Epidemiologic, Regulatory and Methodological Considerations in the Design of a Trial with Both *Pragmatic and Explanatory* Elements: the InterSePT Experience

Ravi Anand, MD

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Pragmatic and Explanatory Trials: Key Considerations

- Pragmatic trials evaluate whether an intervention works in real life conditions, and if the effect is relevant to the patient
  - Do not evaluate how or why the intervention works, and are useful for deciding the use of the intervention
- Explanatory trials determine if an intervention works under ideal or selected conditions
  - Evaluate how/why an intervention works, and are important for evaluation of efficacy
- Key differences
  - Patient selection
    - Pragmatic trials: should reflect routine practice, with broad inclusion, but exclusions restricted to patients for whom intervention may be contraindicated
    - Explanatory trials: selective inclusions, exclude patients with co-morbidities, concomitant treatments
  - Intervention
    - Pragmatic trials: left to investigator judgment
    - Explanatory trials: strictly defined and tightly controlled
  - Control
    - Pragmatic trials: routine practice
    - Explanatory trials: placebo or marketed drug
  - Management of Patients
    - Pragmatic trials: left to discretion of clinical staff
    - Explanatory trials: same management except for intervention under evaluation: protocol driven
  - Blinding
    - Pragmatic trials: key objective is whether patients derive benefit, not how or why; therefore patients and caregivers may not be blinded
    - Explanatory trials: bias reduction is important, hence raters, patients, caregivers are blinded

Key Considerations continued (2)

- Key differences
  - Outcome measures
    - Pragmatic trials: revolve around patient benefit, hard endpoints, include broad measures of health/quality of life
    - Explanatory trials: focus on specific symptoms, dimensions of quality of life, clinical/ biological measures
  - Concomitant Treatments
    - Pragmatic trials: Treatment as Usual (all interventions allowed)
    - Explanatory trials: Only limited interventions that don't affect efficacy of trial drugs
  - Analysis
    - Pragmatic trials: analyze according to treatment allocated as objective is determination of effectiveness
    - Explanatory trials: analyze based on treatment actually received, as objective is demonstration of efficacy
  - Overall conduct of research
    - Pragmatic trials: flexible, with informed decision-taking/amendments based on in-trial observations
    - Explanatory trials: far more rigid with minimal amendments

Background

- Suicide in schizophrenia has been described over the ages:
  - " Patients with dementia praecox often need hospitalization to prevent aggression against other and suicide." (Emil Kraepelin, 1897)
  - " The suicidal drive is clearly the most serious of schizophrenic symptoms. " (Eugen Bleuler, 1911)
- Suicide rate in schizophrenia has not been reduced by neuroleptics
  - Pre-neuroleptic era: Iowa 500 study (Winokur and Tsuang, 1935-1950) rate 13% lifetime; Burgholzi Klinik (Bleuler, 1920-1950) rate 9 %
  - Neuroleptic era: 9-13 % rate on neuroleptics (Axelsson, 1992)
  - Atypical antipsychotics have also not reduced this rate
- Suicidal behavior is a separate domain from psychosis
  - Risk of suicide attempt/suicide not reduced by successful treatment of positive symptoms
  - Lifetime and current suicidal behavior similar between responsive and treatment resistant patients

The Spectrum of Suicidal Behavior

Communicated behavior **Observed behavior**

Suicidal thoughts **Suicide plans** **Suicide attempts** **Suicide**

- 20% - 40% of patients with schizophrenia and schizoaffective disorder attempt suicide[1]
- 4% - 13% die by suicide[2]
- 0.4% - 0.8% of schizophrenic patients die from suicide annually (24,000 patients in NA and Europe)
- Annual number of suicides in US for schizophrenia is 3,600[3]
- 20-40% of all suicides occur in schizophrenia-related illnesses
- Risk for suicide is 1000 fold greater in schizophrenia than the general population

[1]Roy et al, 1984; Landmark et al, 1987; Heila et al, 1998; Harkavy-Friedman et al, 1999.
[2]Tsuang, 1978; Heila et al, 1997; Osby et al, 2000;
[3]US Surgeon General.

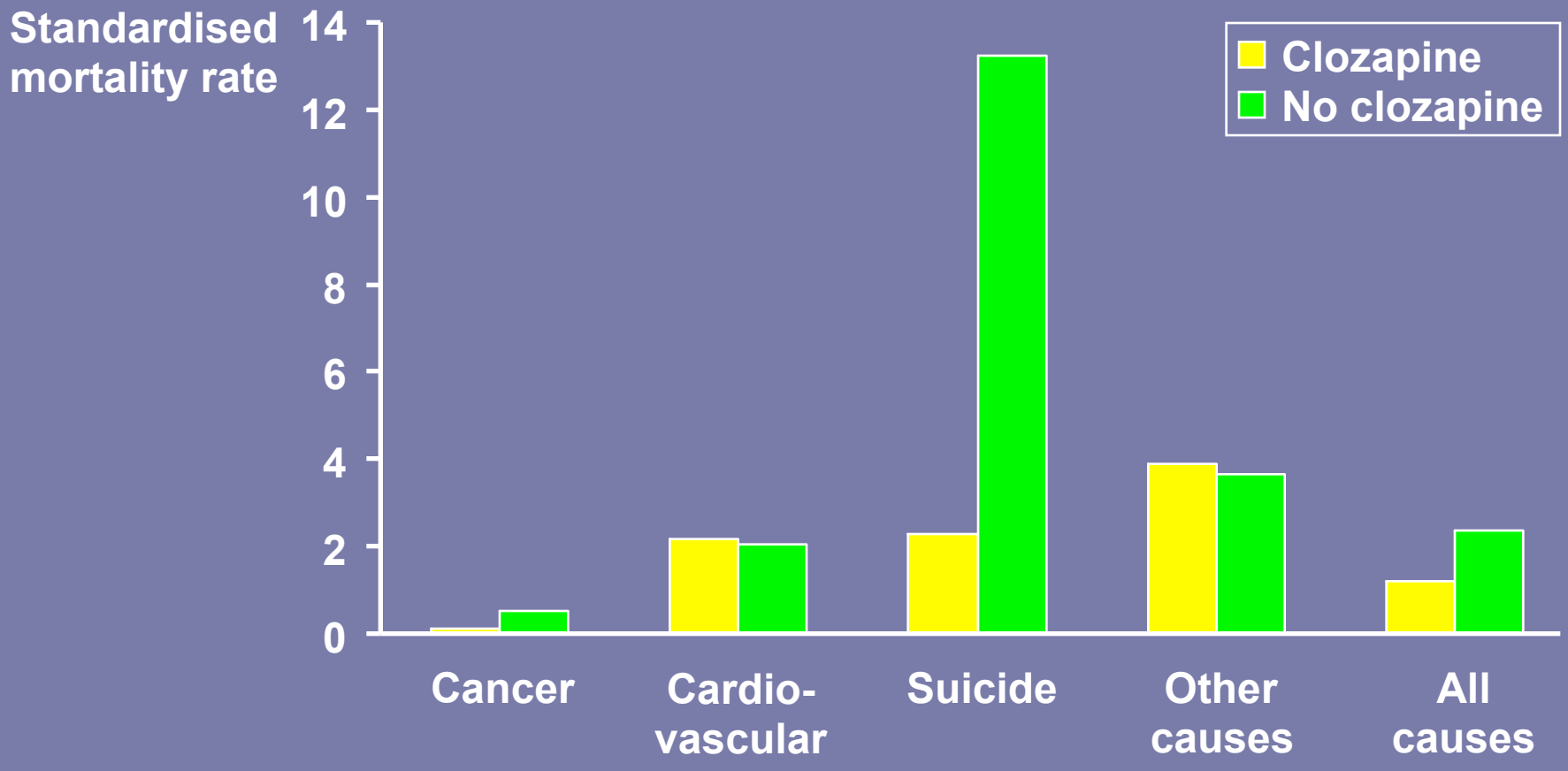
Background to the InterSePT Trial (International Suicide Prevention Trial)

- Numerous anecdotal reports of reduced suicidality in patients treated with clozapine in late 70s and 80s.
- German regulatory authority modified clozapine label to reflect suicide reduction based on review of data from clozapine treated patients
- Rare reports of suicide in US patients led to retrospective review of suicidal behavior before and during treatment ("Mirror image study") with clozapine demonstrating reduced rates of suicidal behavior (Meltzer and Okayli, 1995)
- Data from treatment registries (Texas and UK) demonstrated reduced rate of completed suicide in patients on clozapine

Background to the InterSePT Trial (2)

- FDA's concerns on increased mortality in clozapine users due to cardiac causes, drug interaction, pulmonary embolism, etc. led them to ask Sandoz to investigate mortality based on data in the Clozaril National Registry (CNR)
- Data from CNR for clozapine usage from April 1st 1991, to Dec. 31st 1993 from 74,138 users was linked to data from social security administration death master files, for 1989-1993, and national death index to ascertain deaths
- Records from 67,072 current and former clozapine patients yielded 396 deaths in 85,399 person years
- Clozapine users were grouped into:
  - "current" (0-14 days since last WBC count)
  - "recent" (15-106 days)
  - "past" (> 107 days)

Effect of Clozapine on Standardized Mortality Rate for Schizophrenia in the USA



Walker et al, 1997

Standardized Mortality Ratios for Current and Recent Exposure

	Current	CI	Recent	CI
All causes	0.46	0.37-0.59	1.69	1.28-2.25
Suicide	0.17	0.10-0.30	1.11	0.62-1.99

- Current clozapine users had a 54% lower risk of death from any cause than past clozapine users
- The risk of death by suicide was reduced by 83%
- Suicide accounted for 19% of all deaths

Walker et al, 1997.

Regulatory Considerations in the Design of the InterSePT Trial

- FDA was encouraged by the CNR data showing 83% reduction in mortality due to suicide in patients on clozapine, however, indicated
  - Grant of a suicide reduction indication required a prospective, randomized trial showing superiority of clozapine over a control (agreed that placebo would be unethical/not feasible)
  - Approval of indication could be granted based on a single, overwhelmingly positive trial
  - Endpoint may not be suicide but a “hard” endpoint
  - Based on risks associated with clozapine, population must be “at high risk”
  - No specific recommendations on measures, scales, selection criteria, analytical methodology, etc but agreed to work closely with sponsor in developing trial

Challenges in the Design of the InterSePT Trial, a Combined *Explanatory* and *Pragmatic* Trial

Challenges in the Design of the InterSePT Trial

- No prior suicide prevention trial performed
- Population: All schizophrenics/ treatment resistant only/ suicidal risk only/ treatment resistant suicidal risk only?
- Selection criteria: none established/history?/ current risk ratings?
- Outcomes: completed suicide/ attempted suicide/ ratings of suicidality ?
- Instruments: no validated scales for assessing suicidality risk/ change in suicidality
- Comparator: Neuroleptics worsen suicidality; no atypical showed benefit
- Blinding: clozapine nightmarish to blind;: open-label would add biases
- Sample size : no prior trial/ outcome variables never assessed before

Challenges in the Design of the InterSePT Trial (2)

Primary objective and endpoints

- Ideal would be reduction in completed suicides
  - Would require over 200,000 patients followed for 5 years
- Since suicides represent a successful attempt, the objective of treatment must be to prevent suicide attempts
  - Time to a significant suicide attempt could serve as an endpoint
- Role of clinicians and caregivers is to identify patients at high risk of suicide attempt and intervene, therefore reducing the number of attempts that would be carried out
  - Hospitalization for imminent risk of suicide could also be an endpoint
- Concern that the various safety measures would reduce both of above, therefore an additional measure was considered. Since suicidality would worsen prior to attempt, this could be an endpoint
  - Time to significant worsening on CGI for severity of suicide as rated by a blinded rater
- **Protocol was designed with the following two primary endpoints**
  - ***Time to a significant suicide attempt, or hospitalization for imminent risk of suicide***
  - ***Change from baseline on CGI for severity of suicide as rated by a blinded rater (amended later)***

Issues in Defining the Primary Variable

- Schizophrenic patients make attempts due to suicidality, or bizarre delusions/command hallucinations
  - Impossible to determine reason in successful attempts
  - Both represent life threatening behaviors
  - A pragmatic decision was taken to redefine suicide attempts

  InterSePT protocol definition of suicide attempts

  "For purpose of this study, suicide attempts are defined as actions committed by a patient either with willful intent or as a response to internal compulsions or disordered thinking that put him /herself at risk for death"

Controlling Biases: Issues of Blinding

- Study pivotal to prove anti-suicide efficacy of clozapine (explanatory trial)
- Virtually impossible to conduct trial in double-blind design due to complications of
  - Blinding drugs
  - Differences in titration
  - Side effects such as hypotension, tachycardia, constipation, seizures, sedation, etc.
  - Weekly/biweekly clozapine blood testing
  - Reluctance of Investigators/caregivers to provide blinded treatment to high risk suicidal patients
  - Open-label treatment considered best choice for the pragmatic nature of the trial

Controlling Biases: Minimizing Impact of Open-Label Design

Sources of potential bias

- Suicides
  - Bias in determination of whether death was by suicide (e.g., auto accidents)
- Suicide attempts
  - Bias in assessing seriousness of attempts or whether injury was related to suicide attempt
- Hospitalizations for Imminent Risk of Suicide
  - Bias in assessing imminent risk for suicide as criteria for endpoint
- Antipsychotic efficacy
  - Bias in assessing clinical symptoms of psychosis

Controlling Biases: Eliminating Impact of Un-blinding on Outcome Variables

- Blinded Suicide Monitoring Board
  - International Independent Board that reviewed blinded potential endpoint packages to determine
    - If endpoint was reached
    - If cause of death was suicide
    - If suicide attempts/injuries were serious or gestures
    - Hospitalization was due to imminent risk or social reasons
- Blinded psychiatrist (located at treatment center)
  - Perform same reviews as SMB to provide an alternative assessment
  - Rated the ISST and CGI-SS under blinded conditions
  - No access to safety data or efficacy ratings
- Blinded raters
  - Obviated need for video tapings/centralized ratings for PANSS, CGI, etc.

IMPORTANT : NO INVOLVEMENT/ ACCESS OF SPONSOR TO OUTCOMES

Minimizing Bias due to Effect of Clozapine Monitoring

- Clozapine monitoring required weekly blood draw for first six months, bi-weekly thereafter
  - Requirement that the same frequency would be used worldwide, even if not required locally
- Speculation that anti-suicide effects of clozapine due to therapeutic effect of weekly visits
- **Solution:** Trial allowed similar healthcare worker contact for olanzapine-treated patients (vital signs)
  - Questions about suicidality at each visit for both treatment groups

Choice of Comparator/Concomitant Treatments

Comparator selection

- Neuroleptics worsen suicidality: most patients experienced suicidality on them, hence continuing on a neuroleptic was not an option
- Atypical antipsychotics did not show any reduction also
- Choice of antidepressant/mood stabilizers ruled out as psychosis would worsen
- Olanzapine finally chosen based on usage, low EPS
    - Treatment of suicidality requires higher dosages: US dose limited to 10mg, however, FDA provided special permission to use higher doses
    - Unavailable in Italy/France: special permission obtained for use in study

Concomitant treatments

- no restriction on use of other drugs **(Pragmatic Design)**
- Patients allowed to enter trial on antidepressant, anxiolytics, mood stabilizers
- Freedom for investigators to add any of the above, or another antipsychotic, or switch trial drugs if necessary ***(this would count as a secondary endpoint)***

Issues with Selection Criteria

- Pragmatic design requires evaluation of broad population ("real world" conditions)
  - No definition of suicidality in DSM/RDC/ICD that could guide
  - Should benefit be evaluated in all schizophrenia patients, only in treatment resistant patients, only suicidal patients, or treatment resistant suicidal patients
  - Schizoaffective patients show high rates of suicidality: should they be included?
  - Should enrolment be restricted only to patients who had attempted suicide?
  - Should enrolment include non-attempters but with high current suicidality (how to assess?)?
  - Would attempters and non-attempters show similar progression in two years ?

Ultimately, the final selection criteria defined a "high risk" of suicide patient with schizophrenia or schizoaffective disorder

- Schizophrenic or schizoaffective patients at high risk for suicide demonstrated by any of the following:
  - Attempted suicide within last 3 years
  - Hospitalized to prevent suicide in last 3 years
  - Experience moderate to severe suicidal ideation and depression within 1 week of baseline
  - Experiencing moderate to severe suicidal ideation and command hallucination to self harm within 1 week of baseline

Clinical Issues in the Conduct of the InterSePT Trial

- High risk patient (suicidal) excludes any restriction on concomitant medication/treatment
- Unethical not to prevent suicide/attempts, therefore multiple high frequency contact/visits to center
  - 67 visits in two years with contact with health care worker/psychiatrist/PI
- Every opportunity taken to prevent suicide
  - Addition of new con-meds/antipsychotics/ECT/increase frequency of visits/ hospitalizations/increase surveillance/locked ward
- Duration of participation of patients
  - Because endpoint determined by SMB (not PI), patients should continue in study for duration if at all possible
    - Not dropped if potential endpoint occurred
  - Risk data suggested that two years adequate to achieve necessary endpoints

Statistical Methods

Clinical Assumptions for sample size determination

- Risk greatest for patients with recent attempts (Heila, et al, 1997)
- Lifetime suicide attempt rate in schizophrenic population ~50% (Black, 1988)
- Percent of patients with at least one event by the end of 2 years estimated to be 45% for Clozaril and 55% for Zyprexa
- Empirical analysis suggested 2 year follow up adequate to detect sufficient events (attempts and hospitalizations to prevent suicide) in patients at high risk for suicide

Statistical Assumptions

- Log-rank test with alpha = 5%; drop-out rate = 15%
- Power of the test = 80%; two-sided alternative hypothesis
- Randomization ratio-- 1:1

Implications

- Total of 381 events needed
- Allowing for 15% dropout rate, approximately 900 were to be randomized

Statistical Methods (2)

- During conduct of trial, concern from sponsor that due to aggressive contact with health staff, changes in meds, use of structured instruments, number of events may be lower than assumed
  - SMB rated events not known to sponsor, only the number of SAEs
  - Retention rate may be lower than expected, thus further reducing event rate
  - Unlikely, that the two primary variables could be met after adjusting for multiplicity
- Sponsor convened external statistical experts in Aug. 2000 to consider specific revisions to primary variables and the SAP
  - Consideration given to analyzing multiple events in a given patient
  - Providing differential weights to different type of events, number of events (suicide versus attempts: competing risk issue), hospitalizations for risk of suicide versus pharmacological interventions)
  - Converting the CGI-SS BP rating from a change estimate to a categorical rating and using time to first occurrence of such a rating (CGI-SS BP of 6 or 7)
- The primary analysis should be based on the Wei-Lin-Weiss Method (WLW)
  - WLW never used previously by FDA, or others for treatment trials
  - A semi-parametric method used to analyze multi-varied failure time data
  - Models the marginal distribution with a Coz-proportional hazard model
- Amendment submitted to FDA after database lock, but before analysis **(Pragmatic Trial)**

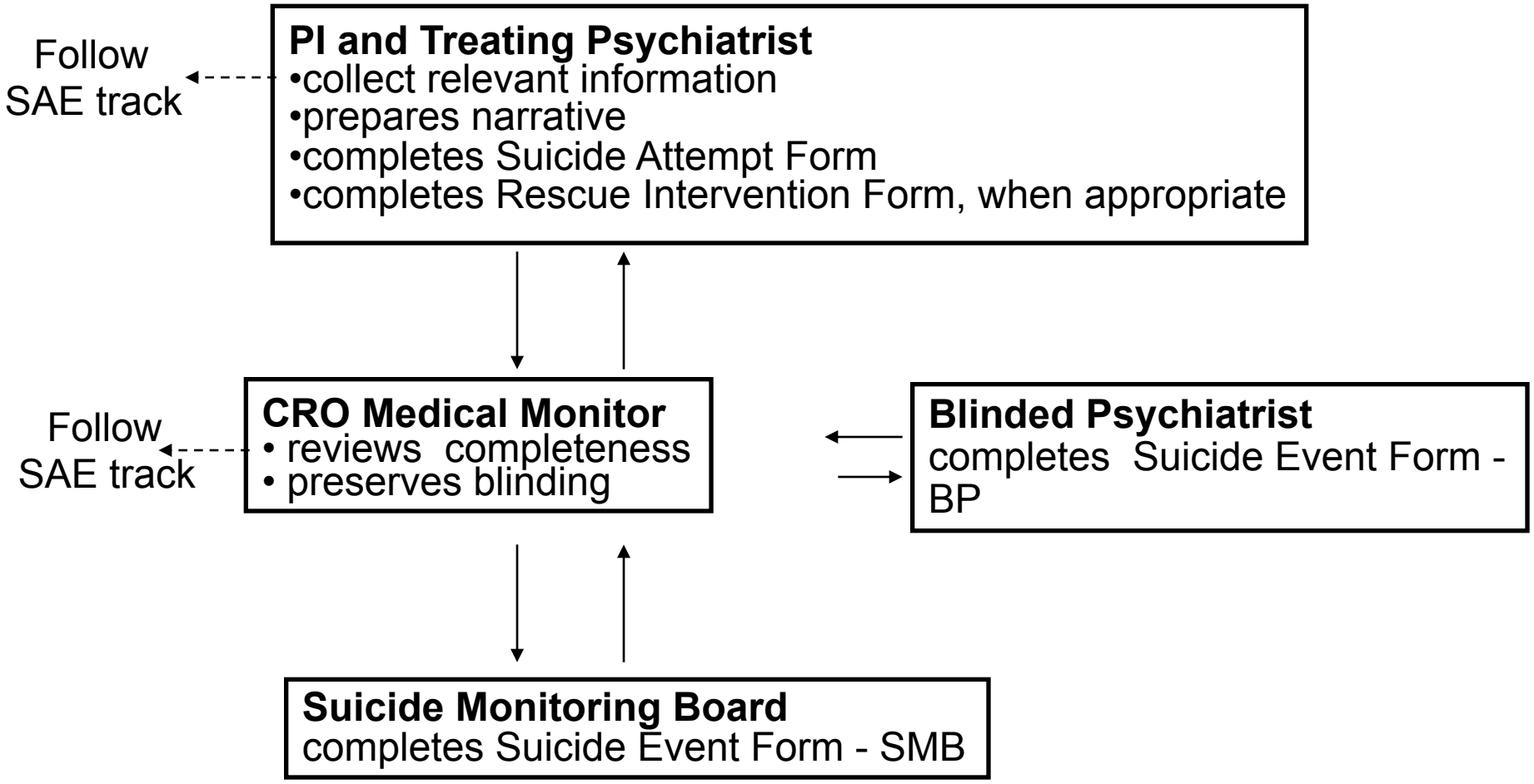
Statistical Methods (3)

- Extensive FDA interaction with sponsor on proposed changes
  - FDA amended the analysis as described below
  - Proposed combining the two estimates for an overall estimate of the treatment effect and its pooled standard error by giving equal weight to each estimate
  - Allowed a single two-sided test of the null hypothesis on either event type at 5% level of significance
- Revised objectives: demonstrate decreased risk for suicide for patients treated with clozapine compared with olanzapine as measured by time in days to ***two types of events***
  - ***Type 1 event:*** significant suicide attempt/suicide, or hospitalization due to imminent suicide risk or increased surveillance due to suicide risk, which ever came first
  - ***Type 2 event:*** worsening of severity of suicidality as manifested by a score of 6 (much worse) or 7 (very much worse) on the CGI-SS as rated by the blinded psychiatrist

InterSePT Study Key Features

- Prospective, randomized open-label, parallel group, 24-month, study in 11 countries
- Clozapine: 200-900 mg/day; olanzapine 5-20 mg/day
- Site staff:
  - PI-selection of patients, treatment decisions , review of event packages, blinding of packages
  - Blinded psychiatrist: ratings of CGI-SS, review of event packages
  - Treating psychiatrist: treatment decisions, assessment of suicidality at visits
  - Blinded rater: ratings of PANSS, CGI, additional measures
  - Nursing staff: blood sampling, vital signs, questioning of patients
- Scales
  - InterSePT Scale for Suicidal Thinking (new)
  - CGI (suicidality)
  - PANSS
  - CGI- (psychosis)
  - Calgary Depression Scale
  - Extrapyramidal Symptom Rating Scale
  - Covi Anxiety Scale
  - Scale of Functioning

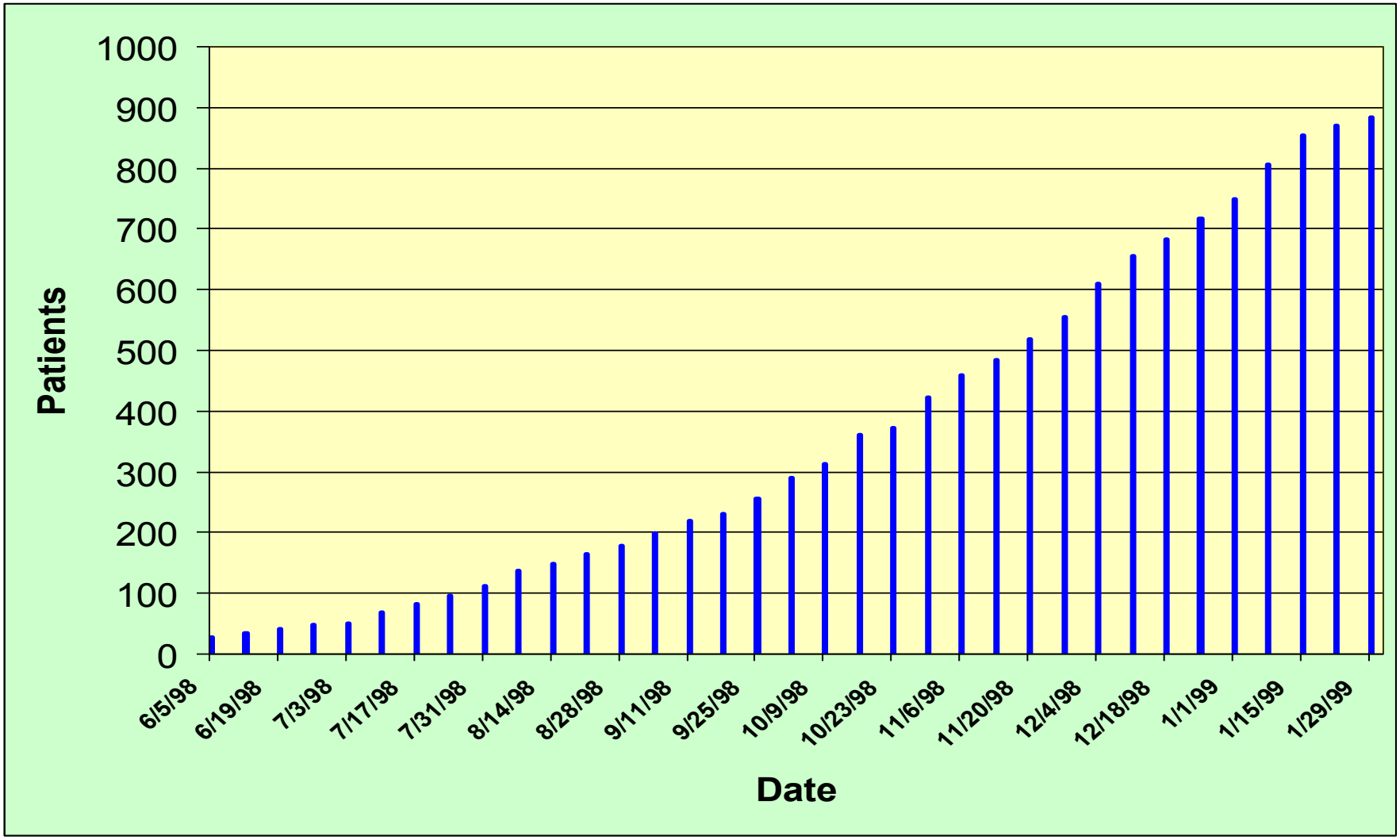
Data Flow: Deaths and Potential Suicide Attempts



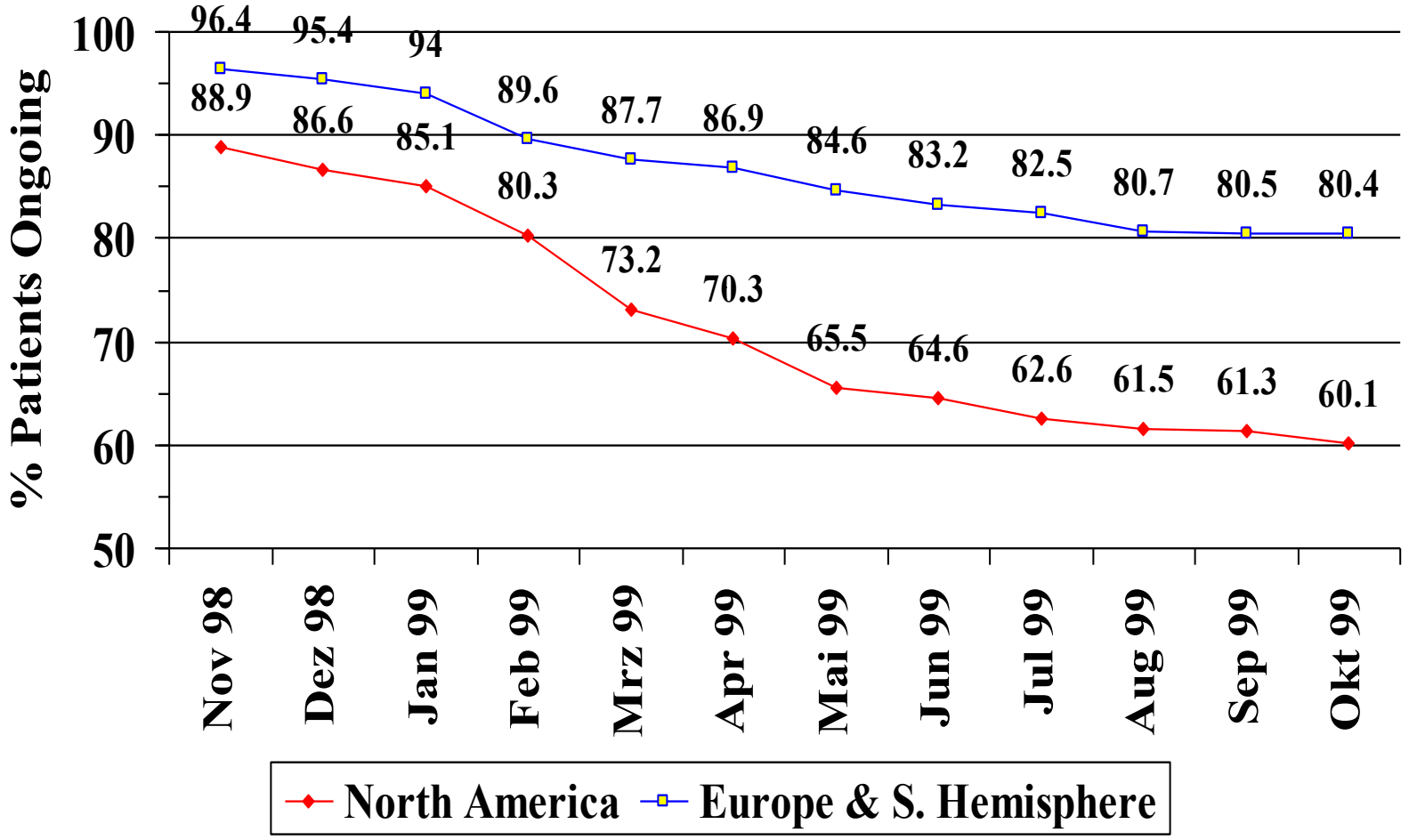
Key Achievements of the InterSePT Trial

- Obtained evidence of efficacy and effectiveness from a single open-label explanatory and pragmatic trial
- InterSePT study set a high standard for cooperation between Industry, Academic Experts, Health Authorities, Investigators, Patient Care Organizations (NAME, SANE), Government Organizations (US Surgeon General's Office)
- Enthusiasm of investigators for an extremely complicated study was extremely high; before, during and after completion of trial. Although performed in 11 countries, 8 languages, conduct of trial was uniform across all centers
- Despite the difficult population, the high demands, the enrolment rate and the retention of patients for a two year period was remarkable

Enrolment Of InterSePT Patients



Rate of Retention in NA and ROW



Key Achievements of the InterSePT Trial

- InterSePT provided impetus for making significant methodological advances
  - Development of new rating instruments
    - InterSePT Scale for Suicidal Thinking (ISST): developed before starting trial, translated and validated during the research(Pragmatic trial)
    - Clinical Global Impression of Severity of Suicidality (CGI-SS): developed for the trial and served as a co-primary endpoint (Pragmatic trial)
  - Use of alternative designs, e.g. open-label treatment with blinded ratings, event monitoring board (i.e. SMB), treatment as usual paradigms in an efficacy trial
  - Added significantly to the knowledge base of suicidality in schizophrenia
  - Use of alternative statistical methods (e.g. WLW)