

# **A Double-Blind, Randomized, Placebo-Controlled Study of Peri-Operative Administration of Olanzapine to Prevent Post-Operative Delirium in Joint Replacement Patients**

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3 = Harvard Medical School

# Disclosures

Drs. Kelly, Larsen & Bode have nothing to disclose.

Dr. Stern is a WiFiMed stockholder and on the speakers bureau of Eli Lilly.

There was no industry support for this study.  
(specifically Eli Lilly)

# Background

- Delirium defined:
  - a disturbing state (with or without agitation), assoc with disordered attention and concentration, hallucinations, delusions, and a fluctuating level of consciousness
- Post-operative delirium is prevalent and problematic
  - Rates vary from 20-60% in post-op orthopedic populations
  - A 2003 retrospective study of 166 NEBH patients confirmed that delirium was prevalent following elective joint and spine surgeries
- Delirium can lead to higher levels of morbidity and to mortality, to long-term brain deficits, to increased length of stay, and increased costs.

# Current State of Knowledge

- Delirium is prevalent and costly in joint replacement patients
- Risk factors include advanced age, a prior history of delirium, and the presence of medical co-morbidities
- Delirium frequently goes unrecognized and untreated unless accompanied by agitation
- Screening for delirium is not part of routine care

# Summary of the Literature

- Seven prospective studies have examined the risk factors for delirium in hospitalized elders
  - Results are discrepant
  - Methodological limitations abound
    - medical and surgical patients not differentiated
    - definitions of delirium vary
    - case-finding methods vary
    - risk factors not consistently defined
    - standardized instruments used uncommonly
  - Efficacy of antipsychotics under investigation
    - One prospective randomized trial comparing haloperidol to placebo failed to show a decrease in incidence of delirium (Netherlands study)

## **Study Objectives**

We sought to establish whether preoperative administration of an atypical antipsychotic (olanzapine) could decrease the incidence of delirium in elderly patients undergoing elective joint replacement surgery.

## **Study Hypotheses**

Prophylactic treatment (with olanzapine) in a high-risk population would reduce the incidence of post-operative delirium.

# The Prophylactic Intervention

- Orally-administered olanzapine
  - Using a rapidly administered & absorbed preparation with a low prevalence of extrapyramidal side effects
  - A similar looking placebo was employed for comparative purposes

# Overview of our Study Design

Single-center, randomized, two-arm, prospective, placebo-controlled study (stratified for complexity)

**N = 400** (complex defined as bilateral joint or revision surgery)

Placebo 5 mg X 2  
(n = 204) Placebo

**RANDOMIZED**

Olanzapine 5 mg X 2  
(n = 196) Zydis

Hospital stay (days)

**Day of  
Surgery**

Monitored daily for  
cognition and behavior

**Discharge**



# Outcomes

## ■ Primary

### ■ Incidence of delirium

Delirium based on  
Mini-Mental State Exam  
(MMSE)  $= < 22$   
Delirium Rating Scale  
(DRS-R-98)  $= > 13$   
Information from the medical  
record (including a diagnosis  
made by an MD or PhD using  
DSM-III-R mental health  
diagnostic criteria)

## ■ Secondary

### ■ Complications

Pneumonia, infections,  
cardiac (e.g., AF),  
use of sitters and restraints,  
number of consults obtained,  
length of stay (LOS),  
disposition,  
& hospital costs.

# Eligibility

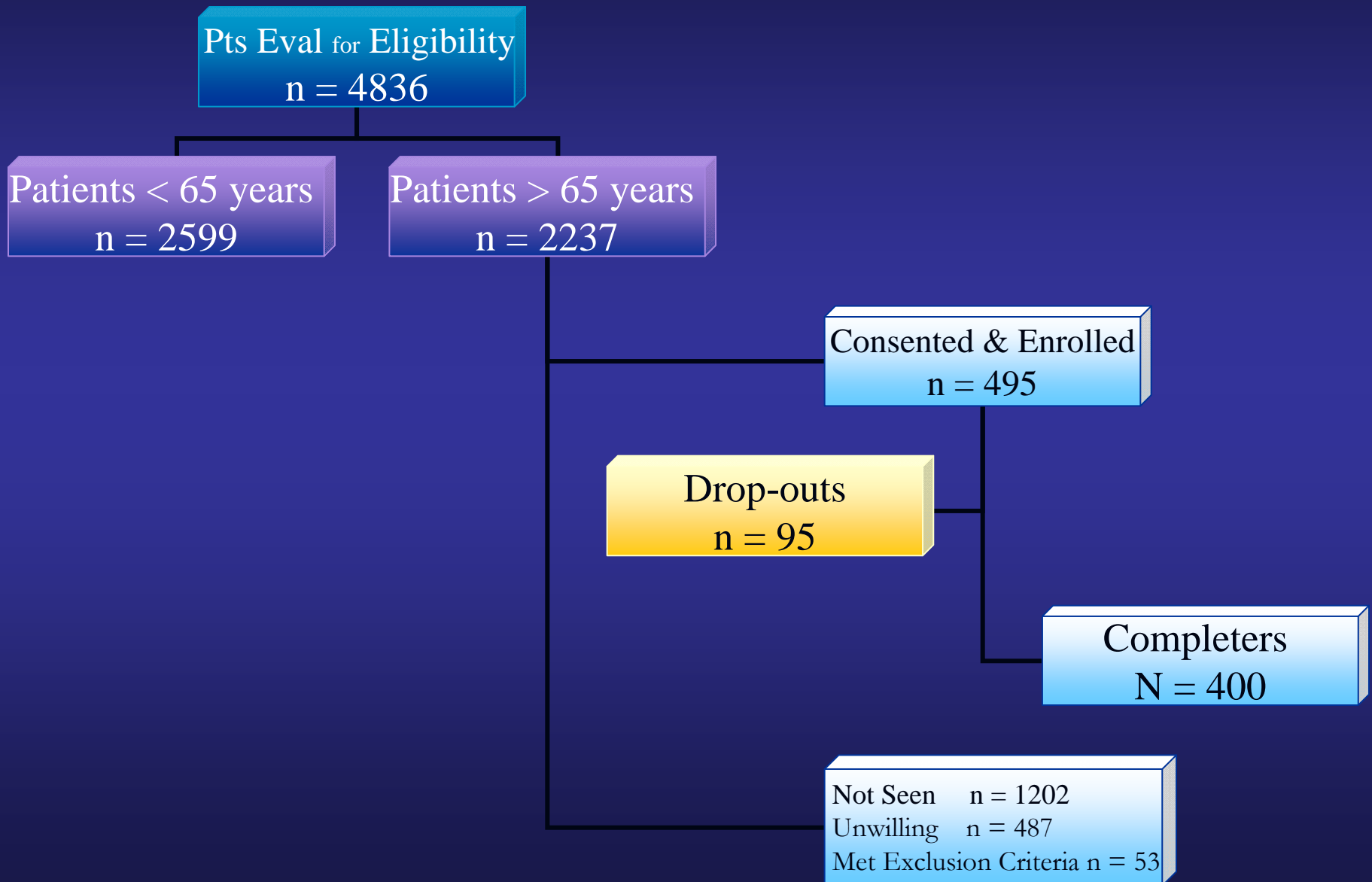
## ■ Inclusion:

- High-risk for delirium:
  - Age > 65
  - History of delirium
  - Medical co-morbidities
- English speaking
- Ability to consent

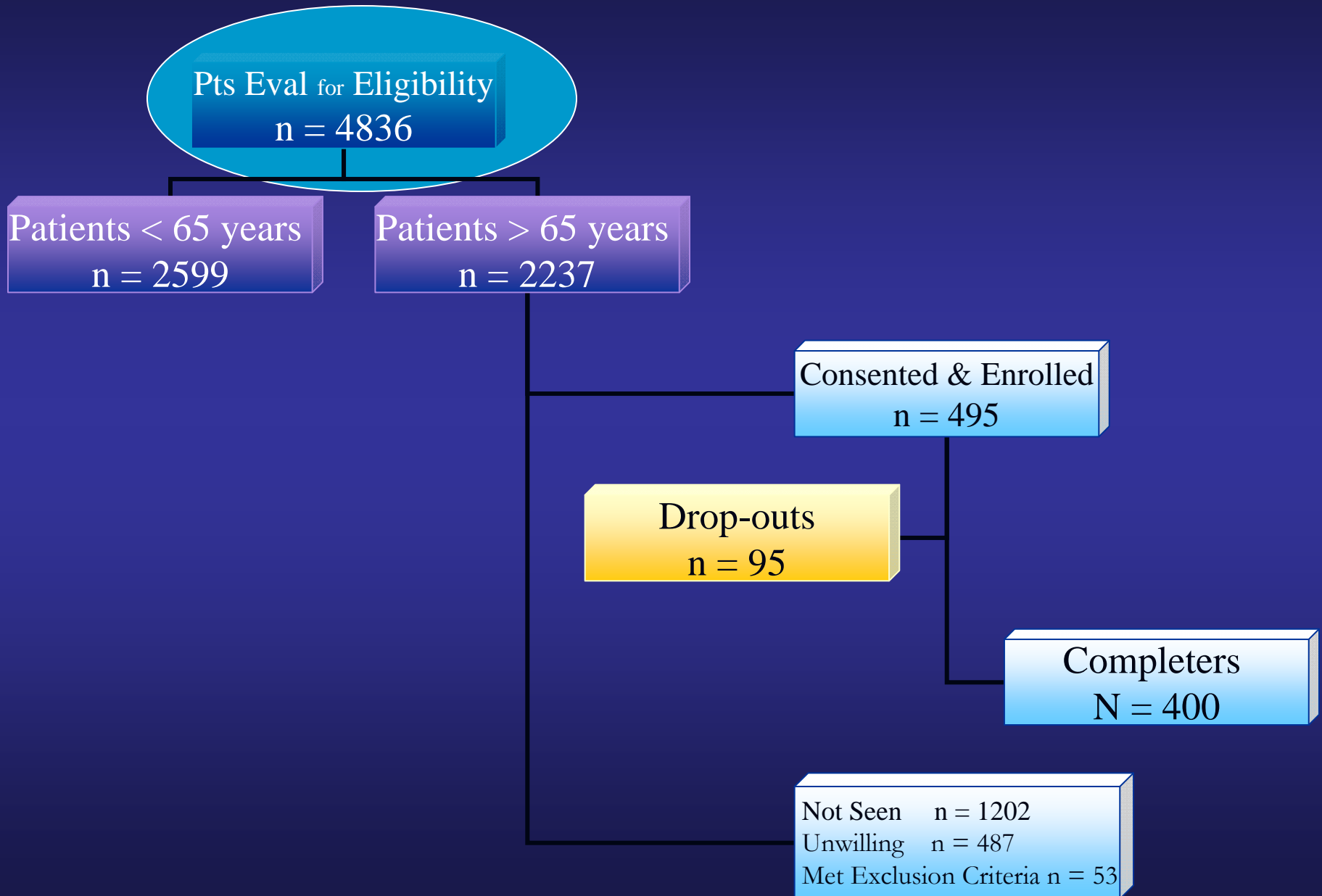
## ■ Exclusion:

- Dementia
- Active alcohol abuse
- Current use of an antipsychotic drug
- Allergy to olanzapine

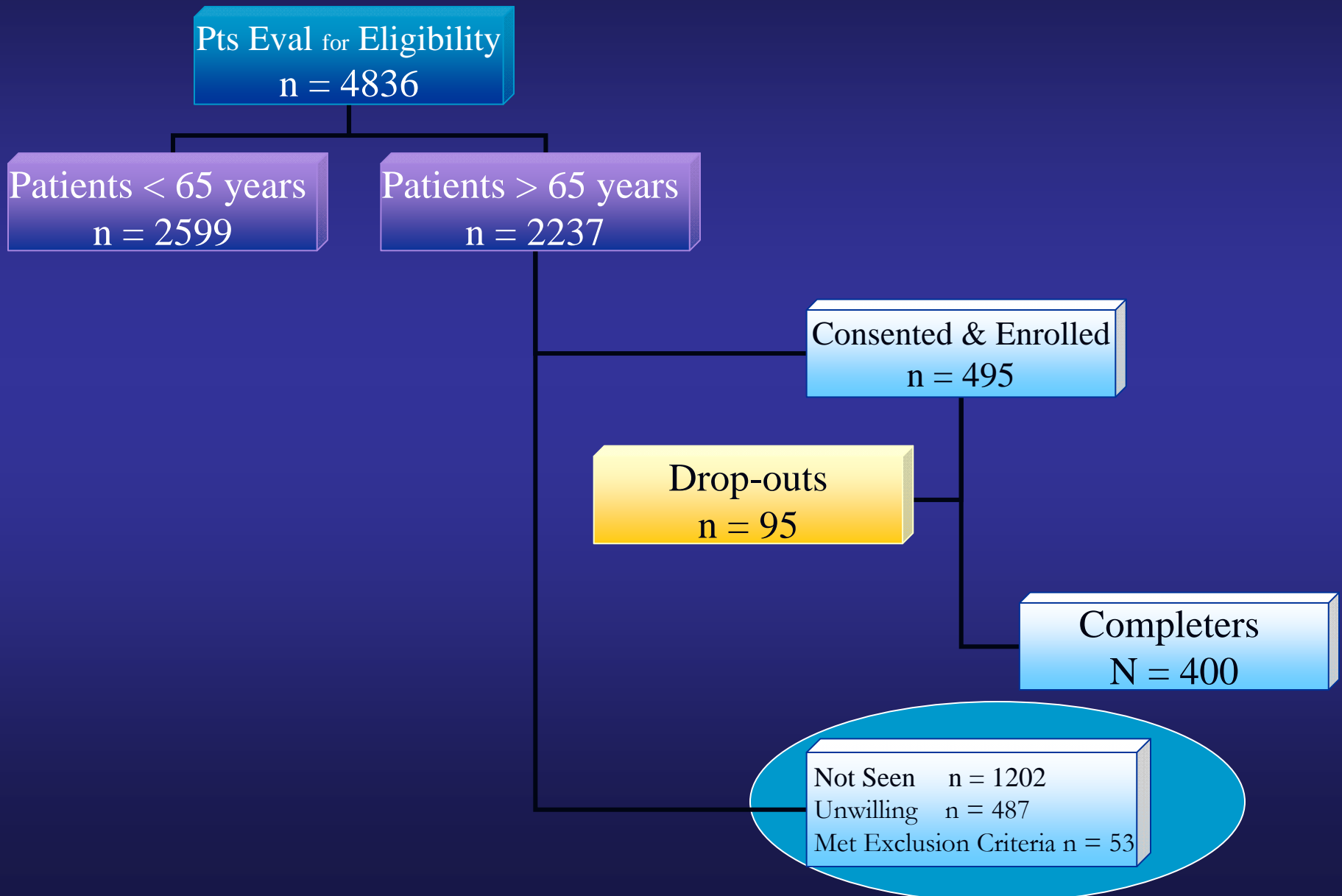
# Patient Screening & Enrollment



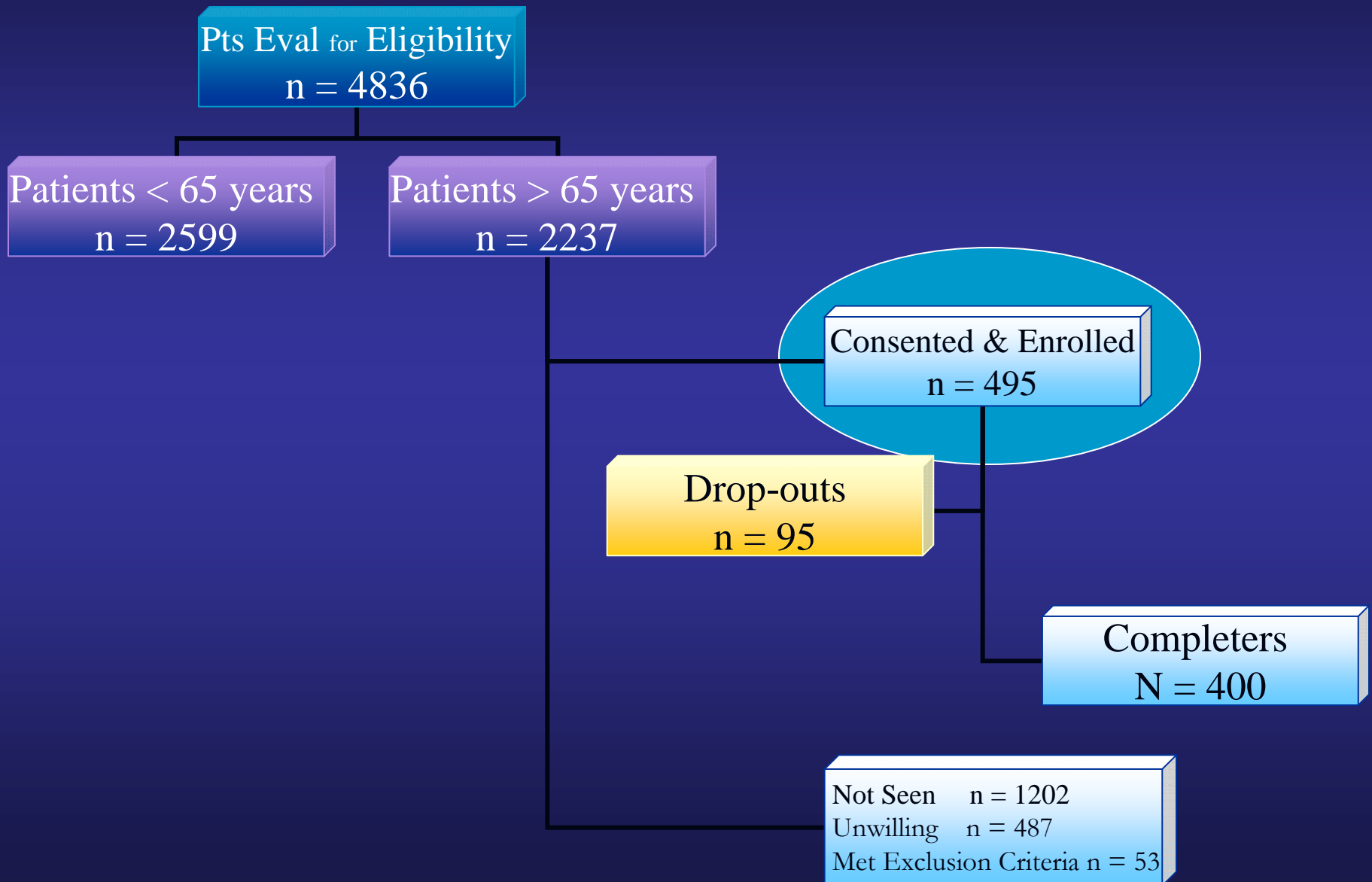
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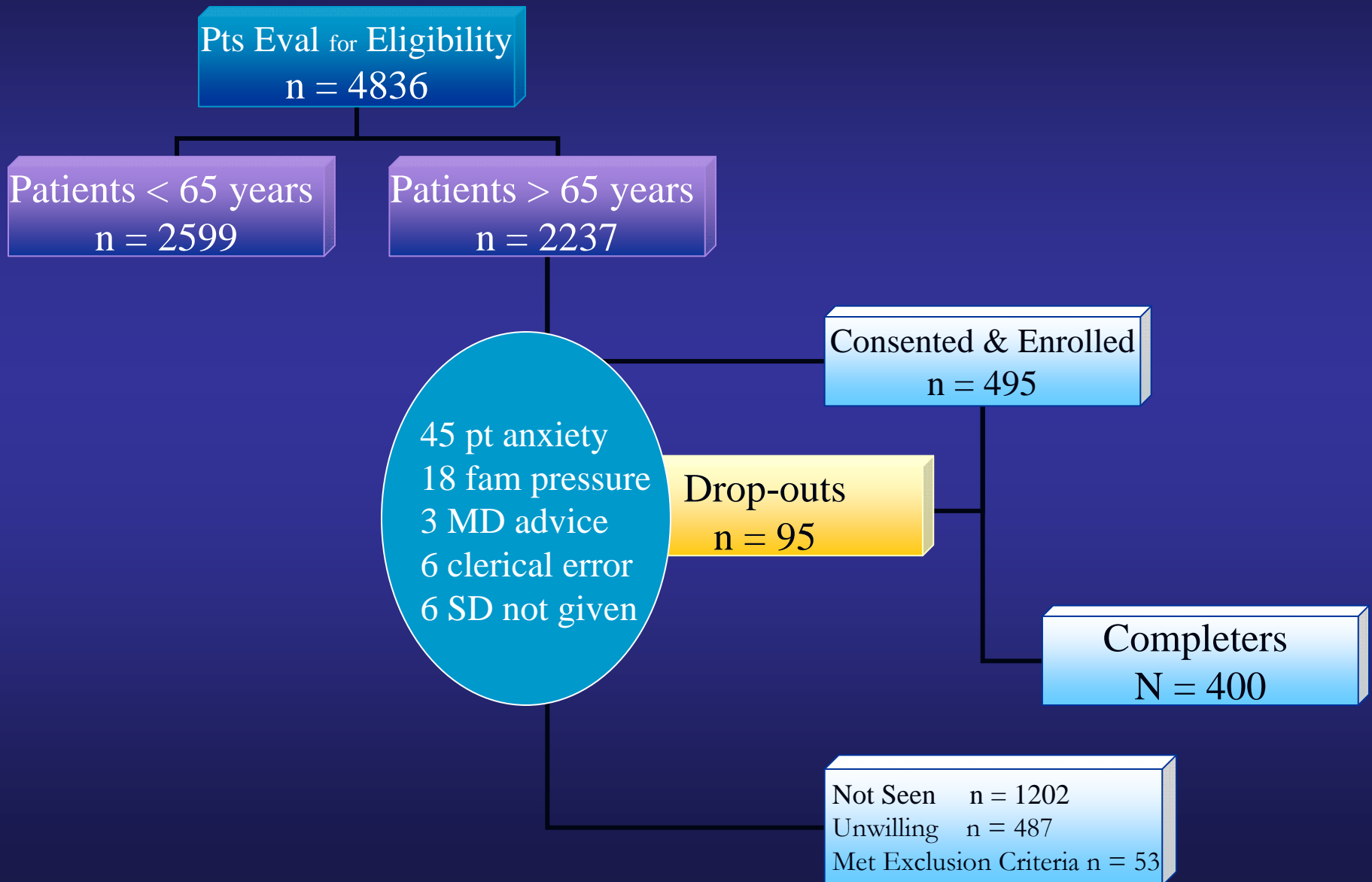
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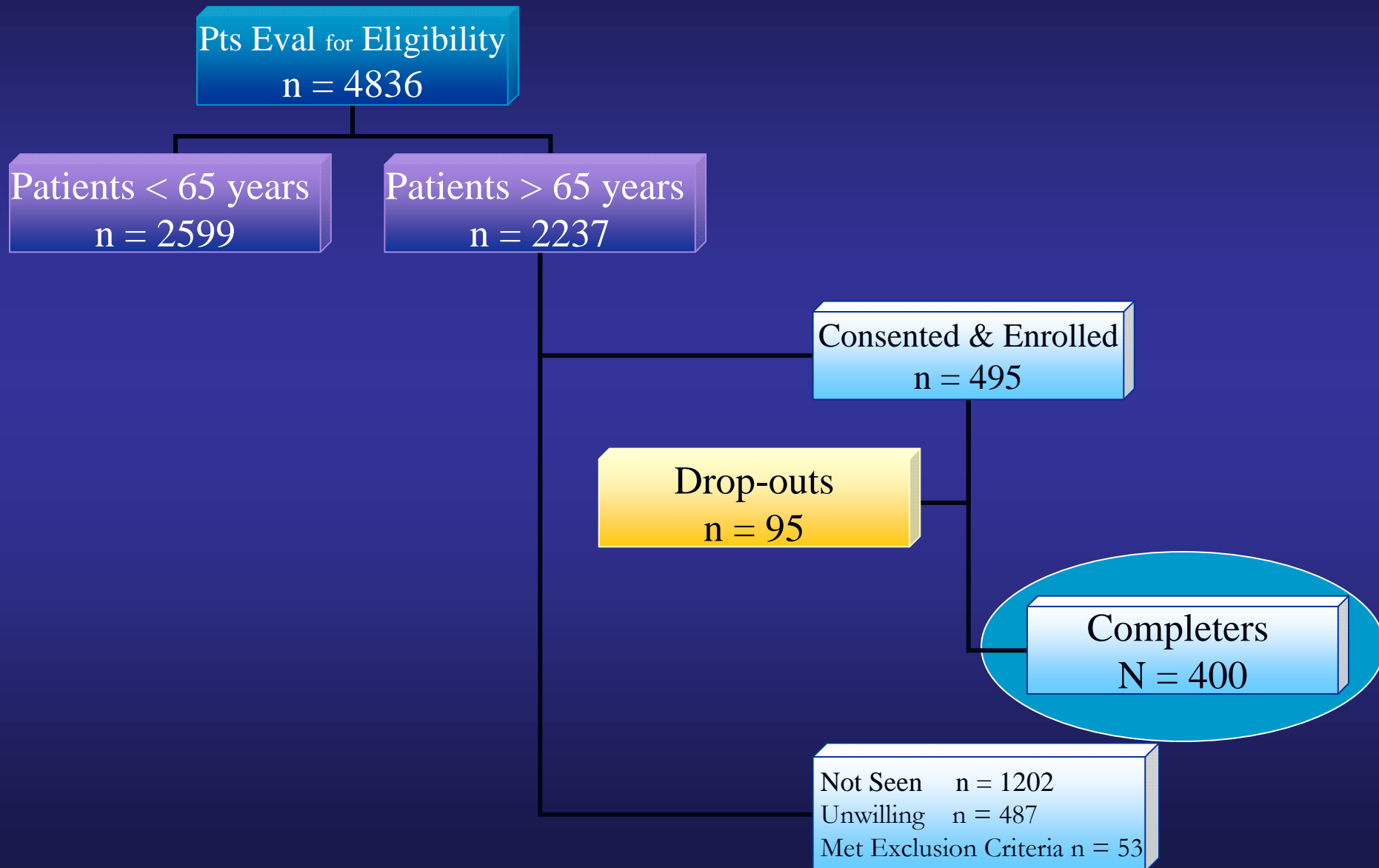
# Patient Screening & Enrollment



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# Description of Study Subjects

	Placebo Group (n = 204)	Olanzapine Group (n = 196)
Age (mean, s.d.)	74 ± 6.18	73 ± 6.08
Female Gender	123 (60%)	94 (48%)
<b>Orthopedic Procedure</b>		
■ Simple Knee	85 (42 %)	117 (60 %)
■ Simple Hip	79 (39 %)	52 (27 %)
■ Complex Knees	28 (14 %)	13 (7 %)
■ Complex Hips	12 (6 %)	14 (7 %)
<b>Discharge Status</b>		
■ Discharged to Rehab Facility	143 (70 %)	116 (59 %)
■ Discharged Home	61 (30 %)	80 (41 %)

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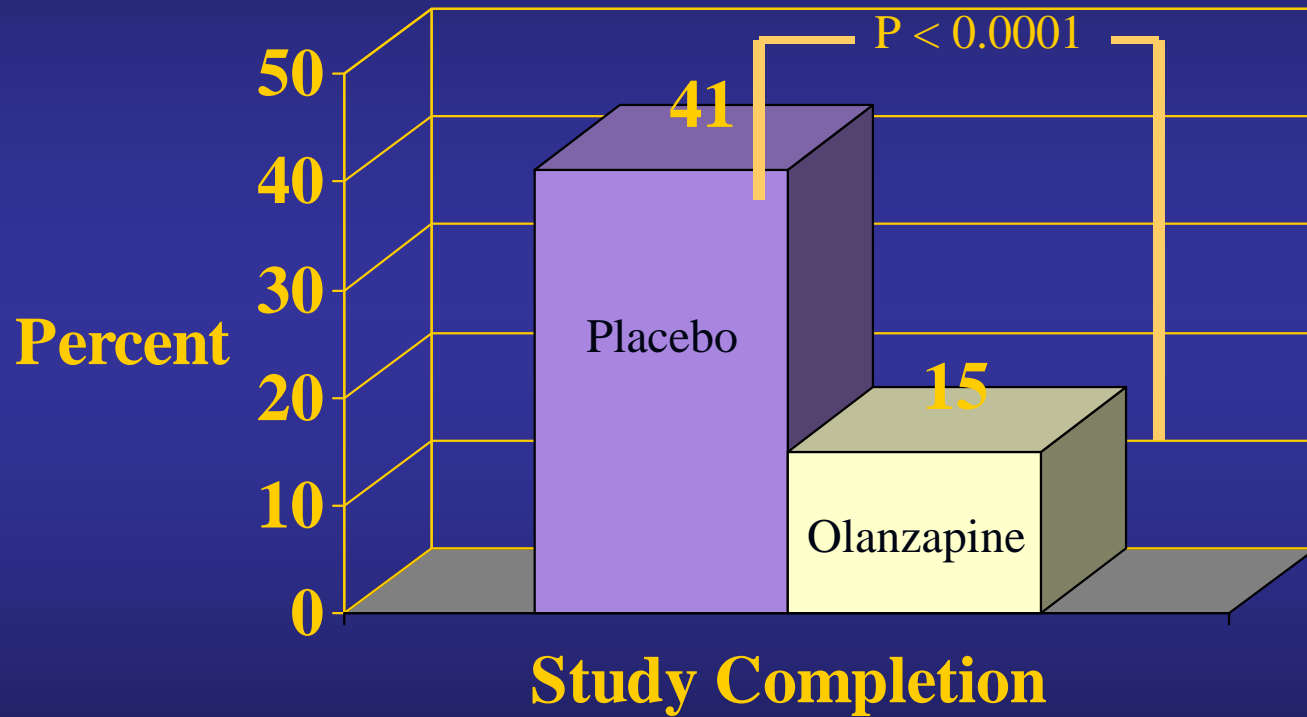
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# Analysis

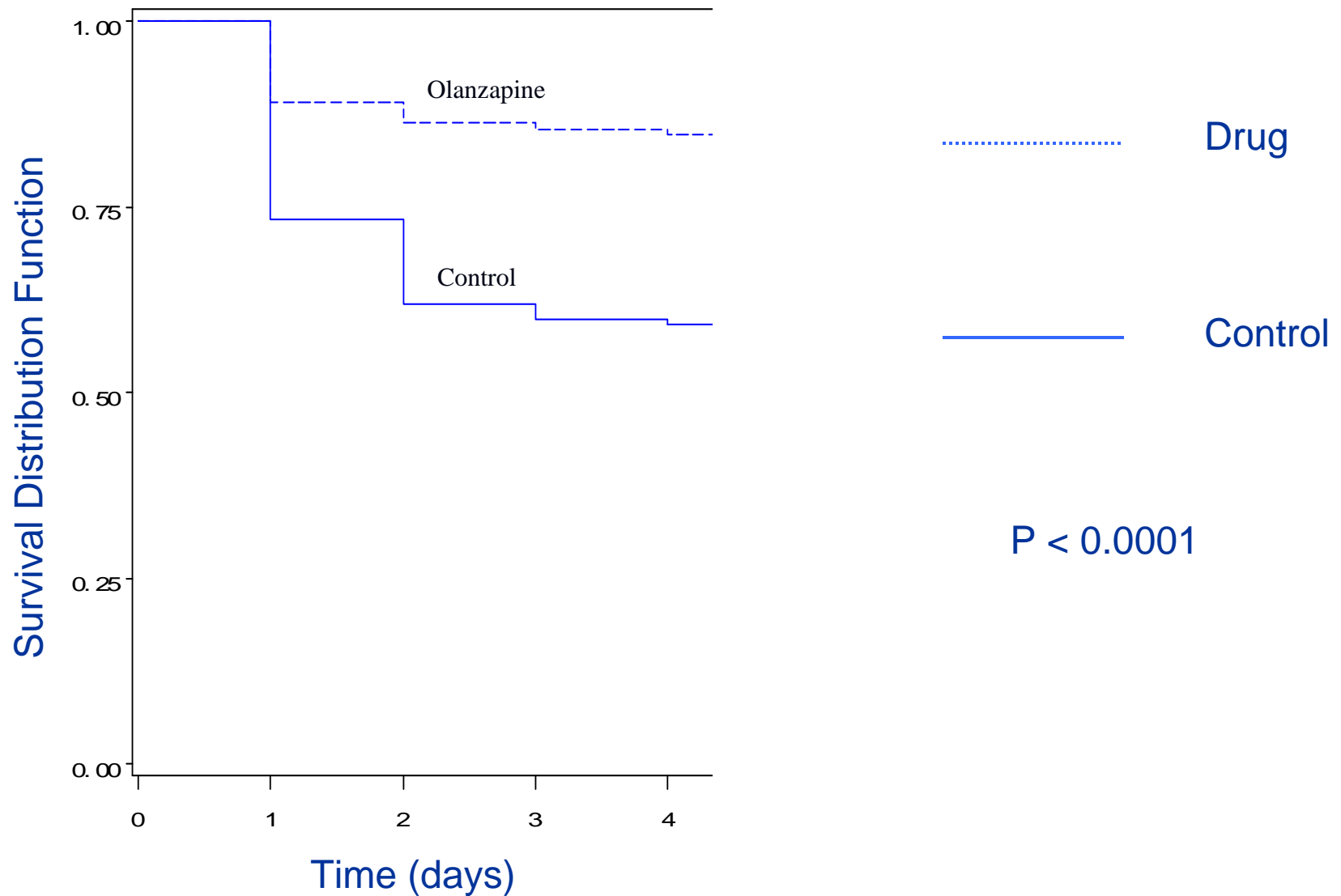
- Compared incidence of delirium between treatment and control groups
- Used Cox Survival Model to ascertain the time to the first day of delirium

# Incidence of Delirium

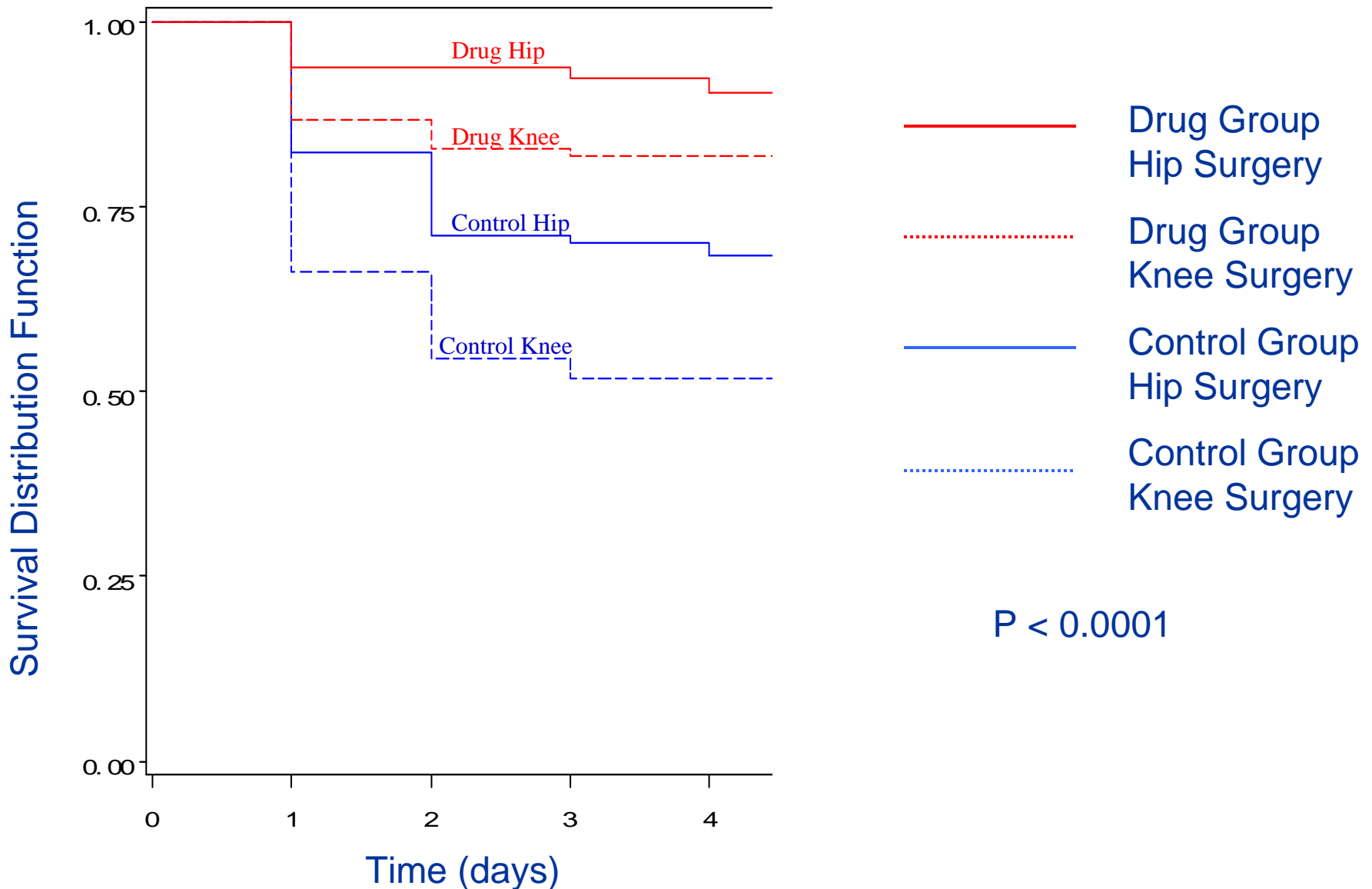


■ Placebo ■ Olanzapine

# Time to first day of delirium



# Time to first day of delirium



# Conclusion

Prophylactic administration of an atypical antipsychotic medication in a high-risk orthopedic population **reduced** the incidence of delirium.

# Thank you from the Delirium Team

Susan Kelly, MD, Kenneth Larsen, DMin, PhD, Theodore Stern, MD,  
Robert Bode, MD, Gerard Sweeney, M.D., Joyce Welsh, RN,  
Karen Hoikala, RPH, Jim Cotter, RPH  
Noreen Howie, RN, Jennifer Silva, PT, Adam Potter, Marie Nolan

Departments: Orthopedics, Anesthesia, Medicine, Nursing,  
Pharmacy, Rehabilitation, Case Management,  
Research, Security, Pastoral Care, Medical Records

Statistical Analysis Team at Tufts-New England Medical Center

**Funded by a grant from the New England Baptist Hospital Department of Research  
Winner of the Dlin/Fischer Award for Research by the Academy of Psychosomatic Medicine**



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