informants can lead to an additional source of variance in a trial.

3.5.2. Discussion

Meeting participants acknowledged that informants may vary substantially according to their contact with the research subject and their availability to provide observations. However, patients with negative symptoms may be poor describers of their behaviors outside of the interview. As a result, other informants may provide valuable observations. Although there were concerns with the quality of these observations, there was agreement that whenever possible, raters should include information from informants. In the post-meeting survey, 10 participants agreed that informants should be included, 6 disagreed and 6 were neutral.

3.5.3. Meeting recommendation

While subjective reports from informants should not be an essential requirement for negative symptom trials, if possible, information from informants should be included in ratings.

3.6. Issue 6. What should be the minimal duration of negative symptom trials?

3.6.1. Background

Negative symptom trials have varied in their duration from as brief as 6 weeks to as long as 6 months.

3.6.2. Discussion

Meeting participants focused on the duration of both Phase 2 and Phase 3 trials. The data from trials such as the study of Roche GlyT1 compound found separation as early as 8 weeks. A majority of participants in the pre-meeting and post-meeting survey proposed 12 weeks as the minimal trial length. EMA representatives pointed out that 6 months was chosen as a time period that would permit change in functioning or functional capacity. A 6 month trial would also assure that improvements were not short lived. If significant effects can be demonstrated in trials shorter than 6 months, that may be acceptable to EMA.

3.6.3. Meeting recommendation

A duration of at least 12 weeks is recommended for Phase 2 trials. A duration of 6 months is preferred for Phase 3 studies.

3.7. Issue 7. What should be the duration of stable negative symptoms that is required prior to study entry? Should persistence be demonstrated prospectively, retrospectively, or both?

3.7.1. Background

Studies of negative symptoms have usually required that these symptoms be stable over a period of time (Kirkpatrick et al., 2006). Since secondary negative symptoms can also influence ratings, it is important that positive symptoms also remain relatively stable.

3.7.2. Discussion

Meeting participants discussed possible sources of instability in negative symptom ratings. To achieve consistent, reliable ratings of negative symptoms over time, the clinical setting in which the participant is managed should be stable along with their medication regime. For example, despite persistent, stable negative symptoms, a patient's clinical ratings may change because of a move from an inpatient to an outpatient setting, and the influence on the ratings of the different demands, opportunities and expectations the patient has experienced in the latter setting. Information about clinical settings, recent life events, and medications can usually be assessed retrospectively. Negative symptoms themselves are difficult to assess retrospectively for many patients. As a result, meeting participants agreed that studies should have a prospective period during which subjects are also assessed. Different periods were discussed, but there was a general agreement that four weeks of prospective stability was a reasonable duration.

3.7.3. Meeting recommendation

Prior to entry into a negative symptom study, subjects should demonstrate clinical stability for a period of 4 to 6 months by collection of retrospective information. Prior to entry, the stability of negative and positive symptoms should be confirmed prospectively for four weeks or longer.

4. Summary

A group of individuals from academia, industry, and regulators discussed key issues in designing clinical trials for treating negative symptoms. The participants did not reach a consensus on all issues, but there was relatively broad agreement on a number of key issues. Fortunately, a number of studies are currently underway and it is likely that the results from these trials will provide valuable information about the inclusion and exclusion criteria for these trials, the duration and design of the trials, and the optimal outcome measures (Table 1).

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Contributors

All of the contributors contributed to the writing and the editing of the manuscript.

Conflicts of interest

Stephen R. Marder has consulted for Abbott, Boehringer Ingelheim, Bristol Meyers Squibb, Genentech, Roche, Otsuka, Pfizer, EnVivo, Targacept, Lundbeck, Shire, and Jazz. He had research support from Glaxo Smith Kline, Novartis, Sunovion, Psychogenics, and Amgen. Larry Alphs is a full time employee of Janssen Scientific Affairs a division of Johnson & Johnson. Ivo Caers is a full time employee of Johnson & Johnson. David Daniel a full time employee of Bracket Global, LLC. Eduardo Dunayevich is a full time Amgen employee. W. Wolfgang Fleischhacker has accepted research grants from Alkermes, Janssen-Cilag, Eli Lilly, BMS/Otsuka, Pfizer and Reckitt-Benckiser. He has received speaking fees from AstraZeneca, Pfizer, Janssen-Cilag, Roche, Lundbeck, BMS/Otsuka, and Richter and has consulted for BMS/Otsuka, Janssen-Cilag, Amgen, Lundbeck, Endo, MedAvante, Roche, Pfizer, Sunovion, Merck, Eli Lilly, Vanda, and Richter and owns MedAvante stocks. Dr. Fleischhacker is a full time employee of the Medical University Innsbruck, Austria. René S. Kahn has consulted for and received speaker's fees from AstraZeneca, Eli Lilly, and Michael F. Green has consulted for AbbVie, Biogen, and Roche; he is a member of the scientific board for Mnemosyne, and he has received research funds from Amgen. Janssen-Cilag and accepted research support from BMS. John M. Kane has consulted with Organon, Eli Lilly, BMS, Intracellular Therapeutics, Boehringer, Rules Based Medicine, Astra Zeneca, Otsuka, Novartis, Merck, Myriad, Esai, Pfizer, Lundbeck, J & J, Targacept, Shire, Amgen, Sunovion, Pierre Fabre, Janssen, Alkermes, Jazz, and Forest Labs. He is on the Speakers Bureau for Janssen, BMS, Lilly, and Otsuka and is a shareholder in MedAvante, Inc. Shitij Kapur has served as a consultant, scientific advisor, or a speaker for AstraZeneca, Bioline, Bristol Meyers Squibb, Eli Lilly, Janssen (Johnson and Johnson), Lundbeck, NeuroSearch, Otsuka, Pfizer, Roche, Servier, Solvay and Wyeth. He has received grant support from AstraZeneca and GSK; and has served as consultant and/or speaker for AstraZeneca, Bioline, BMS-Otsuka, Eli Lilly, Janssen (J&J), Lundbeck, NeuroSearch, Pfizer, Roche, Servier and Solvay Wyeth.

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Table 1
Summary of recommendations.

Issues agreed on prior to the meeting

1. Subjects entered into negative symptom trials should have no fewer than two negative symptoms and at least one should be rated as moderate or greater.
2. Subjects with notable extrapyramidal side effects from antipsychotic medications should be excluded.
3. Scales measuring the extrapyramidal syndromes should be included in negative symptom trials.
4. Subjects prescribed first and/or second-generation antipsychotics should be included in negative symptom trials of co-prescribed medication (that is, medication that is added to an antipsychotic) for negative symptoms.
5. Negative symptom trials should include an assessment battery to measure cognition.
6. Ratings for negative symptoms should include a single global score.
7. Ratings for negative symptoms should include global scores for major domains such as expressiveness and apathy/asociality.
8. Subjects currently treated with clozapine should not be excluded in negative symptom trials of co-medication.

Issues agreed on at the meeting

1. Patients in Phase 2 proof-of-concept studies should be under the age of 65. The inclusion of substantial numbers of subjects early in their illness may be helpful in clarifying if there are age effects.
2. Patients should not be excluded from negative symptom trials on the basis of a cut-off score on the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) or similar scales. They should be excluded for the presence of a selection of depressive symptoms that do not overlap with negative symptoms. Patients with the co-diagnosis of a Major Depressive Episode should be excluded.
3. Since negative symptoms have face validity, a functional measure should not be required as a co-primary. Functional measures, including functional capacity measures or real world functioning measures, should be included in negative symptom trials as key secondary measures.
4. While subjective reports from informants should not be an essential requirement for negative symptom trials, if possible, information from informants should be included in ratings.
5. A duration of at least 12 weeks is recommended for Phase 2 negative symptom trials. A duration of 6 months is preferred for Phase 3 studies.
6. Prior to entry into a negative symptom study, subjects should demonstrate clinical stability for a period of 4 to 6 months by collection of retrospective information.
7. Prior to entry, the stability of negative and positive symptoms should be confirmed prospectively for four weeks or longer.

Issue discussed at the meeting without agreement

Should predominate negative symptoms be required for inclusion in negative symptom trials; or are prominent negative symptoms sufficient?

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