Perspectives on Schizophrenia and Psychosis
pharmacologic treatment and course

Nina R. Schooler, Ph.D.
Professor of Psychiatry & Behavioral Sciences
SUNY Downstate Medical Center
Senior Research Scientist
The Zucker Hillside Hospital
nina.schooler@gmail.com

ASCP Donald F Klein
2015 Lifetime Achievement Award

Address delivered June 23, 2015
ASCP Annual Meeting
Miami Beach Florida

Disclosures of Commercial Interest

- Advisory Boards/Consultations in past 12 months
  - EnVivo/Forum
  - Sunovion
  - Alkermes
- Grants
  - Otsuka
  - Roche

With Gratitude to Colleagues:
Thank you for opportunities, challenges

- Jonathan O. Cole, MD
- Solomon C. Goldberg, PhD
- Gerard Hogarty, MSW
- Jerome Levine, MD
- Joanne Severe, MS
- Samuel J Keith, MD
- Matcheri Keshavan, MD
- John M, Kane, MD
- Peter Weiden, M.D.
- Delbert Robinson, MD
- Peter Buckley, MD

Overview of Presentation

- Long-term treatment with pharmacologic and psychosocial treatments
- Treatment early in the course of illness
  - First-episode psychosis (FEP)
- Relations between researchers and patients/clients

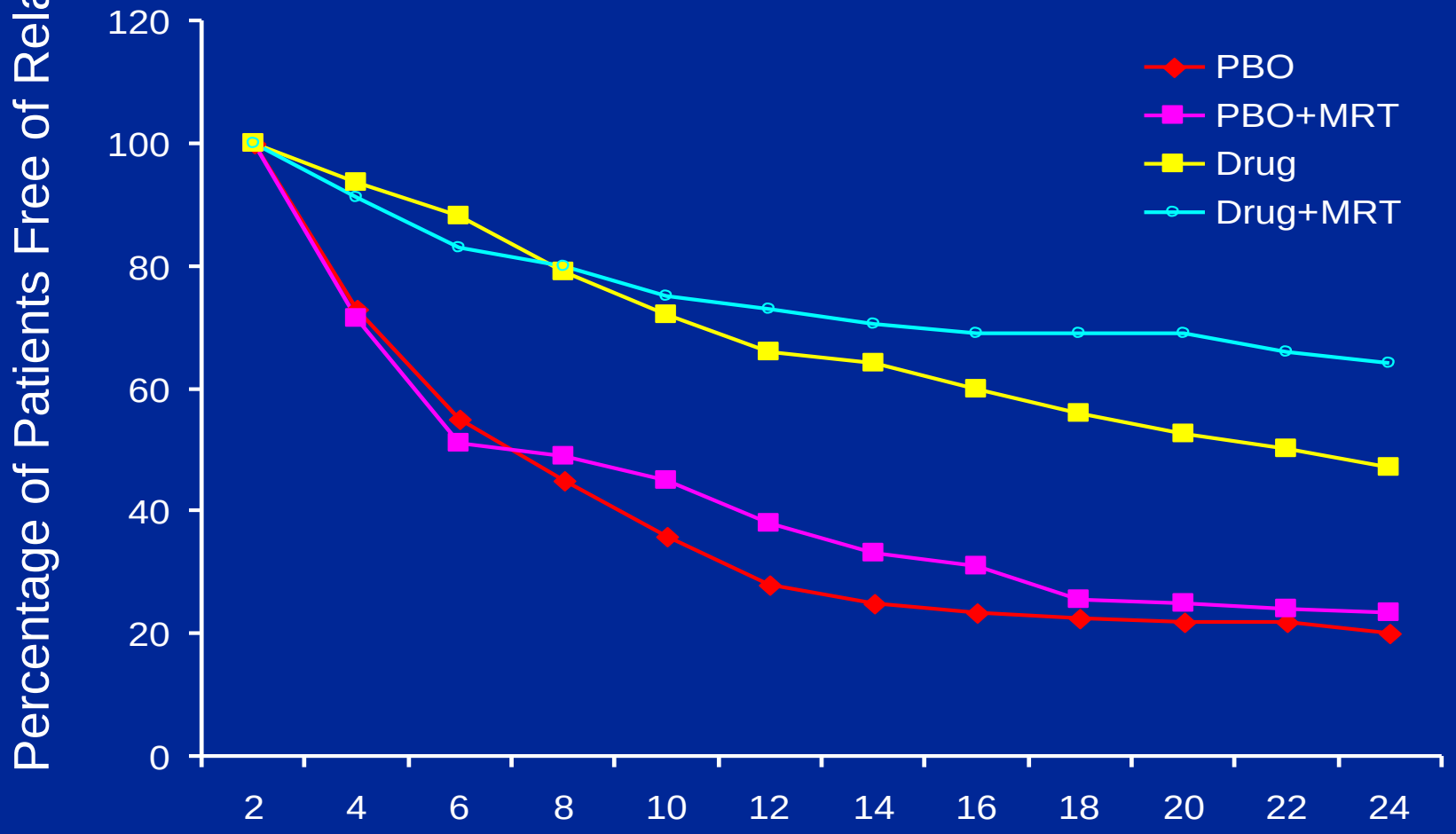
Long-term treatment of schizophrenia

- Two important questions early in the psychopharmacology era
  - Does medication need to continue after actute treatment response?
  - What is the role of psychosocial treatments in long term after care?

MRT Study
an Early Example

- Two-year randomized clinical trial
- Multi-site study that examined the effects of
  - Chlorpromazine versus placebo
  - Major Role Therapy (MRT) versus Usual Care
- 2 X 2 design allows
  - Evaluation of main effects of each treatment
  - Evaluation of interaction effects
    - ◊ Is MRT more effective with medication

Relapse Prevention in Schizophrenia
Chlorpromazine, Placebo and Psychosocial Treatment



From Hogarty , Goldberg, Schooler et al Arch Gen Psychatry1974

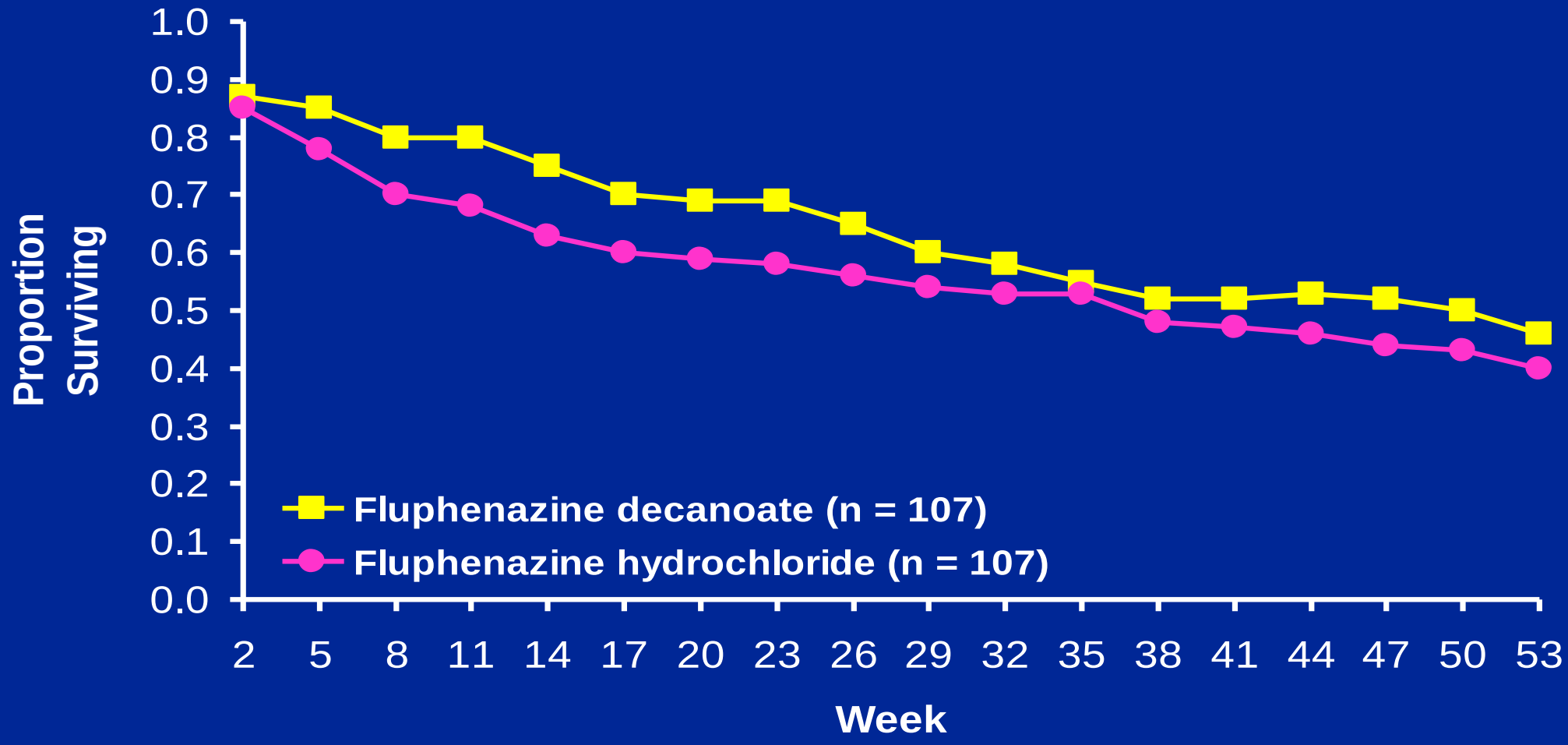
MRT Study
What did we learn

- Chlorpromazine was significantly much more effective than placebo in preventing relapse
  - Relapse meant hospitalization in most cases
- There was no difference between psychosocial conditions in placebo condition –relapse rate 80%
- Trend: MRT prevented relapse in the second year in chlorpromazine patients who had not yet relapsed
- MRT effects on functioning at 18 and 24 months
  - Better with chlorpromazine
  - Worse with placebo

Long-acting injectable antipsychotics
Early Examples

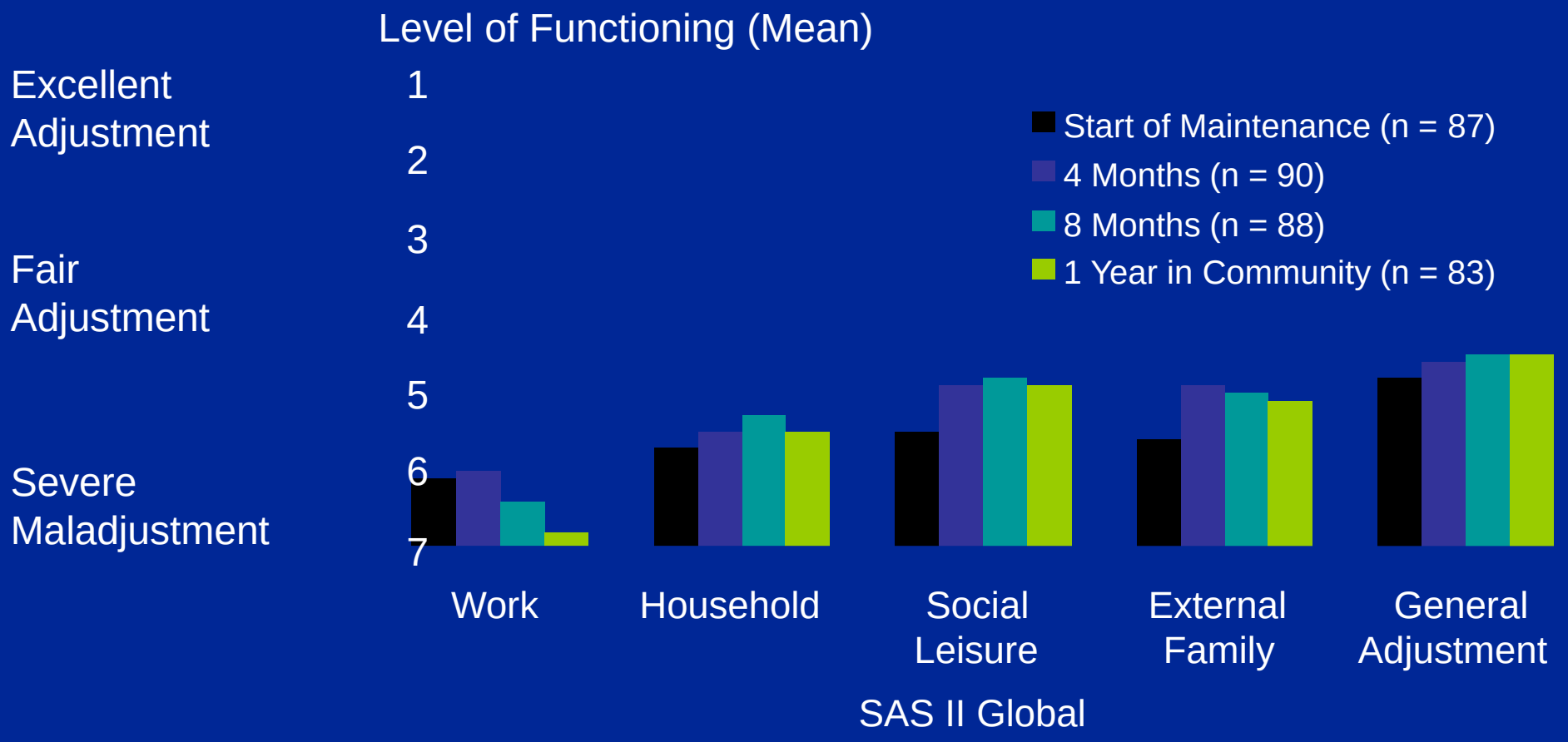
- MRT study and others suggested that even with medication, relapse remained a significant problem
  - Up to 60% in two years
- Could long-acting injectable anti-psychotics address the problem by “insuring” compliance?
- Two multi-site studies using fluphenazine decanoate
  - One-year trial Oral vs Injectable
  - Two-year trial Oral vs Injectable and MRT vs TAU

Oral or Injectable Fluphenazine, 1-Year Study Relapse



Schooler N , Levine J et al. *Arch Gen Psychiatry.* 1980;37:16-24.

Oral and Injectable fluphenazine non-relapsers Social-Adjustment Ratings Over 1 Year



Schooler N, Levine J et al. *Arch Gen Psychiatry.* 1980;37:16-24.

Long-acting injectable antipsychotics
Two year study Design

- Oral vs Injectable fluphenazine
- Social therapy versus Usual Care
- 2 X 2 design allows
  - Evaluation of main effects of each treatment
  - Evaluation of interaction effects
    - ◊ Is social therapy more effective with injectable compared to oral medication?

Hogarty G, Schooler N Arch Gen Psychiatry 1979

Long-acting injectable antipsychotics
Two year study results

- Relapse rates over two years
  - Overall comparable to relapse rates with chlorpromazine
- Fluphazine decanoate + Social therapy
  - No relapses after 8 months
- Later relapse differs from early relapse

Hogarty, Schooler et al Arch Gen Psych 1979

Using long-Acting injectable antipsychotics to insure dose

- Persistent questions in long term-treatment in the 1980s
  - Role of dosage reduction
  - Role of family engagement
- Treatment Strategies in Schizophrenia Study addressed these questions
- Including families in the study created a treatment setting that facilitated monitoring for early signs of relapse

Treatment Strategies in Schizophrenia (TSS)

- Multi-center 2 year study 3 X 2 design
- Three medication conditions
  - Standard dose of fluphenazine decanoate 12.5-50 mg/2wks
  - Low dose 2.5 -10 mg (20%) q 2 wks
  - Targeted/early intervention Vehicle only - placebo
- Two psychosocial treatment condition
  - Applied family management
  - Supportive family management

Schooler NR, Keith SJ et al Arch Gen Psych 1997

TSS Study Results

- Dosage effects
  - Hospitalization
    - ◊ Standard Dose 25%
    - ◊ Low Dose 25%
    - ◊ Targeted 46%
  - Mean time to psychotic relapse
    - ◊ Standard Dose 609 days
    - ◊ Low Dose 520 days
    - ◊ Targeted 431 days
  - Time to first rescue medication
    - ◊ Standard Dose 495 days
    - ◊ Low Dose 346 days
    - ◊ Targeted 187 days

s

PROACTIVE
LAIs in the 21st Century

Relapse

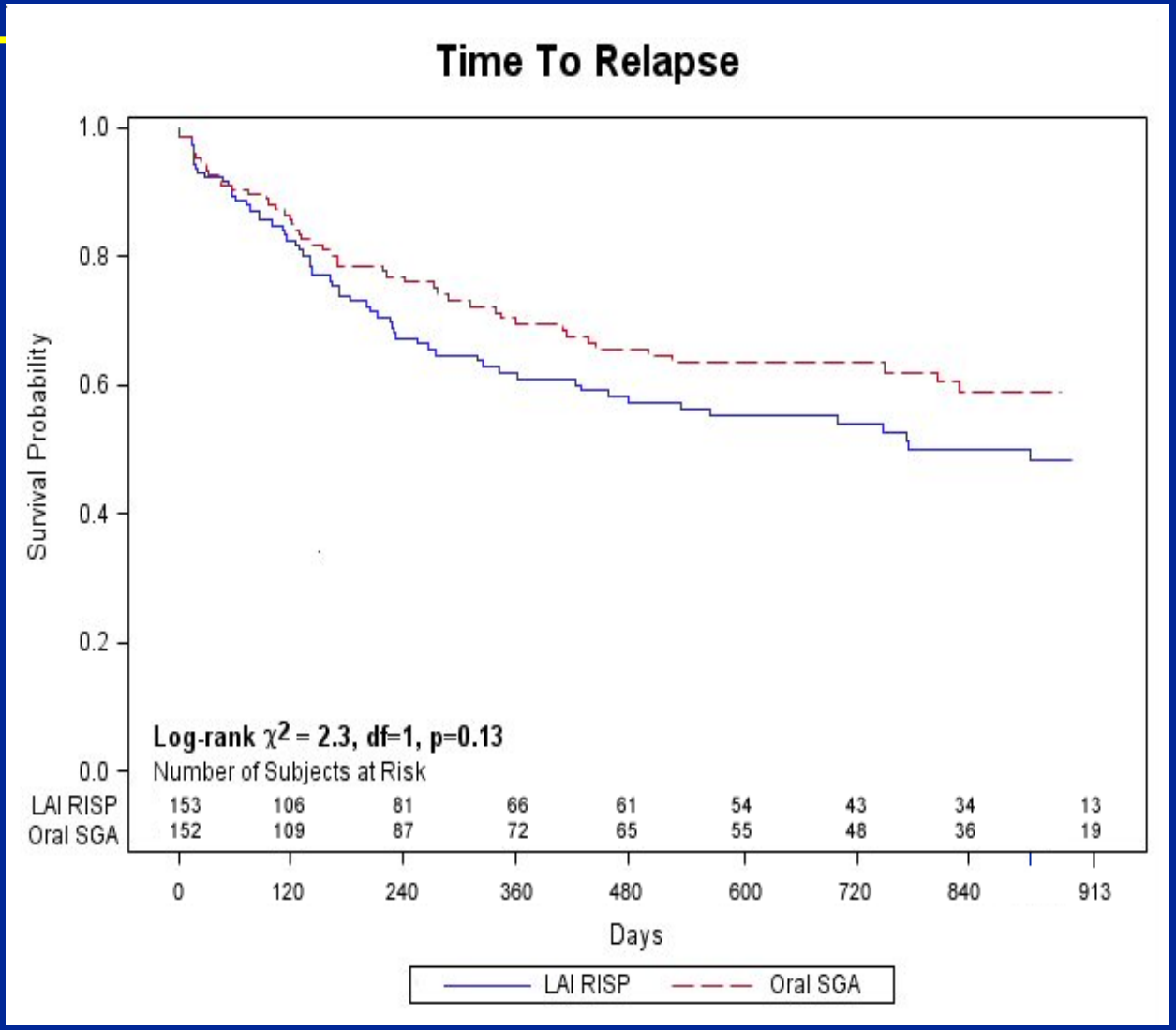
LAI Risperidone

Up to 30 Months

Oral SGAs [risp,olanz,quet,zip,ari, pali]

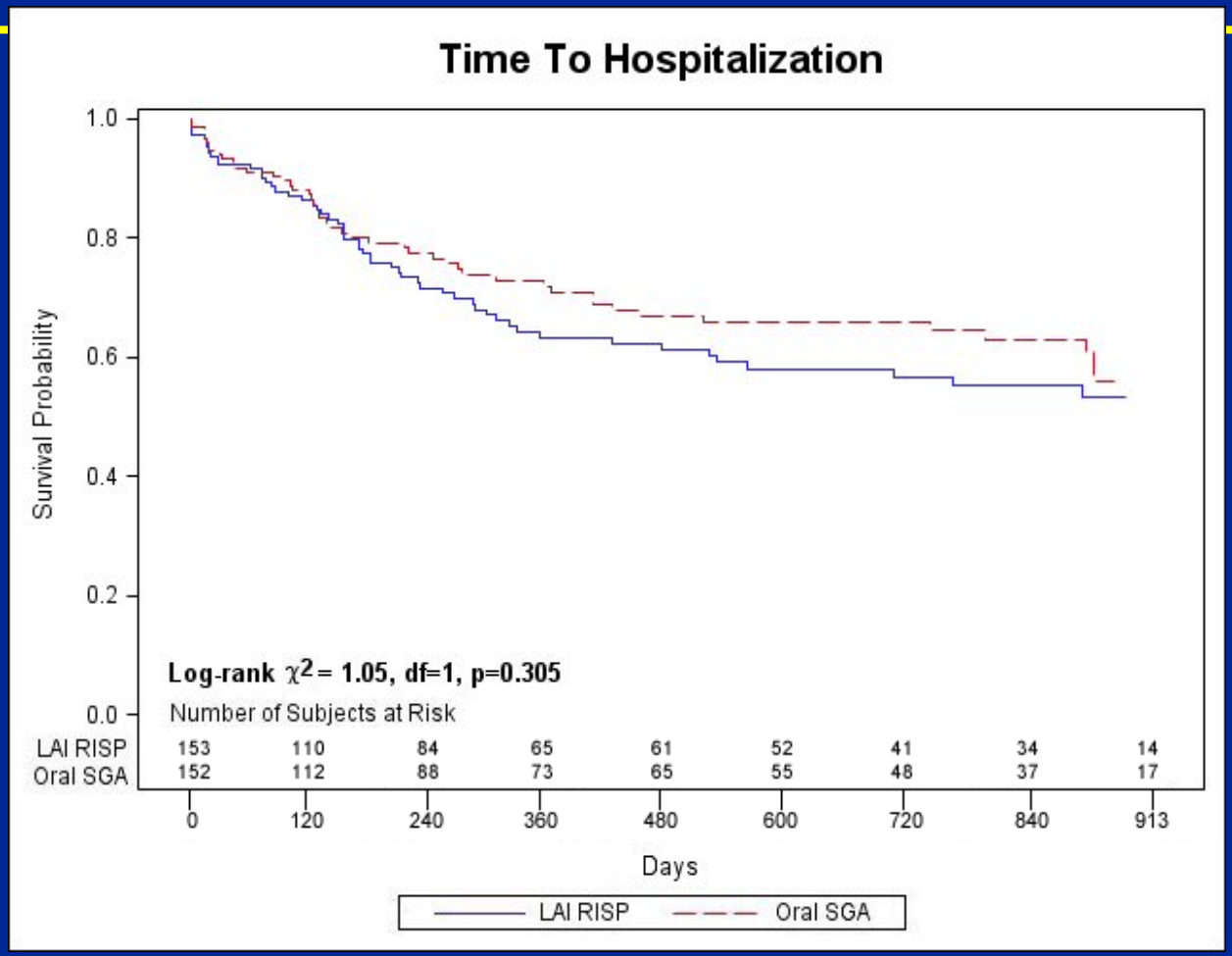
- On-site and masked raters
- Relapse Monitoring Board
- Representative sample
- Randomized but open label treatment

Primary Outcome
Time to First Relapse X Treatment



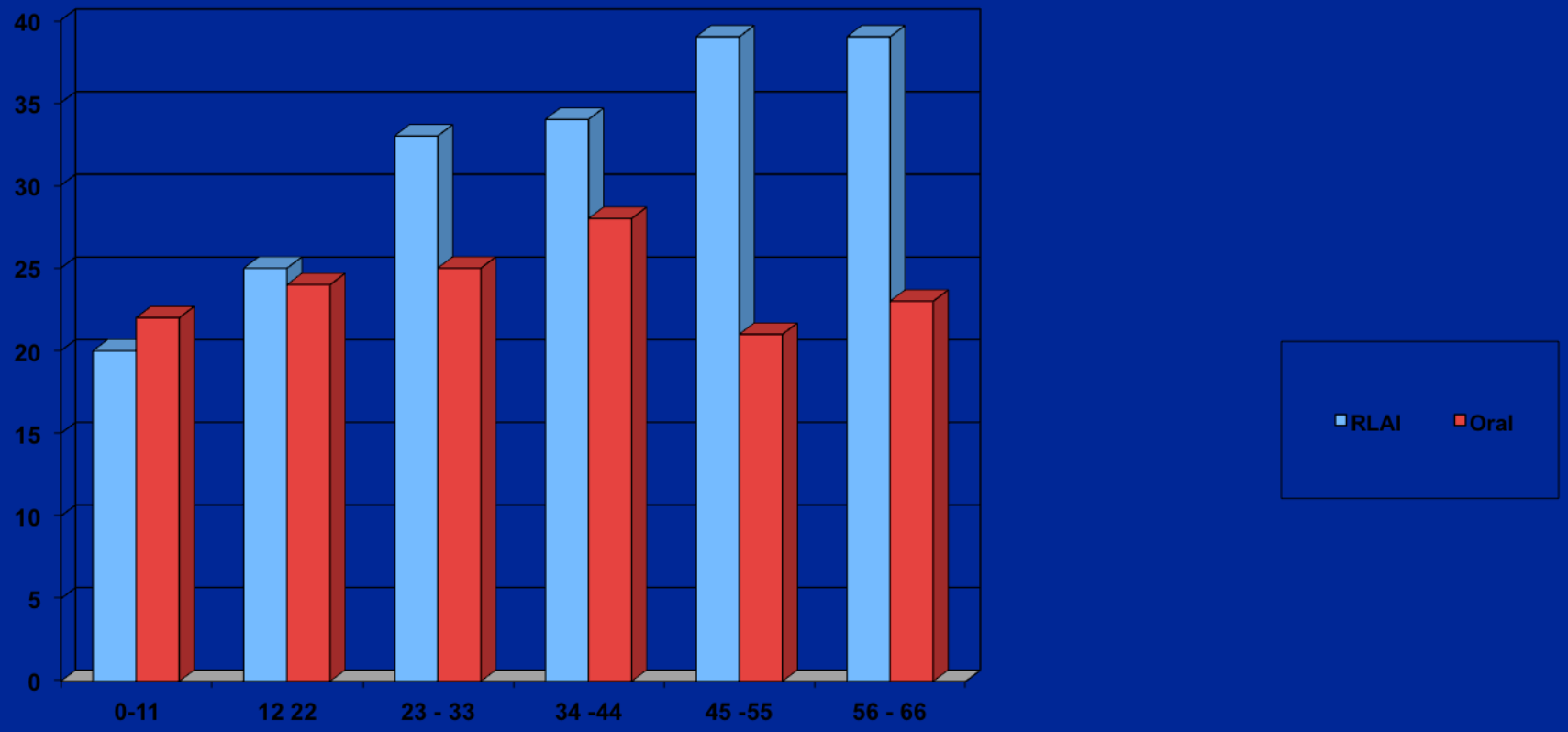
Buckley PB, Schooler NR et al Schizophrenia Bulletin 2014

Time to First Hospitalization X Time



Buckley P, Schooler NR et al Schiz Bulletin 2014

PROACTIVE % of Subjects with no Psychosis Symptoms
Over 30 months RLAI vs. Oral Antipsychotic



Schooler NR ASCP 2014

Long Term Treatment of Schizophrenia

- The obvious
  - Anti-psychotics delay relapse and rehospitalization
- Dosage reduction strategies with older APs increase relapse risk
- Dosage reduction strategies are laregely unstudied with newer antipsychotics
- The psychosocial treatments in older studies I did provided limited added benefit.
  - Newer psychosocial treatments eg CBT may be much more valuable

What do we mean by First Episode Psychosis

- Time of first psychotic symptoms?
- Time of first treatment for psychotic symptoms?
- Time of first hospitalization?
- Time of first treatment with anti-psychotic medication?
- Time of first diagnosis of schizophrenia?

Risperidone and Haloperidol in First Episode Psychosis

- Diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder
  - no more than one year
- Treatment with anti-psychotic medications
  - no more than 12 weeks
- Psychiatric hospitalizations
  - No more than 2 during the index year
- Age
  - 16 to 45

Schooler et al Am J Psychiatry 2005

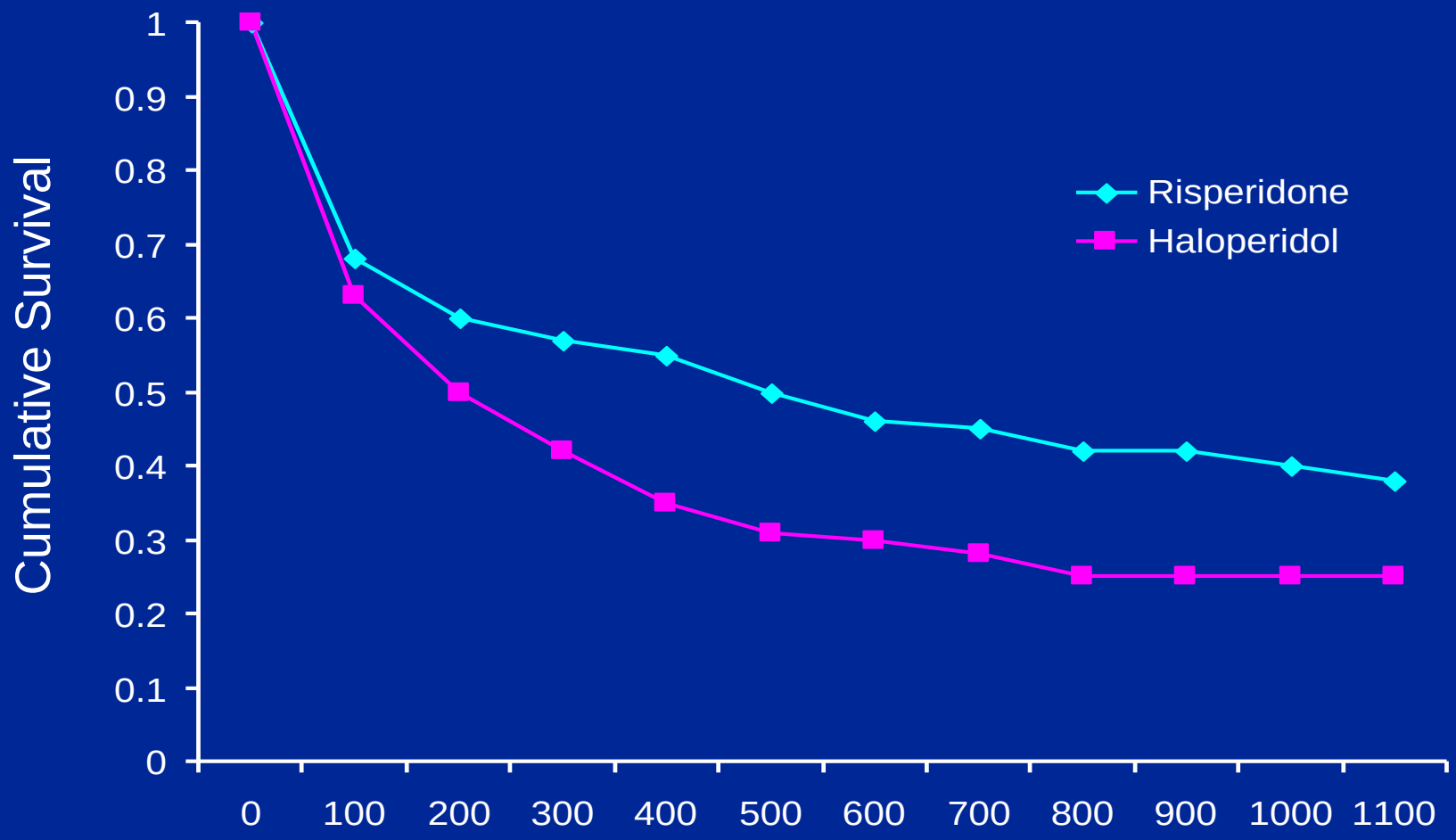
Risperidone vs Haloperidol First Episode Study

- Multi-site, multi-national trial
- Dosage
  - Risperidone 3.3 mg/d
  - Haloperidol 2.9 mg/d
- 12 week treatment response – 20% PANSS reduction
  - Risperidone n=192 73.6%
  - Haloperidol n = 199 76.2%
- Treatment exposure
  - Risperidone 192 days
  - Haloperidol 218 day

Schooler et al Am J Psychiatry 2005

Risperidone vs Halperidol in First Episode Schizophrenia

Time to Relapse



Schooler et al Am J Psychiat 2005

Maintenance Treatment and Relapse Prevention
First Episode Treatment Paradox

- Good initial treatment response is interpreted as “cure”
  - Treatment is no longer needed
- Drive among first episode patients to discontinue medication
- Medication discontinuation strongest predictor of symptom exacerbation
- FEP person’s sylogism
  - Medication “worked”
  - I am better
  - Therefore I should stop medication

A Two Stage Model for Long Term Medication Treatment

- **STAGE 1**

Develop an alliance for evaluation and stabilization

  - Initial contact during hospitalization
  - Engagement of both patient and family
  - Monitor treatment progress
  - Initiate discussion of need for continued treatment

- **STAGE 2**

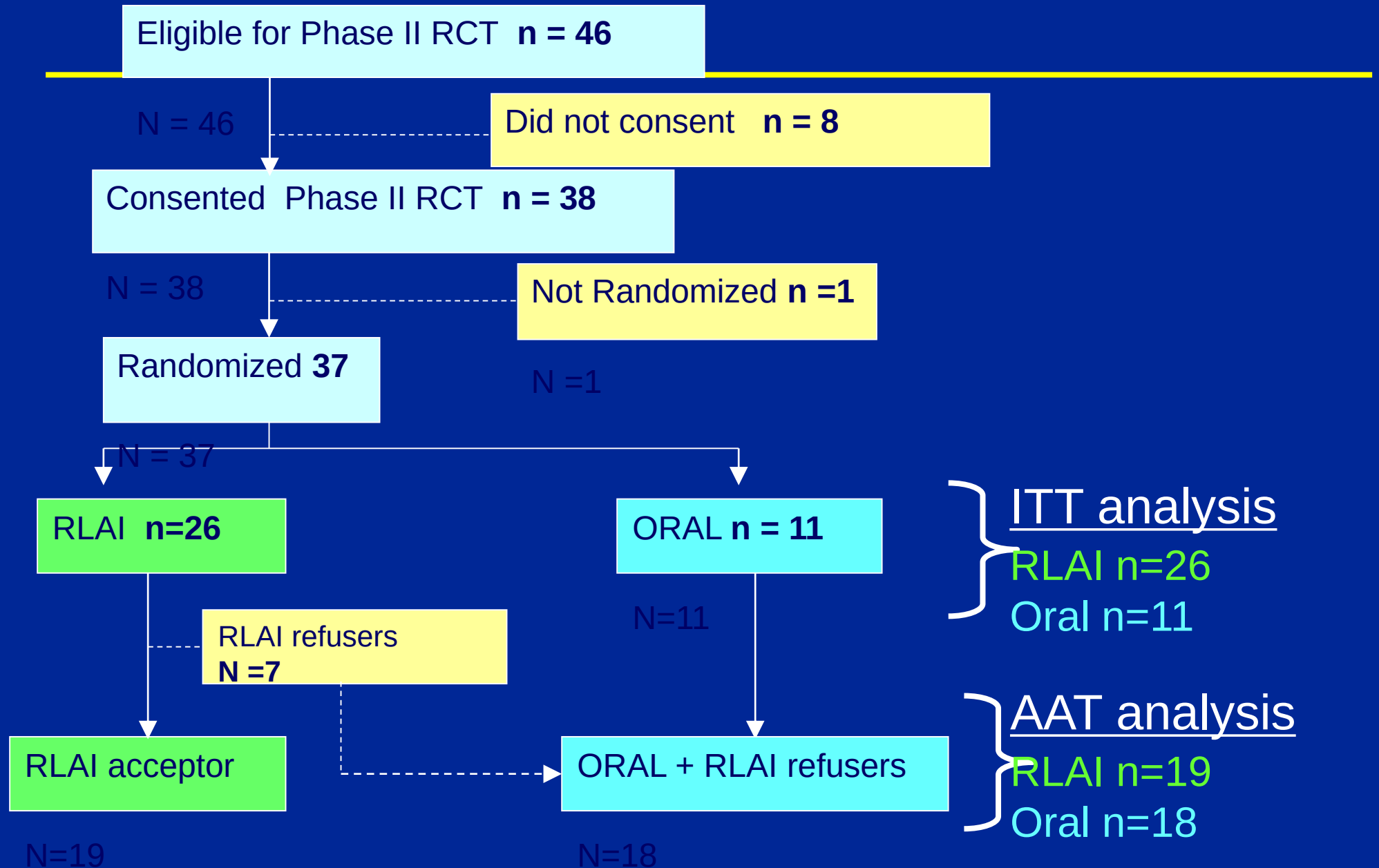
Introduce long term medication program

PREventFirstEpisodeRelapse study
PREFER

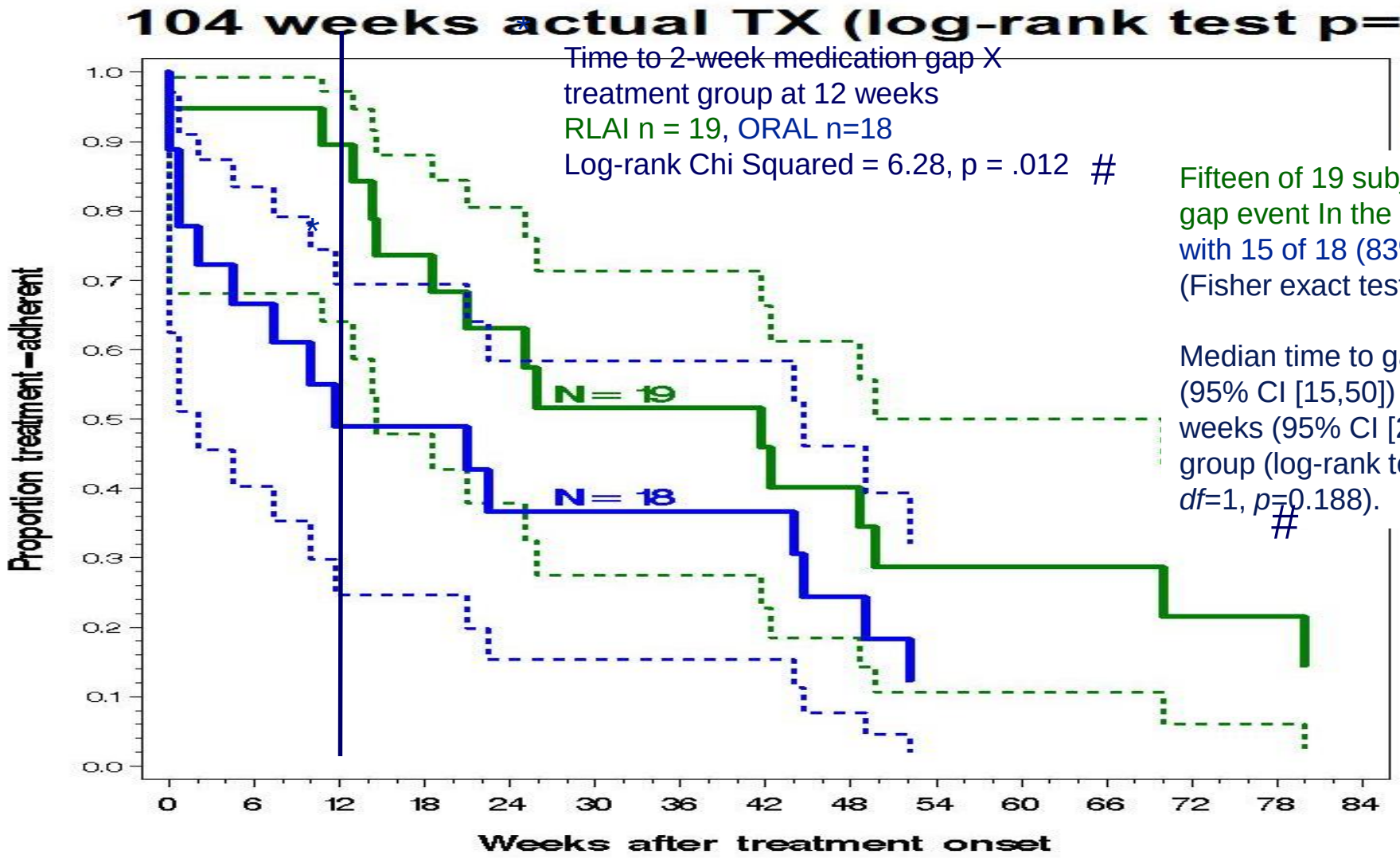
- RCT with open label treatment and blinded assessment
  - Risperidone microspheres long acting injectable
  - Oral second generation anti-psychotics
- Uses two-stage model to engage, recruit and consent trial participants
- N = 37, Mean age 25.3; 70% male

Weiden PJ, Schooler NR et al J CliniPsych 2012

PREFER CONSORT Chart



PREFER
Oral vs. RLAI Time until First Medication Gap
As Actually Treated



Time to 2-week medication gap X treatment group at 12 weeks
RLAI n = 19, ORAL n=18
Log-rank Chi Squared = 6.28, p = .012 #

Fifteen of 19 subjects (79%) reached a gap event In the RLAI group, compared with 15 of 18 (83%) in the ORAL group (Fisher exact test *p*=1.000).

Median time to gap event was 42 weeks (95% CI [15,50]) in the RLAI group, 12 weeks (95% CI [2.0, 45]) in the ORAL group (log-rank test chi-square=1.73, *df*=1, *p*=0.188).

#

Summary thus far

- FEP and long term treatment themes merge to address long term treatment trjaectories in schizophrenia
- The first episode represents a unique opportunity to affect the course of the illness
- Combine pharmacologic and psychosocial interventions
  - 21st century psychosocial aramentarium includes a number of evidence based psychosocial and service interventions
- How to combine and study multi-component interventions
- Engagement in long term treatment requires innovative strategies

Recovery **A**fter an **I**nitial **S**chizophrenia **E**pisode
The NIMH **RA1SE** Project

- Design and test effective interventions for early phase schizophrenia that can be implemented on a population-level basis
- Engineer rapid adoption and implementation of effective treatment packages by engaging “end users” at the start of intervention development
- Assess clinical, functional, and economic outcomes
- Generate information relevant to key stakeholders, including health care policy makers

Robert Heinssen NIMH RAISE Project Officer , 2009

Recovery After Initial Schizophrenia Episode – Early Treatment Program

Kane JM, Schooler NR et al J Clinical Psychiatry 2015

Relations between Researchers and …

- Patients
- Clients
- Subjects
- Participants

Clinical research becomes a collaborative venture

- Questions and research designs can influence who participates
- Current ethical protection methods may restrict and bias the kinds of people who are will to become research participants
- IRBs tell us that consent is a porocess.
  - A process that should take place largely out of the sight of consent forms
- Particularly in FEP consent and participation involves families