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# Models for Increasing Real World Evidence in Registration and Post-Approval Clinical Trials

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# Disclaimer

- Former employee of Novartis, Knoll (AbbVie), Pfizer (Warner-Lambert), Janssen Pharmaceuticals
- Current employee of Newron Pharmaceuticals, LLC
- Stock in Johnson & Johnson and Newron

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# Types of Real World Evidence Clinical Trials

- Episode-level retrospective cohort study
- Prospective, randomized comparative treatment design
- Model-Informed Drug Development (MIDD)

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# First Steps in Designing a Real World Trial

- What type trial provides real world evidence?
  - Any trial…but it maybe very restricted population (just the study being done)
  - No trial…the real world is more diverse than can be addressed in a single trial
  - Real question is ‘How generalizable is the study that you are doing?’

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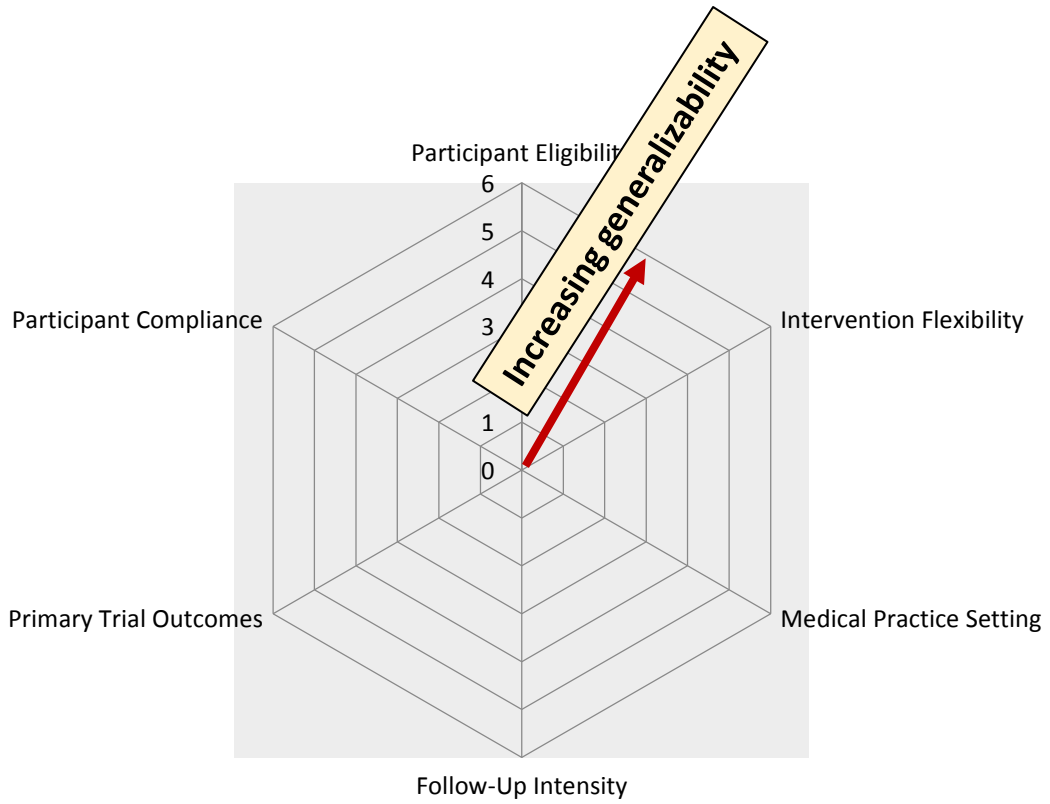
# Considerations for Designing Real World Trial

- To determine generalizability of data the study question must be very clearly identified
  - Who are you studying?
    - Do these subjects reflect the expected real world population?
  - What treatment(s) are you studying and what restrictions on their use are applied in the studies?
    - Does this reflect expected real world practice?
  - For how long are the treatments being delivered?
    - Are they long enough to capture real world value?
  - Who is delivering the treatments?
    - Do they reflect planned delivery in the real world?
  - How are outcomes being assessed?
    - Do the associated activities affect the overall outcome?
  - What are the outcomes?
    - Do they reflect outcomes of real world interest?

# ASPECT




http://innovationscns.com/?s=ASPECT-R

| |
|---|
| 0 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are very explicitly and precisely defined by the study protocol. These visit parameters are much greater than those which would be seen in normal clinical practice. |
| 1 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are explicitly defined and go considerably beyond those outlined in available treatment guidelines or standard practice. |
| 2 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are defined such that they are more constrained than those outlined in available treatment guidelines or standard practice. |
| 3 = Some elements of the visit frequency/structure/duration/intensity or the duration of the study, but not all, are more constrained than those outlined in available treatment guidelines or standard practice. |
| 4 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are defined such that they conform to available treatment guidelines or standard practice. |
| 5 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are defined such that flexibility is allowed beyond that found in available treatment guidelines or standard practice. |
| 6 = No constraints are put on visit frequency/structure/duration/intensity or follow-up period. |

# CASE # 1 InterSePT
# International Suicide Prevention Trial

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# The Public Health Problem for InterSePT

- Patients with schizophrenia and schizoaffective disorder exhibit high rates of suicide behavior (suicide attempts and deaths by suicide)
  - Lifetime risk of death by suicide is approximately 5%.
  - Lifetime risk of suicide attempts is 25-50%
- This outcome represents a under-treated life-threatening mental health condition.

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# GOAL of InterSePT

Demonstrate that clozapine is better than olanzapine (surrogate for SOC) for reducing the risk for suicidal behavior in patients with schizophrenia or schizoaffective disorder who are known to be at high risk for suicide.

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# InterSePT Study Question

- Is suicide behavior or perceived risk for imminent suicide is during 2-year follow up treatment with clozapine or olanzapine in patients with schizophrenia or schizoaffective disorder known to be at high risk for suicide?
  - **Population:** patients with schizophrenia or schizoaffective disorder known to be at high risk for suicide
  - **Treatment:** clozapine or olanzapine
  - **Duration:** 2-years
  - **Treatment Provider:** Psychiatrists familiar with clozapine or olanzapine who could conduct a complicated clinical trial
  - **Outcomes Procedures:** Many scales; masked raters with an independent suicide monitoring board
  - **Primary Outcome Measures:** Suicide behavior or significant perceived increase risk for imminent suicide

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# Design

- A 2-year, multicenter, international, randomized, open-label, rater-/suicide monitoring board-blinded study
- Compared the risk for suicidal behavior in patients with schizophrenia or schizoaffective disorder treated with clozapine vs olanzapine
- 980  high risk patients enrolled
  - A suicide attempt in the last year
- Global Study at 67 sites in 11 countries
  - United States
  - United Kingdom
  - Czech Republic
  - Canada
  - France
  - Croatia
  - Chile
  - Italy
  - South Africa
  - Argentina
  - Hungary

# Design

| Week 1-4 | Week 5-26 | Week 27-104 |
|---|---|---|
| **CLOZAPINE** | | |
| 12.5 mg, BID | 300-900 mg, daily<br>26 Weekly Visits | 300-900 mg, QD<br>37 Biweekly Visits |
| **OLANZAPINE** | | |
| 5 mg, QD | 5-30 mg, daily<br>26 Weekly Visits | 5-30 mg, daily<br>37 Weekly Visits |

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# InterSePT Results

**Any suicidal behavior/severity endpoint**

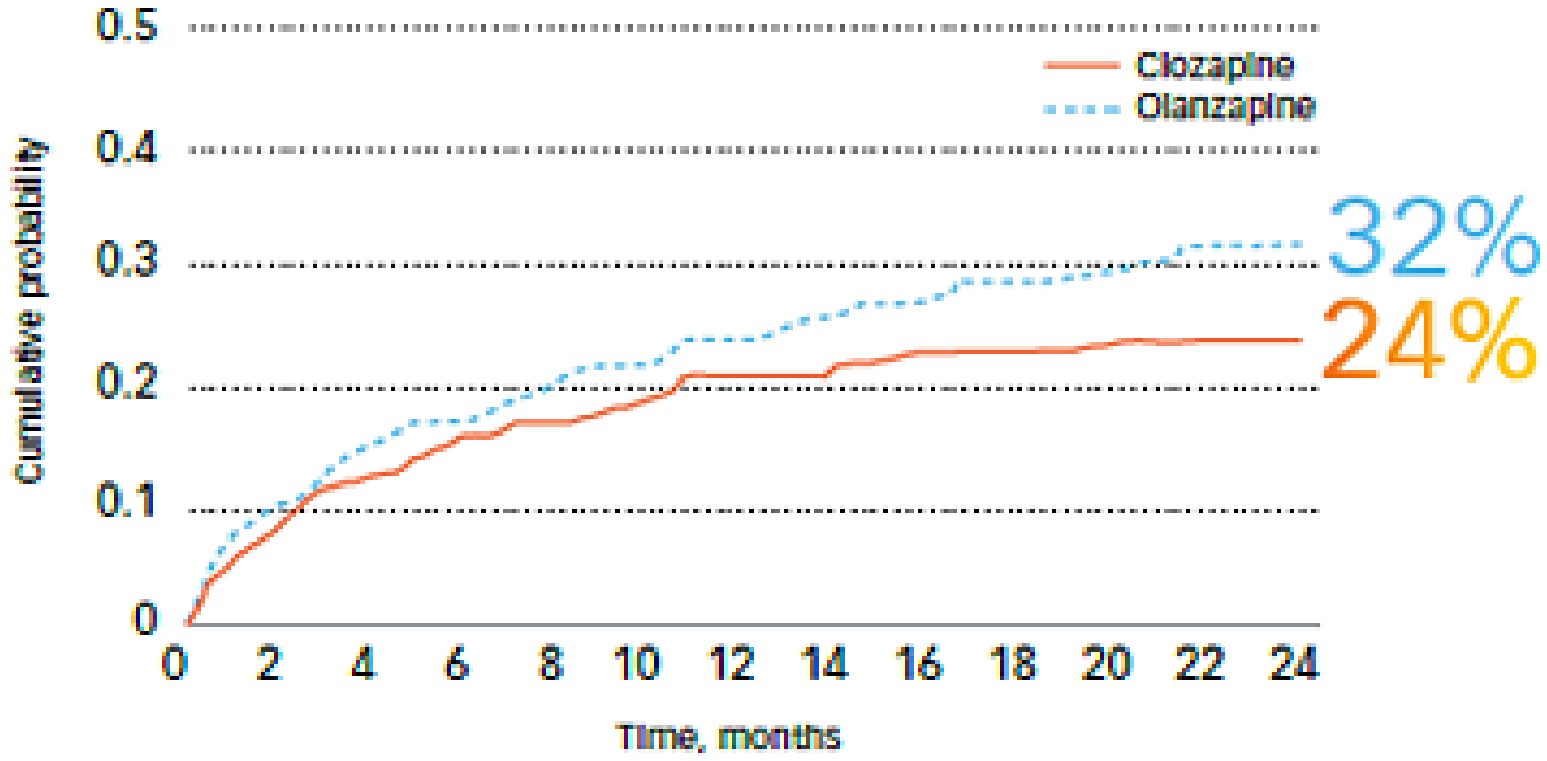
- Significantly less with clozapine **(P = .03; HR = 0.76; CI = 0.58 – 0.97)**

**Components (robustness):**

- **Attempted suicide:** Significantly less with clozapine (P = .03; 34 vs 55).
- **Required hospitalizations:** Significantly less with clozapine (P = .05; 82 vs 107).
- **Required rescue interventions:** Significantly less with clozapine (P = .01; 118 vs 155)
- **Required concomitant antidepressants:** Significantly less with clozapine exhibited (P = .01; 221 vs 258)
- **Required concomitant anxiolytics/soporifics** Significantly fewer patients treated with clozapine exhibited (P = .03; 301 vs 331)
- **Died by suicide:** Similar (5 clozapine vs 3 olanzapine-treated patients; P = .73)

# Results

**Cumulative probability of experiencing a significant suicide attempt or hospitalization to prevent suicide[1]**



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# Key InterSePT Design Considerations that Promote Pragmatism

- **Population:**
  - Persons with SCZ/SCA at high risk for suicide
  - Conducted in a broad range of sites across the world
- **Treatment:**
  - Clozapine and Olanzapine
  - 4 week titration required, but generally as used in real world
  - Prescribed and taken following general practice
  - All concomitant medications were allowed
  - Unblinded treatment.
- **Duration**
  - 2 years of follow up
- **Treatment Providers**
- **Outcomes Procedures**
  - Suicidal behavior was assessed at each visit to prevent suicide
  - Extensive follow ups
- **Outcomes Endpoints**
  - Attempts (including those that led to death),
  - Hospitalizations to prevent suicide
  - Major interventions to prevent suicide
  - Rating of "much worsening of suicidality" from baseline
  - Most identified by independent suicide monitoring board

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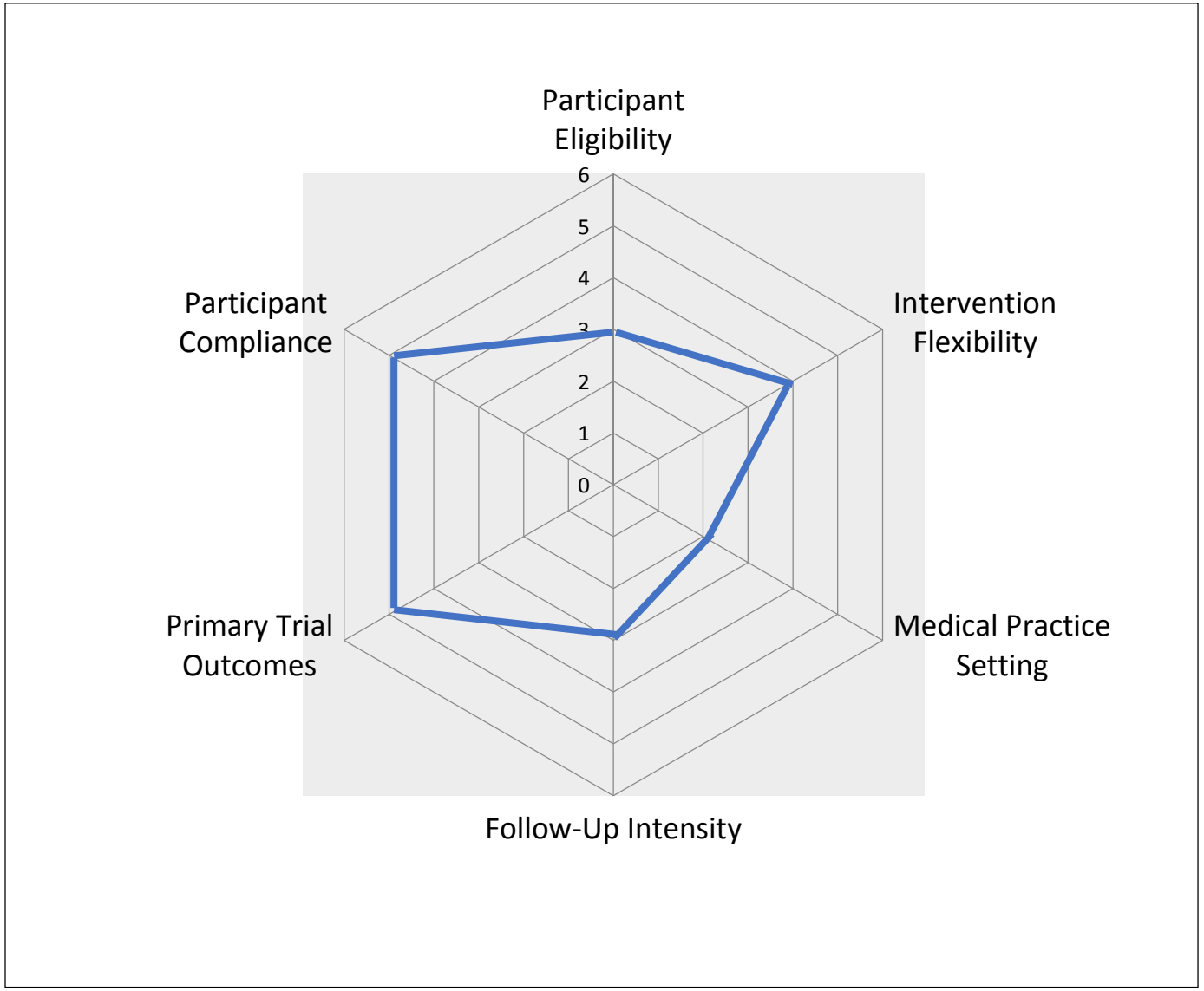
# Key InterSePT Design Considerations that Limit Pragmatism

- **Population**
  - Multiple inclusion/exclusion criteria
- **Treatment**
  - Treatment provided at no cost
  - Treatment in major study centers
- **Duration—**No problem
- **Treatment Providers**
  - Prominent, experienced treatment experts
  - Differential monitoring requirements for clozapine vs olanzapine
- **Outcomes Procedures**
  - Many assessments at each visit
  - Blinded and unblinded raters
  - Ethical considerations required suicide attempts and deaths be minimized
- **Outcomes Measures**
  - Positive and Negative Syndrome Scale, Covi Anxiety Scale, Calgary Depression Scale), adverse events, pharmacoeconomics, and pharmacogenetics

# ASPECT- InterSePT



# InterSePT Summary Findings (FDA Label)

## Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders

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 reexperiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that puts him/herself at risk for death.

The effectiveness of CLOZARIL in reducing the risk of recurrent suicidal behavior was demonstrated over a 2-year treatment period in the InterSePT Trial (see Clinical Trial Data under CLINICAL PHARMACOLOGY). Therefore, CLOZARIL treatment to reduce the risk of suicidal behavior should be continued for at least 2 years (see DOSAGE AND ADMINISTRATION).

The prescriber should be aware that a majority of patients in both treatment groups in InterSePT received other treatments as well to reduce suicide risk, such as antidepressants and other medications, hospitalization, and/or psychotherapy. The contributions of these additional measures are unknown.

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# CASE # 2 PRIDE

# Treating Schizophrenia in Real World Settings with Paliperidone Palmitate Once Monthly vs Oral Antipsychotics

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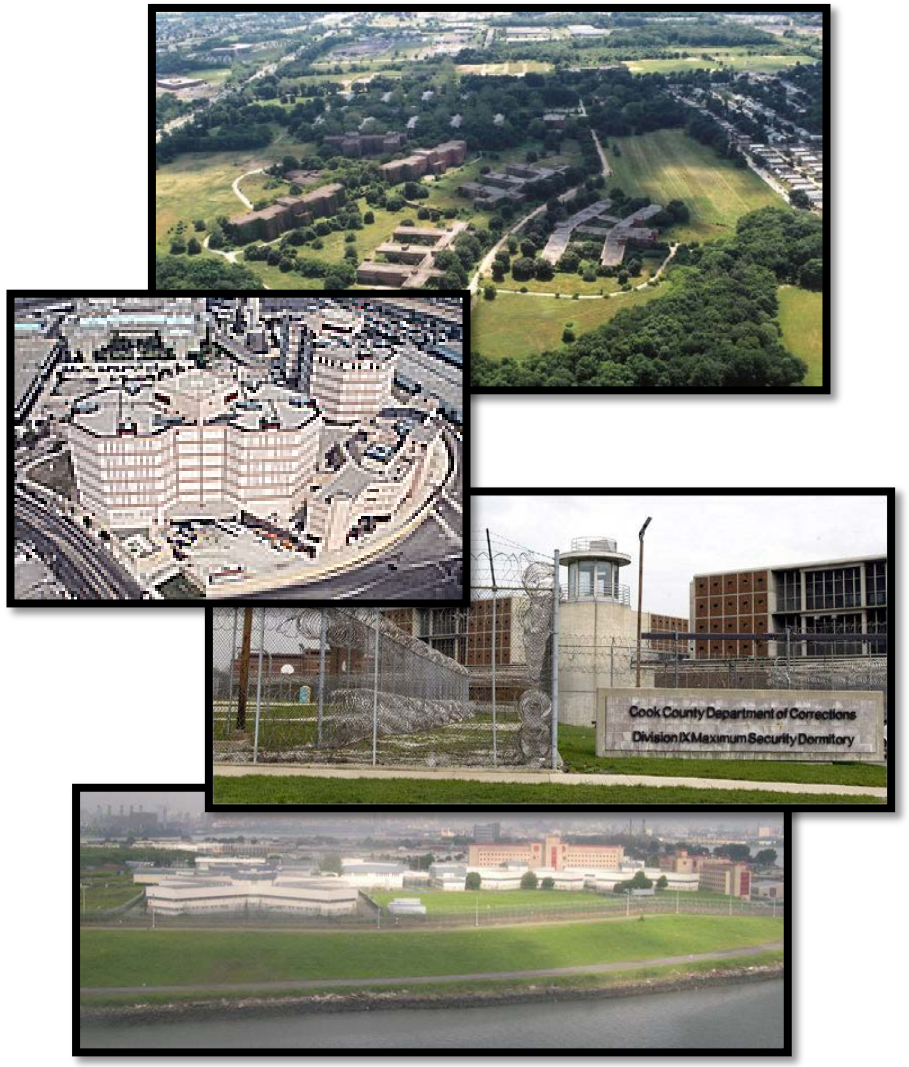
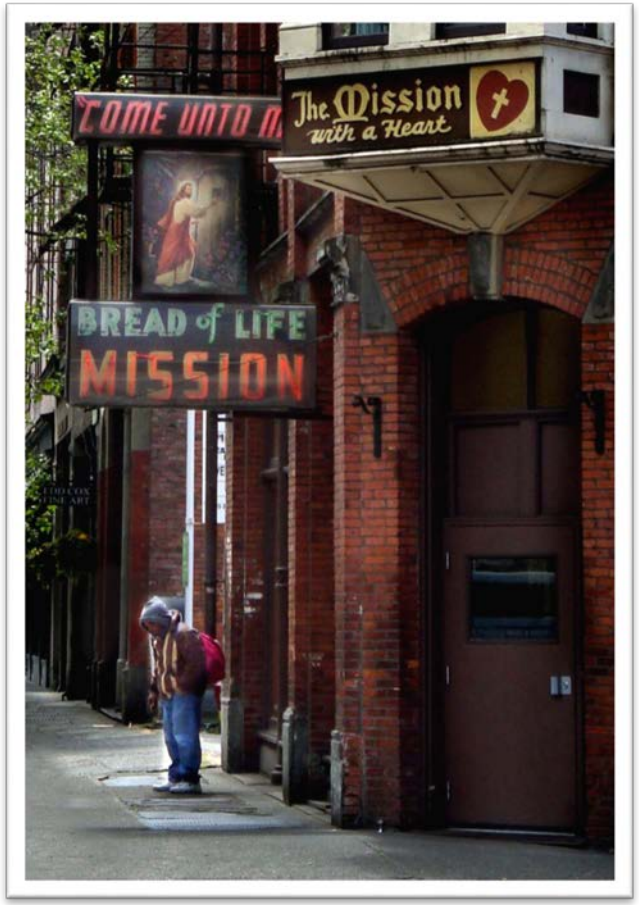
# PRIDE Public Health Problem

- **Deinstitutionalization** of the mentally ill over the past 50 years and changes in health policy has **shifted the burden** of care for mental illness **to jails and prisons**
- The **largest facilities** for psychiatric patients in the United States are **not hospitals but jails**
- It is **more costly** to provide mental health care in the correctional system



# PRIDE Study Goal

- To determine if treatment with long acting injectable antipsychotic paliperidone palmitate has clinical and economic advantages over oral antipsychotic treatments provided to persons with schizophrenia who had recently been released from incarceration.



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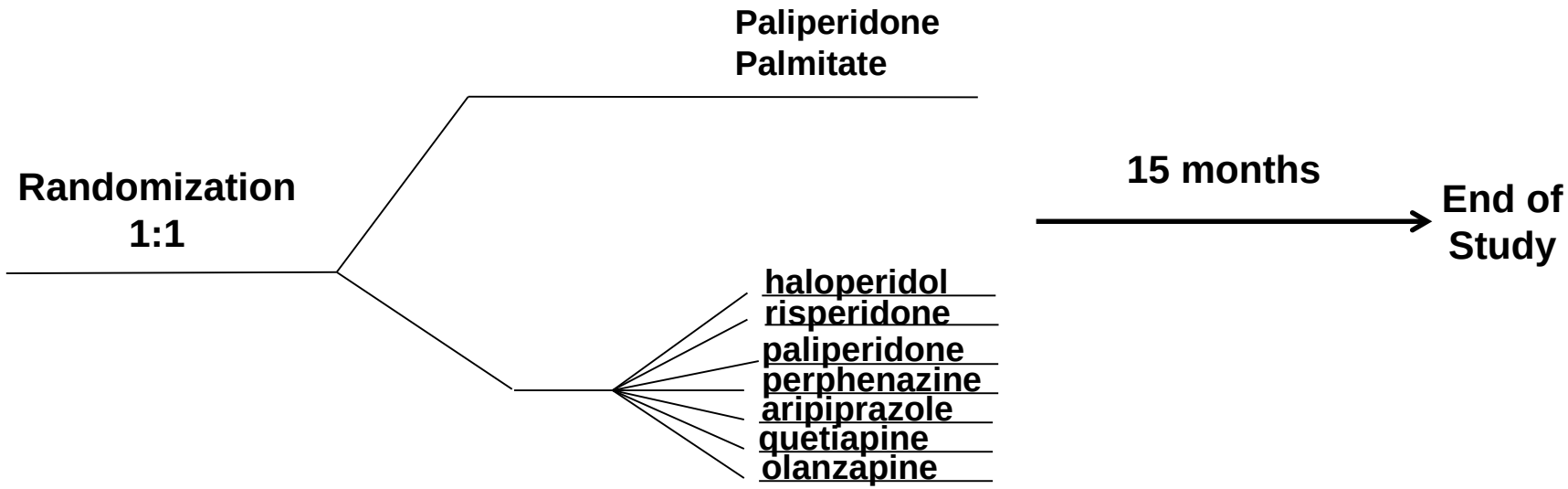
# PRIDE Study Question

Is treatment failure (hospitalization, re-incarceration, adding antipsychotic to prevent a treatment failure) is similar during 15-month follow up treatment with either paliperidone palmitate once monthly or one of 7 commonly used oral antipsychotic treatments in patients with schizophrenia who have recently been incarcerated and/or arrested?

- **Population:** US patients with schizophrenia who have recently been incarcerated and/or arrested
- **Treatment:** Paliperidone palmitate once monthly or one of 7 commonly used oral antipsychotic treatments
- **Duration:** 15 months
- **Treatment Provider:** Psychiatrists familiar with paliperidone palmitate and other allowed antipsychotic drugs who could conduct a complicated clinical trial
- **Outcomes Procedures:** Many scales; masked raters with an independent suicide monitoring board
- **Outcome Measures:** Time to hospitalization or suicide; Time to arrest/incarceration; Time to intervention to prevent hospitalization or arrest

# PRIDE Study Design

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



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# Key PRIDE Design Considerations that Promote Pragmatism

- **Population:**
  - Persons with SCZ who have been recently incarcerated
- **Treatment:**
  - Paliperidone palmitate vs Risperidone, Paliperidone, Olanzapine, Aripiprazole, Haloperidol
  - Concomitant medications were allowed
  - Unblinded treatment—Blinded Endpoint Review Board
- **Duration**
  - 15 months
- **Treatment Providers**
  - Psychiatrists throughout the US
  - Unblinded to treatment
- **Outcomes Procedures**
  - Suicidal behavior was assessed at each visit
- **Outcomes Endpoints**
  - Time to hospitalization or suicide
  - Time to arrest/incarceration
  - Time to intervention to prevent hospitalization or arrest

# Key PRIDE Design Considerations that Limit Pragmatism

- **Population:**
  - 442 persons with SCZ who have been recently incarcerated
- **Treatment:**
  - Paliperidone palmitate vs Risperidone, Paliperidone, Olanzapine, Aripiprazole, Haloperidol
  - Injectable paliperidone palmitate was free
  - Open label treatment
- **Duration**
- **Treatment Providers**
  - Psychiatrists had teams capable of doing research and doing many scales
- **Outcomes Procedures**
  - Ethical considerations required that the design minimize incarcerations and psychotic relapses
  - Blinded raters
- **Outcomes Endpoints**
  - Many assessments for efficacy and safety

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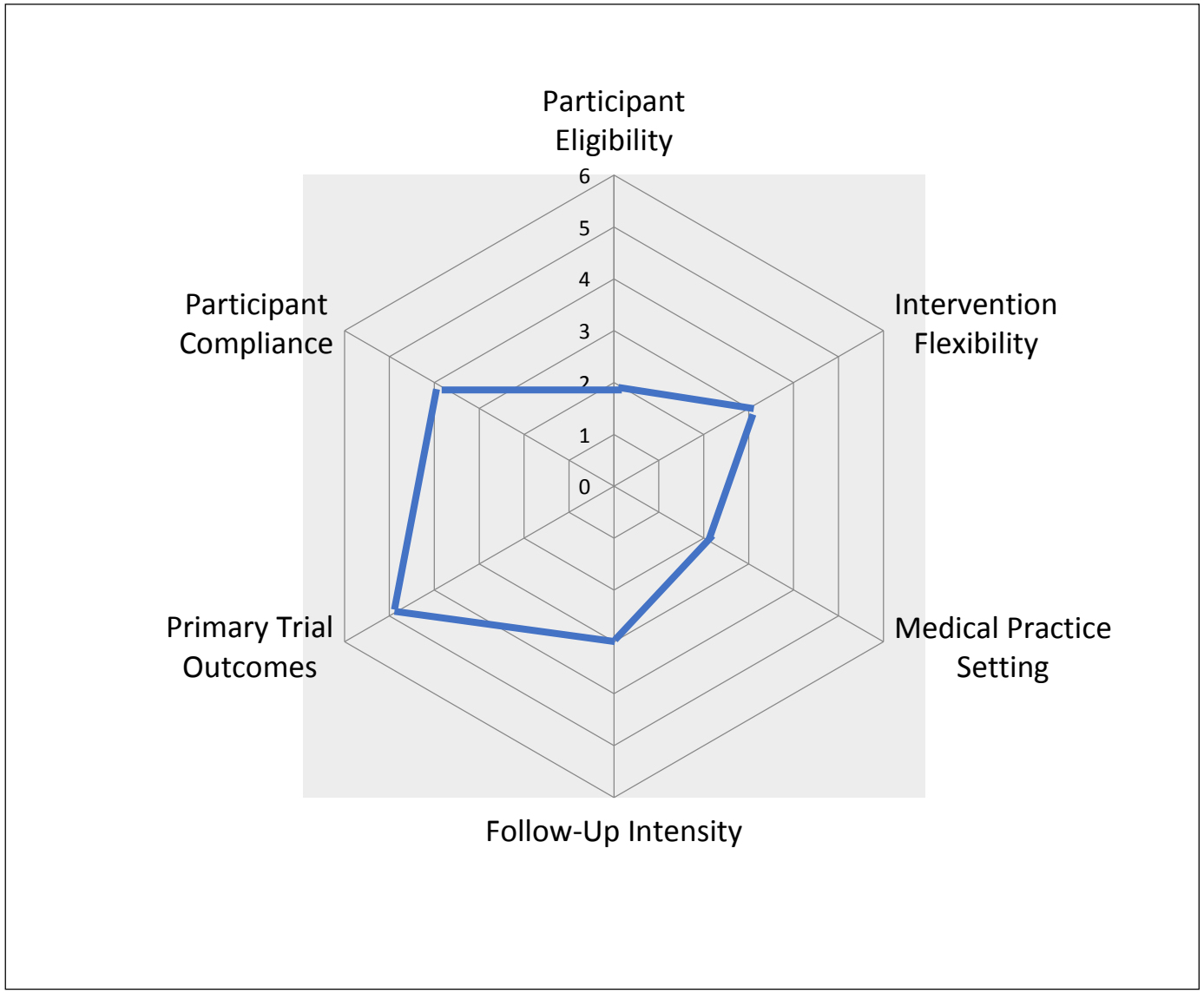
# PRIDE Results

- Paliperidone palmitate delayed time to treatment failure compared to the most commonly used daily oral antipsychotic treatments
  - Risk of treatment failure was **1.4 times higher** with oral antipsychotics (95% CI: 1.09, 1.88, P=0.011)
  - Median days to treatment failure **416 days** for paliperidone palmitate vs. **226 days** for oral antipsychotics
  - **Arrest/incarceration** and **psychiatric hospitalization** were the most common reasons for treatment failure in the paliperidone palmitate and oral antipsychotic groups (21.2% vs 29.4% and 8.0% vs 11.9%, respectively)

# ASPECT- PRIDE



# PRIDE Summary Findings

## INDICATION

**INVEGA SUSTENNA® (paliperidone palmitate) is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.**

## CLINICAL TRIALS

**Table 15: Components of Composite Endpoint in a Long-Term, Randomized, Flexible-Dose Study in** Subjects with Schizophrenia and a History of Incarceration (Schizophrenia Study 6)

| Event Type | INVEGA SUSTENNA® N=226 frequency (%) | Oral Antipsychotics N=218 frequency (%) | Hazard Ratio[a] 95% CI |
|---|---|---|---|
| **First Treatment Failures** | 90 (39.8%) | 117 (53.7%) | 0.70 [0.53, 0.92] |
| **First Treatment Failure Component Events** | | | |
| • Arrest and/or incarceration | 48 (21.2%) | 64 (29.4%) | |
| • Psychiatric hospitalization | 18 (8.0%) | 26 (11.9%) | |
| • Discontinuation of antipsychotic treatment because of safety or tolerability | 15 (6.6%) | 8 (3.7%) | |
| • Treatment supplementation with another antipsychotic because of inadequate efficacy | 5 (2.2%) | 6 (2.8%) | |
| • Need for increase in level of psychiatric services to prevent an imminent psychiatric hospitalization | 3 (1.3%) | 4 (1.8%) | |
| • Discontinuation of antipsychotic treatment because of inadequate efficacy | 1 (0.4%) | 9 (4.1%) | |
| • Suicide | 0 | 0 | |
| **Arrest and/or Incarceration or Psychiatric Hospitalization Events, regardless of whether they were first events[b]** | 76 (33.6%) | 98 (45.0%) | 0.70 [0.52, 0.94] |

[a] Hazard ratio of INVEGA SUSTENNA® to Oral Antipsychotics based on Cox regression model for time-to-event analysis. Note that the hazard ratio did not appear constant throughout the trial.

[b] Analysis results, which incorporated relevant events collected after discontinuation for those who discontinued, were consistent with the results from the pre-specified analysis of this secondary endpoint

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# PRIDE Modeled Analyses

- **Approach:**
  - Decision modeling of PRIDE study results were used to predict outcomes in stable schizophrenic Medicaid patients
- **Method:**
  - Used data from PRIDE and Control group results from 3 month and 6 month studies
  - Primary outcome for decision model study was PSYCH hospitalizations.
  - Final target real-world Medicaid sample size: n = 4,609.
- **Results:**
  - Compared to oral antipsychotic treatment, paliperidone palmitate produced a per-patient decrease:
  - PSYCH-related hospitalizations of 0.27 (95% confidence interval [CI]: –0.43, 0.97)
  - All Cause-related hospitalizations 0.28 (95% CI: –0.28, 0.84)
  - Validation exercises assured that the reweighting methodology used could replicate observed outcomes in the Medicaid sample.
- **Conclusions**
  - These incremental reductions in hospitalization rates are worth about $3.4 to $3.8 billion over an 18-month period in patients with schizophrenia receiving Medicaid.

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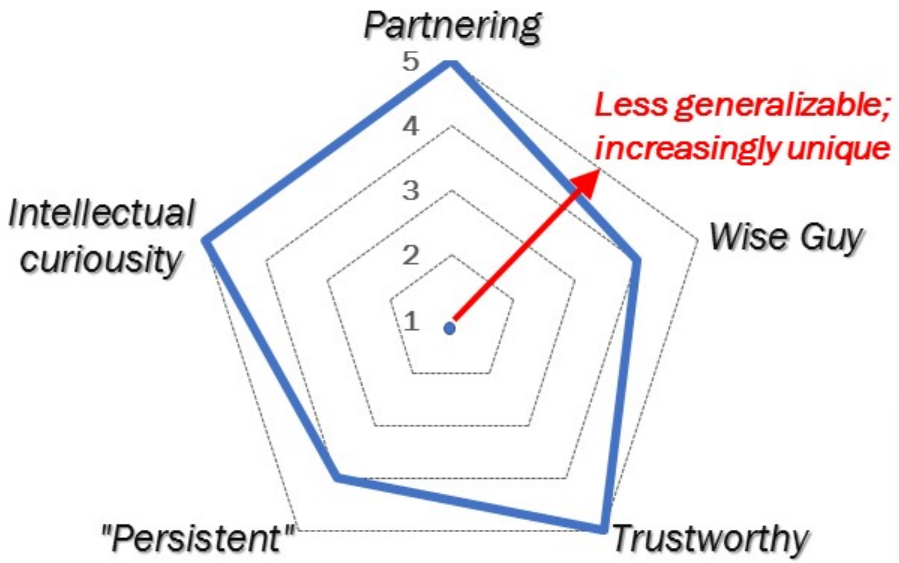
# ASPECT-L
## A Scale to Portray Exceptional Characteristics & Traits of Larry

Author: Cyndi Bossie, Medical Affairs, Janssen Neuroscience

**Objective:** To satisfy Larry's desire for another ASPECT scale

**Population of interest:** Author's world of friends, family, & acquaintances




**Domain Rating Anchors:**

1=generalizable to nearly all of pop. of interest
2=represents a large proportion of pop. of interest
3=represents ~50% of pop. of interest
4=represents a low proportion of pop. of interest
5=unique; represents <5% of pop. of interest

**Conclusion:**

- Larry is a unique & great guy who will be missed!

**ASPECT-L Limitations:**

- Single developer
- No inter-rater reliability
- Not broadly applicable
- Data on file, unpublished

Presented at: Larry's retirement celebration. Titusville, NJ. March 29, 2018

# Thank You