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Critical Issues in the Design of Clinical Trials for Negative Symptoms

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Study Design Issues

- **Clinical Status**
  - Medication status
  - Symptom severity
- **Medications**
  - Antipsychotics
  - Concomitant medications
- **Study Design**
  - Adjunctive agents
  - Broad spectrum agents
    - Duration of study
    - Assessments

Negative Symptom Study Design

Inclusion Criteria: Clinical Status

- What design approaches should be used to isolate changes in negative symptoms from changes in other symptom domains?
  - i.e., how to isolate a specific effect on negative symptoms from other concurrent changes in clinical status that may effect negative symptoms (Pseudospecificity)?

Negative Symptom Study Design

Inclusion Criteria: Clinical Status

- Include subjects who:
  - Are clinically stable and in the non-acute phase of illness for a specified period of time (e.g. 12 weeks)

Negative Symptom Study Design

Inclusion Criteria: Clinical Status

- Include subjects who:
  - Have been maintained on current antipsychotic and other concomitant psychotropic medications for a specified period of time (e.g. 8 weeks)
  - Have been on current dose for a specified time period (e.g. 4 weeks) sufficient to minimize potential complications of assessment of negative symptoms

Negative Symptom Study Design

Inclusion Criteria: Clinical Status

- Include subjects who:
  - Have a predefined minimum level of negative symptoms
  - Have a predefined maximum level of positive, depressive, and extrapyramidal symptoms

Negative Symptom Study Design

Inclusion Criteria: Clinical Status

- **Rationale:**
  - **Negative symptoms may either be primary or secondary to:**
    - **exacerbations of psychosis**
    - **antipsychotic side effects**
    - **dysphoric mood states**
    - **understimulating environments**
- **There are currently available effective treatments for many secondary negative symptoms**

Negative Symptom Study Design

Inclusion Criteria: Clinical Status

- Patients who are clinically stable and in the non-acute of illness, with restricted concurrent symptoms:
  - More likely to have primary negative symptoms
  - Secondary negative symptoms with no current treatment
- Pseudospecificity is best dealt with by restricting symptom severity prior to randomization
  - Statistical approaches cannot be used to rule out pseudospecificity
  - Cannot infer causality through statistical adjustment of post-randomization covariates

Negative Symptom Study Design

Inclusion Criteria: Medications

- **Second Generation Antipsychotics other than clozapine**
  - **Further restriction would depend on:**
    - **Mechanism of action**
    - **Type of study, e.g. PD/PK**
    - **Stage of development**
- **Concomitant Medications: Yes, but …**
  - **Further restriction would depend on:**
    - **Mechanism of action**
    - **Stage of development**

Negative Symptom Study Design

Inclusion Criteria: Medications

- **Rationale:**
  - Conventional antipsychotics
    - Treat negative symptoms secondary to positive symptoms
    - More likely to cause secondary negative symptoms due to EPS and dysphoric symptoms
  - Second generation antipsychotics
    - Treat negative symptoms secondary to positive symptoms
    - Less likely to cause negative symptoms secondary to EPS and dysphoric symptoms

Adjunctive Agents

- **Overall design: parallel group; double-blind comparison of placebo and study drug**
  - **Lead-in Phase: 2 - 4 weeks**
    - **Longer duration minimizes likelihood of change in other symptoms during double-blind phase**
  - **Double-Blind Treatment Phase: 6 – 24 weeks**
    - **Duration depends on type of study, i.e., proof of concept vs clinical efficacy trial**
- **Adjunctive agent added to current medication regimen**
  - **Restriction of antipsychotics and concomitant medications as described above**

Broad Spectrum Agents

- **Evaluation of negative symptom effects should be separated from the evaluation of antipsychotic efficacy (Pseudospecificity)**
- **Major issue is the selection of an appropriate comparator**
  - **Ideal comparator should be neutral or better**

Broad Spectrum Agents

- **Possible comparator agent options:**
  - **Placebo**
    - **Minimizes potential confounding from EPS**
    - **Potential for significant symptom exacerbation**
  - **Conventional Antipsychotic**
    - **Potential of differential EPS and other neurological side effects**
    - **May have dysphoric effects**
  - **Second Generation Antipsychotic**
    - **Minimize potential confounding due to dysphoric and neurological side effects**

Negative Symptom Study Design

Assessments:

- **Primary outcome measure: SANS total score***
  - **SANS provides broader coverage of different negative symptom constructs**
  - **Multiple items assess each construct**
  - ***Exclude: poverty of content of speech, inappropriate affect, and attention items**
- **Secondary outcome measures:**
  - **SANS subscales**
    - **Affective flattening; Alogia; Avolition; Anhedonia/Asociality**
  - **Cognition**
    - **MATRICS battery**
    - **Negative symptom-centric battery**