Enhancing CNS Product Labels with Pragmatic Trials: Challenges, Solutions and Outcomes That Support the Road to RWE

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Disclosures

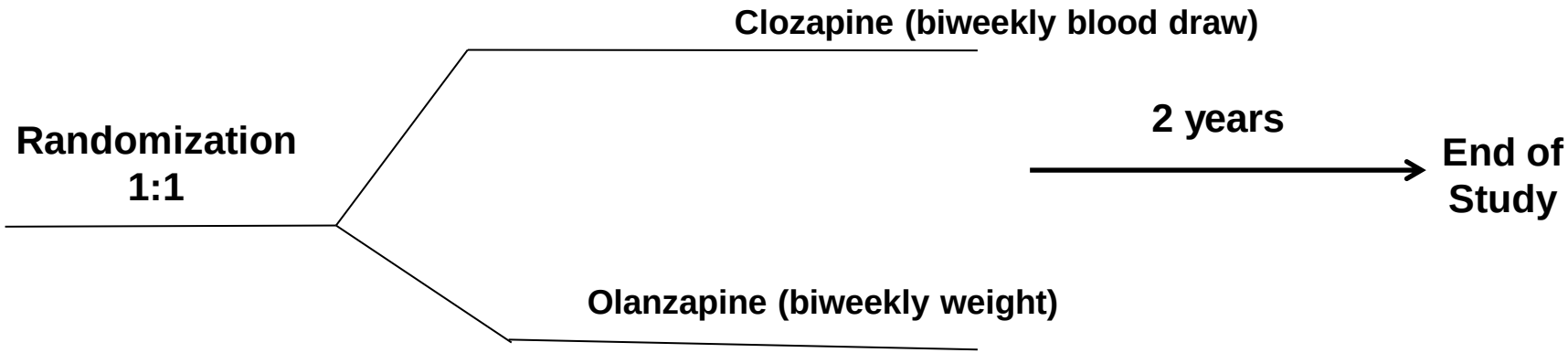
- Current employee Denovo Biopharma
- Past employee Novartis, Pfizer, Knoll (Abbvie), Janssen, Newron
- RSUs Denovo Biopharma
- Stock Johnson & Johnson

InterSePT (International Suicide Prevention Trial

- **Goal:** To demonstrate that clozapine is superior to olanzapine in reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder who have recently attempted suicide
- **Preliminary Data:** Post hoc work examining safety of clozapine suggested it might reduce suicide in patients with schizophrenia
- **Study population**
  - Attempted suicide within the 3 years prior to their baseline evaluation.
  - Hospitalized to prevent a suicide attempt within the 3 years prior to their baseline evaluation.
  - Demonstrated moderate-to-severe suicidal ideation with
    - depressive component within 1 week prior to baseline.
    - command hallucinations for self-harm within 1 week prior to baseline.

InterSePT Study Design

2-year, multicenter, 11-country, randomized, open-label, event monitoring board-blinded study comparing the risk for suicide behavior in patients with schizophrenia or schizoaffective disorder treated with clozapine vs olanzapine



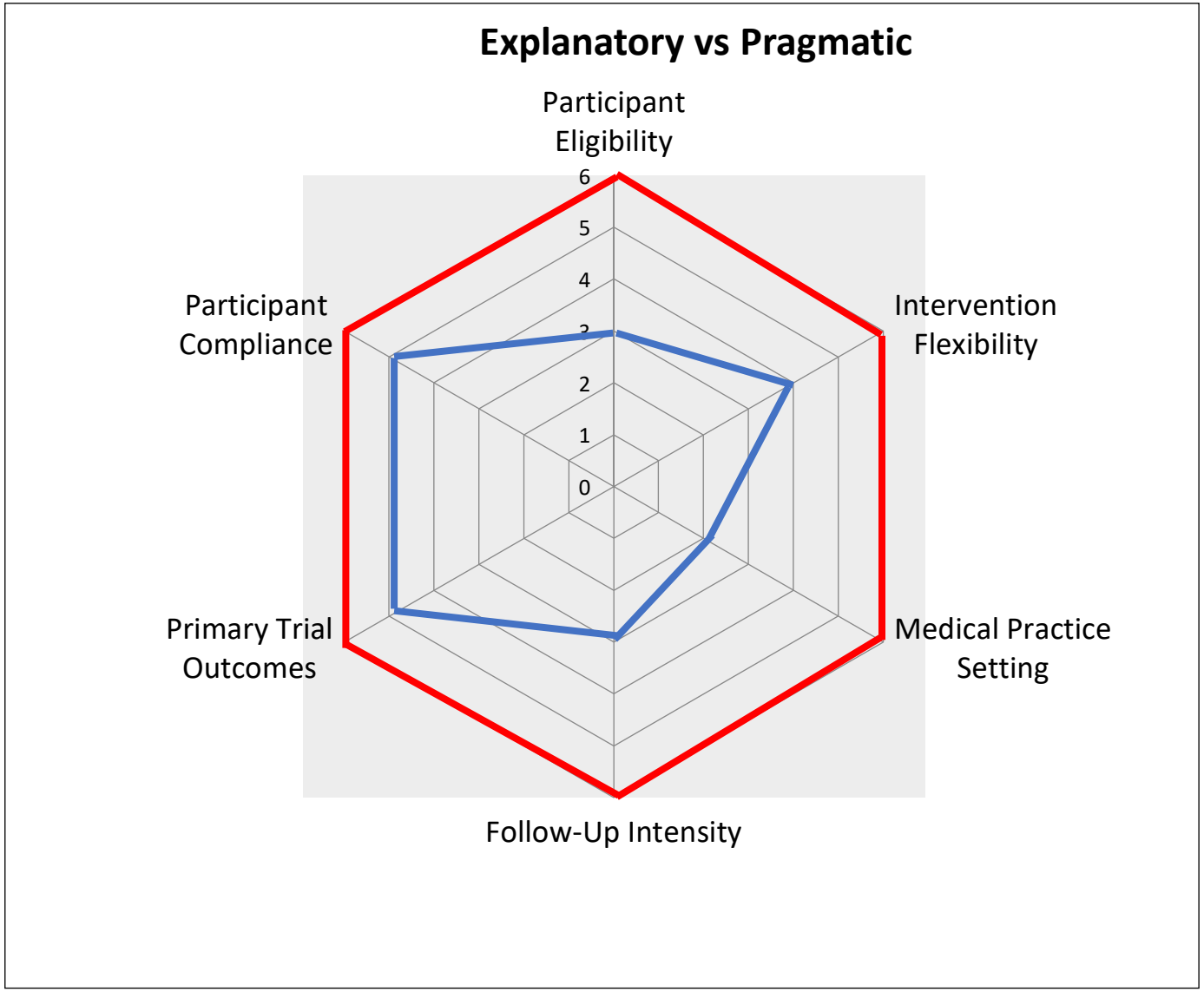
InterSePT Design Challenges

- **End point selection**
  - Need to prevent primary endpoint (i.e., suicidal behavior)
- **Scale selection:** no established scales
- **Inclusion and exclusion criteria:** High risk population
- **Blinding:** Verification of endpoints by blinded event monitoring board
- **Endpoints:** Time to significant increase in suicidal thinking; suicide attempt; death by suicide
- **Sample size**
  - Large study effect anticipated
  - 980 high risk patients enrolled with a suicide attempt in the last year
  - Global Study at 67 sites in 11 countries
- **Study duration**
  - A time to event endpoint with no prior experience in this population
  - Guessed: 2 years

InterSePT Design Challenges

- **Comparator Treatment: Active control required**
  - Olanzapine vs haloperidol
    - Mean dosing of olanzapine (and clozapine) differed from country to country
    - **Control for contact bias**
      - Clozapine required weekly blood draws to identify impending agranulocytosis;
      - Weekly contact might cause large one-sided study effect
      - Frequency of blood draws was not consistent across all countries
  - **Concomitant medications**
- **Recruitment**
- **Regulatory Challenges**
  - Need to clarify that death or suicide attempt are related to suicidal behavior
  - Timing of that event
  - Not due to differences in use of concomitant mediations
  - No fundamental differences in population subgroups

ASPECT-R Rating for InterSePT



InterSePT Results

Endpoint

- Probability of experiencing (1) a significant suicide attempt, including a completed suicide, or (2) hospitalization because of imminent suicide risk, including increased level of surveillance for suicidality for patients already hospitalized,
  - Lower for clozapine patients than for olanzapine patients at Week 104
    - Clozapine 24% versus olanzapine 32%
    - 95% CI of the difference : 2% , 14%.

InterSePT (International Suicide Prevention Trial

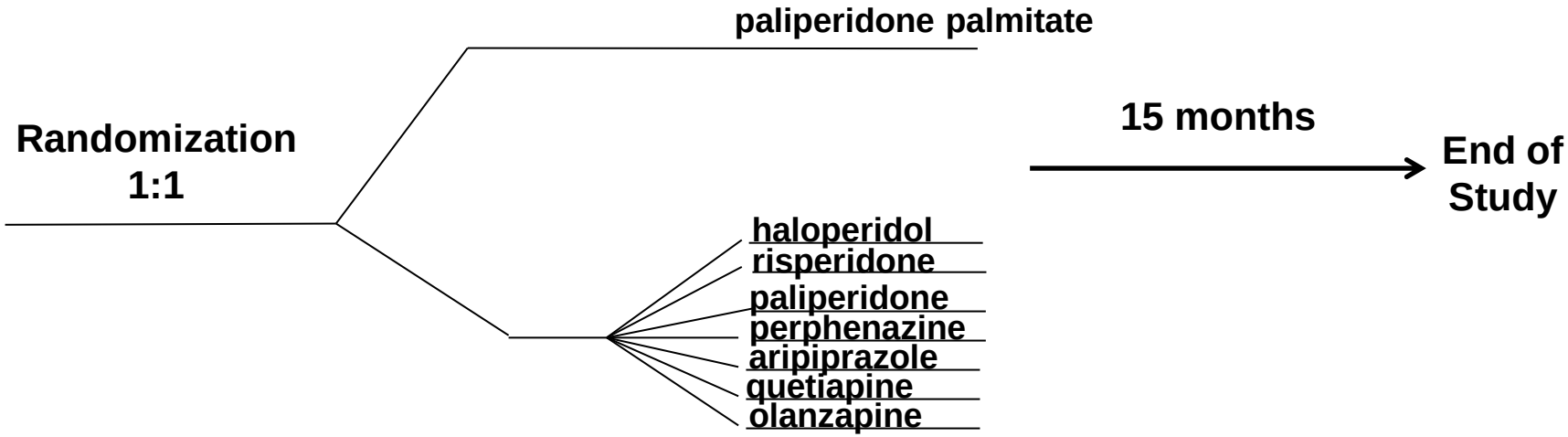
- **Label enhancement: “**CLOZARIL is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at risk for death.”

PRIDE Study

- **Goal:** To demonstrate that injectable paliperidone palmitate is superior to oral paliperidone in preventing treatment failure in persons with schizophrenia who have been recently incarcerated.
- **Study population:** Persons with schizophrenia who have been recently released from incarceration

PRIDE Study Design

15-month, multicenter, US-based, randomized, open-label, event monitoring board-blinded study comparing the risk for treatment failure in recently incarcerated patients with schizophrenia treated with paliperidone palmitate once monthly vs oral antipsychotics



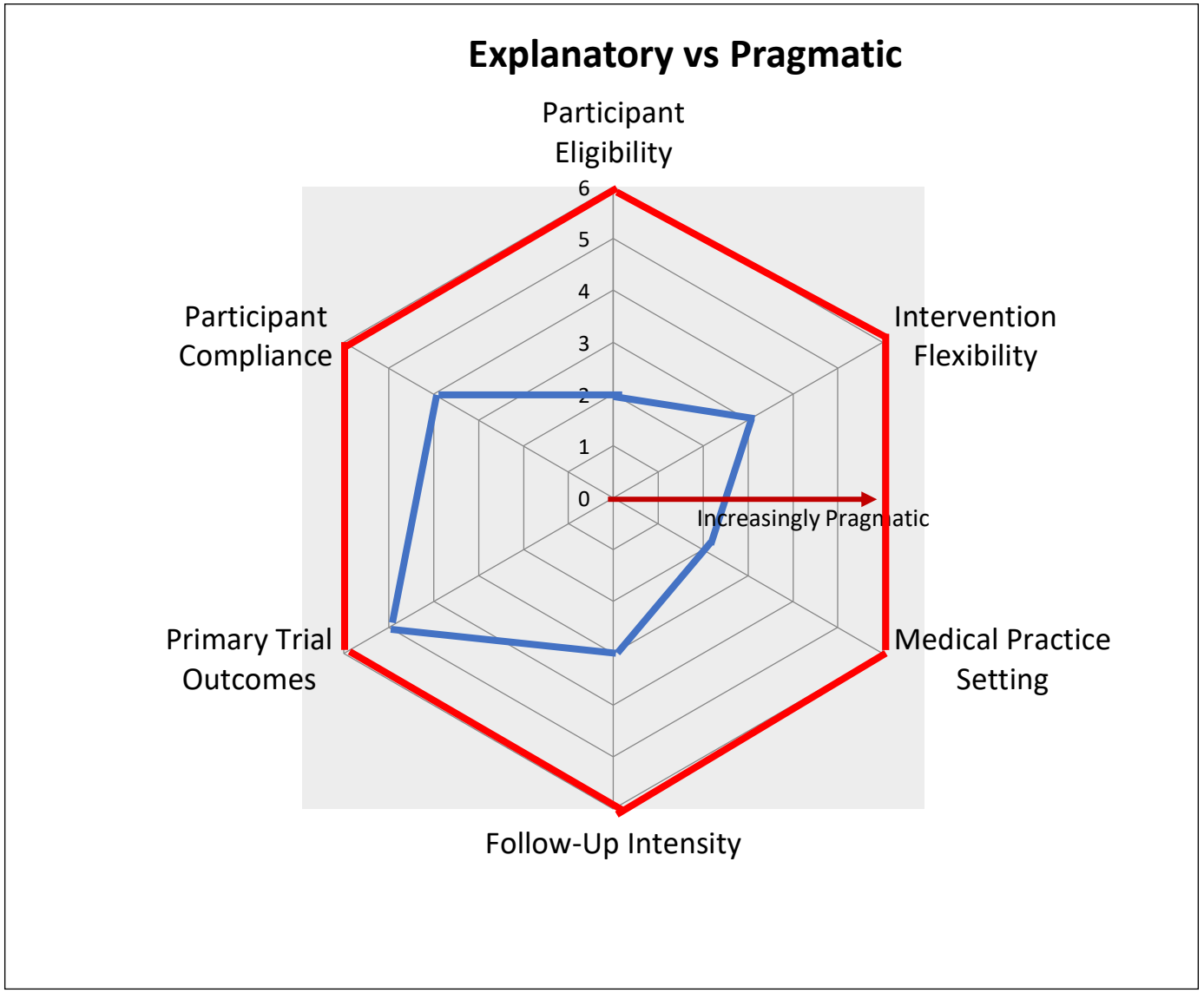
PRIDE Challenges

- **Endpoints:** Time to first treatment failure.
  - Arrest and/or incarceration;
  - psychiatric hospitalization;
  - discontinuation of antipsychotic treatment because of safety or tolerability;
  - Treatment supplementation with another antipsychotic because of inadequate efficacy;
  - Need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization;
  - Discontinuation of antipsychotic treatment because of inadequate efficacy;
  - Suicide
- **Legal definitions** (jail/prison/arrest/incarceration)
- **Scale selection** – None
- **Inclusion population:** Schizophrenic patient with history of recent incarceration
  - Very difficult to identify as not well connected to mental health system
  - High risk
- **Sample size estimation—**Expected large study effect
  - 444 randomly assigned subjects

PRIDE Design Challenges

- **Study duration**
  - A time to event endpoint with no prior experience in this population
  - Guessed 15 months
- **Blinding:** Oral vs Injectable antipsychotic
  - Verification of endpoints by blinded event monitoring board
- **Recruitment**—Non-traditional (e.g., soup kitchens)
- **Active control requirement with 2-step randomization**
  - Step 1: randomized to oral or injectable antipsychotic
  - Step 2: Oral group randomized to one of 7 oral antipsychotics (could deselect)
- **Regulatory challenges**
  - Follow up of dropouts

ASPECT- R Ratings for PRIDE



PRIDE Results

- Statistically significantly longer time to first treatment failure for paliperidone palmitate 91 month) compared with oral antipsychotic medications.
- Median time to treatment failure was 416 days paliperidone palmitate versus and 226 days oral antipsychotic medications
- Time to first arrest and/or incarceration or psychiatric hospitalization statistically significantly longer for paliperidone palmitate compared to oral antipsychotics

PRIDE Label Enhancement

The efficacy of INVEGA SUSTENNA® in delaying time to treatment failure compared with selected oral antipsychotic medications was established in a longterm, randomized, flexible-dose study in subjects with schizophrenia and a history of incarceration. Subjects were screened for up to 14 days followed by a 15-month treatment phase during which they were observed for treatment failure. The primary endpoint was time to first treatment failure.

Treatment failure was defined as one of the following: arrest and/or incarceration; psychiatric hospitalization; discontinuation of antipsychotic treatment because of safety or tolerability; treatment supplementation with another antipsychotic because of inadequate efficacy; need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization; discontinuation of antipsychotic treatment because of inadequate efficacy; or suicide. Treatment failure was determined by an Event Monitoring Board (EMB) that was blinded to treatment assignment.

A total of 444 subjects were randomly assigned to either INVEGA SUSTENNA® (N = 226; median dose 156 mg) or one of up to seven pre-specified, flexibly-dosed, commonly prescribed oral antipsychotic medications (N = 218; aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, or risperidone).

The selection of the oral antipsychotic medication was determined to be appropriate for the patient by the investigator. A statistically significantly longer time to first treatment failure was seen for INVEGA SUSTENNA® compared with oral antipsychotic medications. The median time to treatment failure was 416 days and 226 days for INVEGA SUSTENNA® and antipsychotic medications, respectively. A KaplanMeier plot of time to first treatment failure is shown in Figure 4. The frequencies of first treatment failure events by type are shown in Table 15. The time to first arrest and/or incarceration or psychiatric hospitalization was also statistically significantly longer for the INVEGA SUSTENNA® group compared to the oral antipsychotic group. Figure 4: Kaplan-Meier Plot of Time to First Treatment Failure in a Long-Term, Randomized, Flexible- Dose Study in Subjects with Schizophrenia and a History of Incarceration (Schizophrenia Study 6)

Conclusions

- **InterSePT and PRIDE trials faced problems in design similar to those to be addressed in fully RWE studies**
  - **Endpoint selection** (objective measures that are completely documented; no scales)
  - **Study population identification** (inclusion and exclusion): well defined study question dependent ensuring lack of bias based on treatment assessment)
  - **Study duration**: Study dependent
  - **Choice and follow up of active controls**: Assure no bias based on treatment assignment
  - **Management of study bias:** Identify potential sources of bias and address
  - **Dropout follow up:** Assume drop out is not at random
  - **Blinding**: Independent verification of endpoints by blinded event monitoring board
  - **Management of regulatory challenges:** Get prior regulatory input