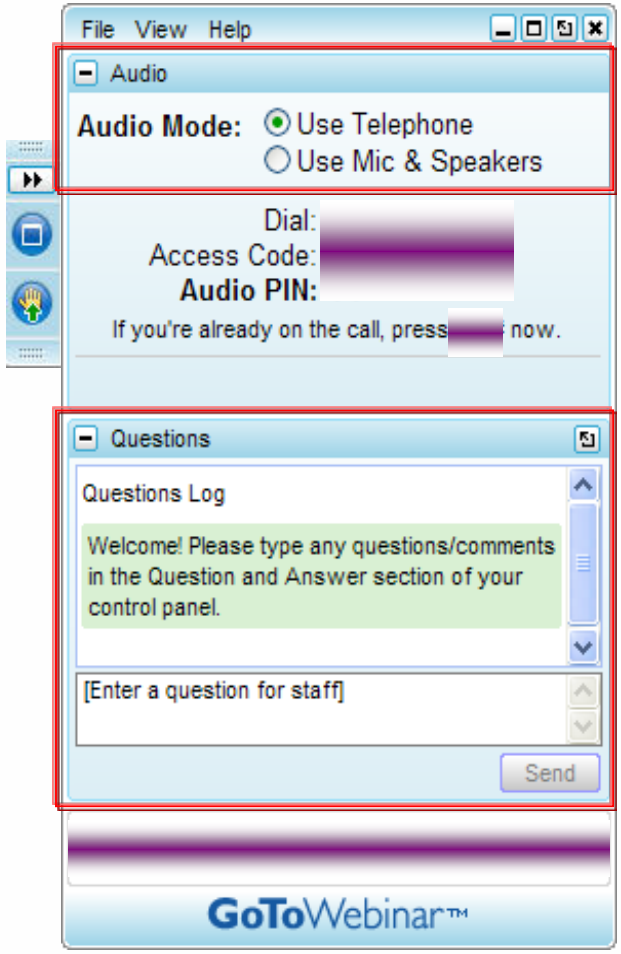
Preventing Disability: Examining Outcomes for New Youth Psychosis Treatments

John M. Kane, M.D.
Professor and Chairman
The Zucker Hillside Hospital and
Hofstra North Shore-LIJ School of Medicine
Senior VP Behavioral Health
North Shore-LIJ Health System

Housekeeping



How to participate

- Dial the conference by selecting "Use Telephone" in your Audio window. See example
- Submit your text question using the Questions pane
- **Note:** A copy of this presentation and the recording will be made available within 48 hours

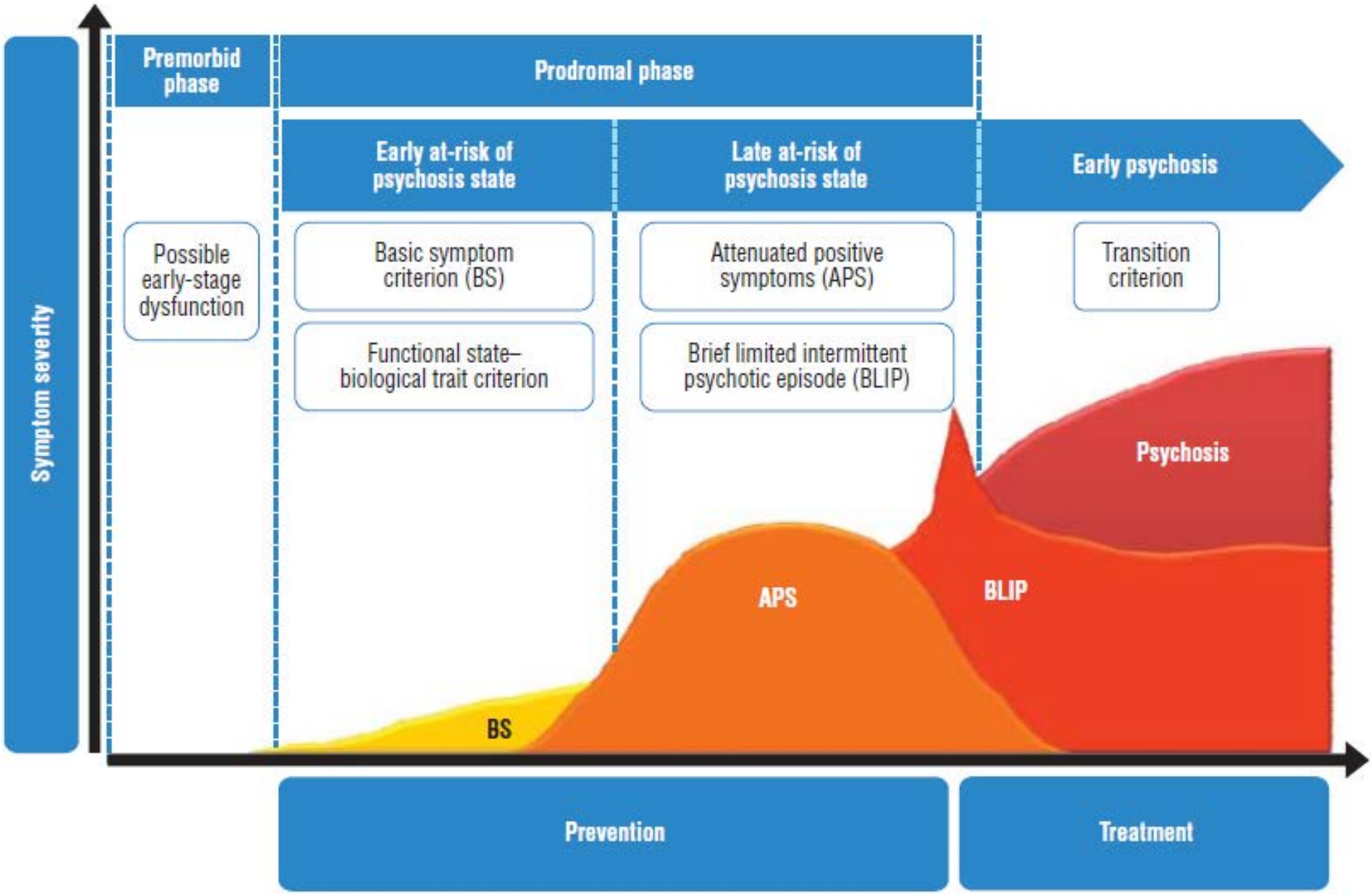
John M. Kane Disclosures 2015

- Dr. Kane has been a consultant for Alkermes, Eli Lilly, EnVivo Pharmaceuticals (Forum), Forest, Genentech, H. Lundbeck. Intracellular Therapeutics, Janssen Pharmaceutica, Johnson and Johnson, Otsuka, Reviva, Roche and Sunovion

- Dr. Kane has received honoraria for lectures from Janssen, Genentech, Lundbeck and Otsuka

- Dr. Kane is a Shareholder in MedAvante, Inc.,Vanguard Research Group and LB Pharmaceuticals

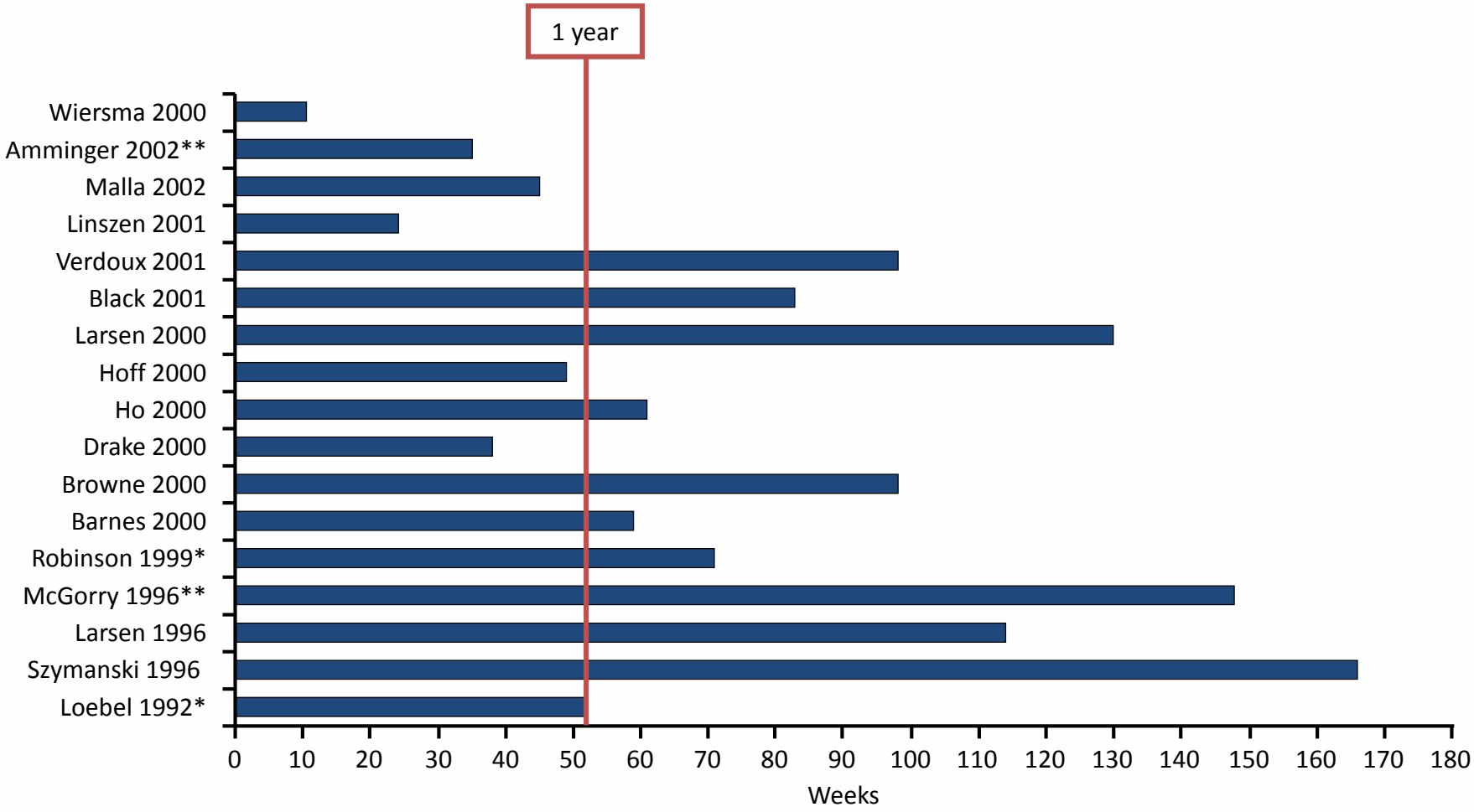
Evolution of Psychosis



Clinical Characteristics of First-episode Psychosis

- Typically adolescent or young adult
- Have lived with severe untreated psychotic symptoms
  - On average, for at least a year
- Compared to peers
  - Cognitively impaired
  - Poorer psychosocial functioning
  - More likely to smoke
  - More likely to abuse substances
- Families are typically actively engaged
- Goals are to return to mainstream functioning

Reported Mean Duration of Untreated Psychosis



Presented by Diana O. Perkins, MD, MPH. University of North Carolina at Chapel Hill, 26th Sept 2003 (available at: www.medscape.org/viewarticle/460974)

Implications of Delayed Treatment

- Greater decrease in functioning
- Loss of educational opportunities
- Impaired psychosocial and vocational development
- Personal suffering/family burdens
- Potential poorer response once treatment is provided
- Greater costs

Key Concepts for Optimal First-Episode Medication Treatment

- Response rates for positive symptoms are very high
  - No antipsychotic has demonstrated superior efficacy for the treatment of the initial psychotic episode. Tolerability is key
- Effective antipsychotic doses are usually lower than those needed for multi-episode patients
- Despite low antipsychotic doses, rates of side effects are high
- Relapse is frequent and the most important factor driving relapse is medication non-adherence
- There is often an overwhelming drive by patients and their families to stop treatment

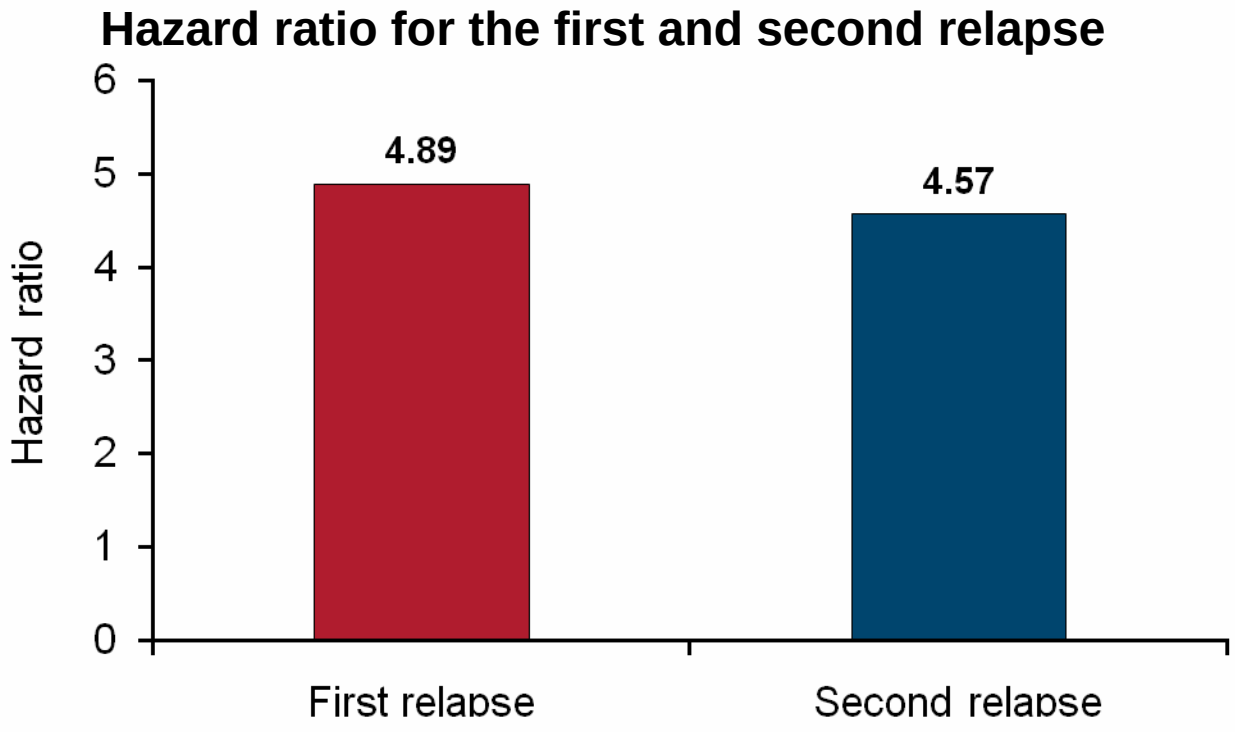
The Risk for Psychotic Relapse Is High

Year*	Relapse rate (%)	95% CI		Patients still at risk at end of year, n
		Lower limit	Upper limit	
1	16.2	8.9	23.4	80
2	53.7	43.4	64.0	39
3	63.1	52.7	73.4	22
4	74.7	64.2	85.2	9
5	81.9	70.6	93.2	4

n=104 first-episode schizophrenia patients; *year(s) after recovery from the previous episode;
CI=confidence interval
Robinson et al. Arch Gen Psychiatry 1999;56:241–247

Stopping Medication is the Most Powerful Predictor of Relapse

- Survival analysis: risk of a first or second relapse when not taking medication is ~5 times greater than when taking it



n=104

Robinson et al. Arch Gen Psychiatry 1999;56(3):241–247

Relapse Fuels the Progression of Illness

- With each relapse:
  - Recovery can be slower and less complete
  - More frequent admissions to hospital
  - Illness can become more resistant to treatment
  - Increased risk of self-harm and homelessness
  - Regaining previous level of functioning is harder
  - Patient has a loss of self-esteem and social and vocational disruption
  - Greater use of healthcare resources
- Increased burden on families and caregivers

Kane. J Clin Psychiatry 2007;68(Suppl 14):27–30

Consequences of a First and Second Relapse in Early Phase Illness

- After a first episode a young person might go back to school or work
- What happens if they relapse, will they be able to return a second time, or a third time?
- How do close friends or lovers react to a psychotic episode, and then a relapse?
- Many of life's opportunities, and a person's potential, can be eroded by a small number of relapses early in the illness

UCLA Recovery Criteria

- Recovery criteria must be met in each of 4 domains
- Improvement in each domain must be sustained concurrently for ≥2 years
- Level of recovery in these 4 domains is measured by symptom remission, appropriate role function, ability to perform day-to-day living tasks without supervision, and social interactions

Liberman et al. Int Rev Psychiatry 2002;14:256–272

Cumulative Recovery Rates by Year in Study

Year	Cumulative recovery rate (%)	95% CI	
		Lower limit	Upper limit
3	9.7	3.7	15.8
4	12.3	5.4	19.1
5	13.7	6.4	20.9

CI=confidence interval

Robinson et al. Am J Psychiatry 2004;161(3):473–479

A Systematic Review and Meta-analysis of Recovery in Schizophrenia

Erika Jääskeläinen[*,1,6], Pauliina Juola[1], Noora Hirvonen[1,2], John J. McGrath[3,4], Sukanta Saha[3], Matti Isohanni[1], Juha Veijola[1], and Jouko Miettunen[1,5,6]

[1]Department of Psychiatry, University of Oulu and Oulu University Hospital, Oulu, Finland; [2]Information Studies, Faculty of Humanities, University of Oulu, Oulu, Finland; [3]Queensland Centre for Mental Health Research, the Park Centre for Mental Health, Wacol, Australia; [4]Queensland Brain Institute, University of Queensland, St Lucia QLD 4072, Australia; [5]Institute of Health Sciences, University of Oulu, Oulu, Finland
[6]These authors contributed equally to the article.

*To whom correspondence should be addressed; Department of Psychiatry, PO Box 5000, FIN-90014 University of Oulu, Finland; tel: +358-40-7474376, fax: +358-8-336 169, e-mail: erika.jaaskelainen@oulu.fi

Conclusions:

Based on the best available data, approximately, 1 in 7 individuals with schizophrenia met our criteria for recovery. Despite major changes in treatment options in recent decades, the proportion of recovered cases has not increased

Jääskeläinen et al. Schizophr Bull 2013;39(6):1296–1306

Recovery After Initial Schizophrenia Episode – Early Treatment Program

A Research Project of the NIMH

Early Treatment Program

Tread softly because you tread on my dreams.

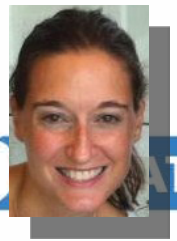
W.B. Yeats

Timeline

- NIMH Issues Request for Proposals June 2008
- Contract Awarded July 2009 (bolstered by funds from the American Recovery and Reinvestment Act of 2009)
- Enrollment Begins July 2010
- Enrollment Ends July 2012
- Last Patient In Reaches Two Years July 2014

RAISE-ETP: Executive Committee

John Kane (PI)	Zucker Hillside Hospital (ZHH)
Delbert Robinson	ZHH
Nina Schooler	SUNY Downstate
Jean Addington	University of Calgary
Mary Brunette	Dartmouth
Christoph Correll	ZHH
Kim Mueser	Boston University
David Penn	UNC
Sue Estroff	UNC
Robert Rosenheck	Yale University
Patricia Marcy	ZHH – Project Director



Principal NIMH Collaborators

Robert Heinssen
Susan Azrin
Amy Goldstein
Joanne Severe

Specified Aims of RAISE

- Develop a comprehensive and integrated intervention to
  - Promote symptomatic recovery
  - Minimise disability
  - Maximise social, academic, and vocational functioning
  - **Be capable of being delivered in real-world settings utilising current funding mechanisms**

- Assess the overall clinical impact and cost-effectiveness of the intervention as compared to currently prevailing treatment approaches
  - **Conduct the comparison in non-academic, real-world community treatment settings in the United States**

RAISE Trial Design: Subjects

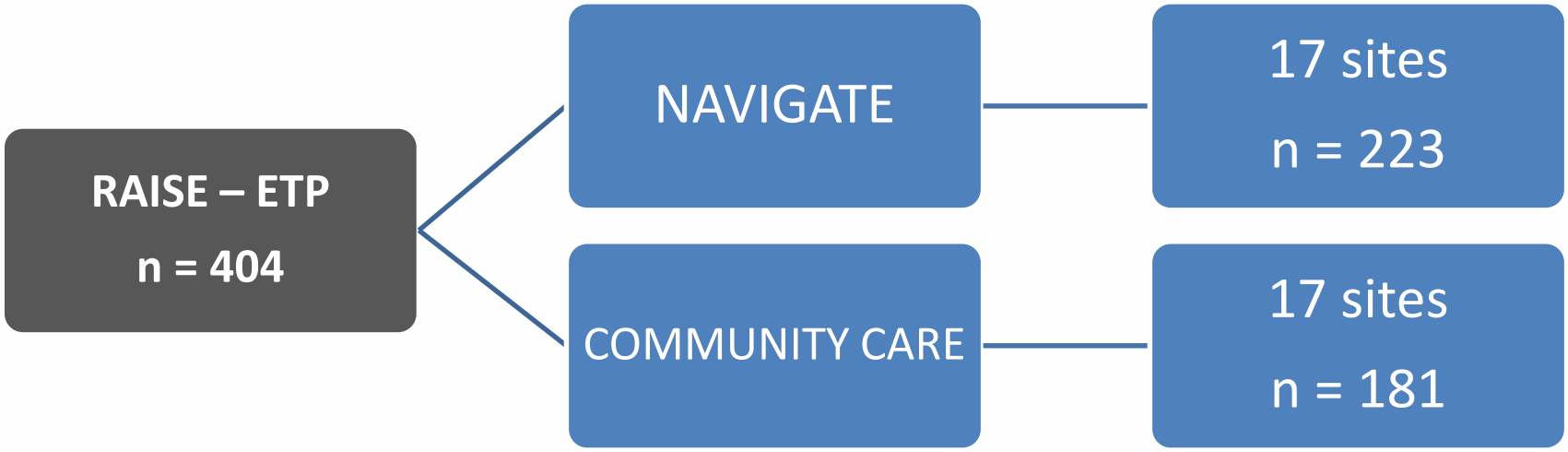
- Sample size: 404
- Age 15-40
- The following diagnoses are included in the differential
  - schizophreniform disorder
  - schizophrenia
  - schizoaffective disorder
  - psychotic disorder NOS
  - brief psychotic disorder
- Less than six months of treatment with antipsychotic medications

Randomized Controlled Trial (RCT)

- RCT to compare
  - NAVIGATE – experimental intervention
  - Community Care – treatment as offered in local clinics in the United States
- Cluster/site randomization of 34 sites in 21 states
- Two-year treatment period
- Assessment model includes
  - On-site recruitment , engagement and retention
  - Remote assessors of primary and secondary clinical outcome

Conduct the Comparison in Non-academic, United States Community Treatment Settings ETP Sites are in 21 US Contiguous States

RAISE-ETP Study Design with Cluster/Site Randomization



Addressing the Problem of Masking Assessments

- Rigorous RCTs demand unbiased and therefore masked or blinded assessment
  - Masked Assessors at the site
    - Requires training of many assessors and insuring reliability over time
    - Needs oversight to insure masking is maintained
  - Masked, remote assessors
    - Clinical evaluators trained to determine diagnosis and evaluate symptoms and functional status
    - Insures that assessments are consistent across sites and treatment condition
    - Masked to which sites are in which treatment condition and what treatment participants are receiving
    - Participants are interviewed over live and secure two-way video connection

Summary of RAISE -ETP

A novel Clinical Trial Model - Site or cluster randomization

- Patient consent does not involve randomization
- Treatment is provided openly mirrors clinical reality
- Valid assessment by centralized masked clinical raters using live video connection

Long term treatment – two years

- Delivered in United States community settings

Multi-dimensional treatment incorporating known effective elements

- Team based
- Shared decision making

RAISE Trial: Outcomes

- Primary outcome measure: Quality of Life scale
  - Primary hypothesis
    - RAISE intervention compared to community care will improve Quality of Life
- Other measured outcomes
  - Service utilization
  - Cost
  - Consumer perception
  - Prevention of relapse
  - Enhanced recovery

Navigate

- Team based
  - Shared decision-making
  - Strength & resiliency focus
  - Psychoeducational teaching skills
  - Motivational enhancement teaching skills
  - Collaboration with natural supports

- Four components
  - **Psychopharmacology – COMPASS**
  - **Individual Resiliency Training (IRT)**
  - **Family psychoeducation**
  - **Supported employment/education**

Individual Resiliency Training (IRT)

- Strength and Goal oriented
- Skill based
- Recovery emphasis
  - Motivational techniques utilized throughout
  - Connecting skills and information to goals
  - Reframing events in positive light
  - Promoting hope and positive expectations
- Tailored for first-episode clients
- Clinicians have at least Bachelor's level education and prior clinical experience
  - Most have Master's level degrees
- Modular and sequenced
  - But sequence can be modified to address client's needs

Family Psychoeducation

- Begins soon after initial contact
  - Includes client, relatives, other significant persons
- Basic and Advanced modules
- Coordinated with Individual Resiliency Training
- Assessment and identification of client and family goals
- Education about disorder and treatment
- Opportunity to process experience of psychotic episode and reduce stigmatizing beliefs about mental illness
- Strategies for improving quality of communication and problem solving

Supported Education / Employment

- Established principles of supported employment in chronic populations modified for first episode
- Focus on return to school or work as soon as possible after symptom stabilization
- Goals determined by client preferences
- Supports provided to
  - enroll/re-enroll in school
  - re-enter or obtain work
- Ongoing supports provided to maintain school/work
- Coordination with clinical treatment and team
- Benefits counseling

COMPASS

A computer decision support system to facilitate patient provider communication and medication choice within a **shared decision making** framework.

A Web-Based application available on Desktops, Laptops or iPAD

Computerized Decision Support System
Longitudinal Symptom Assessment

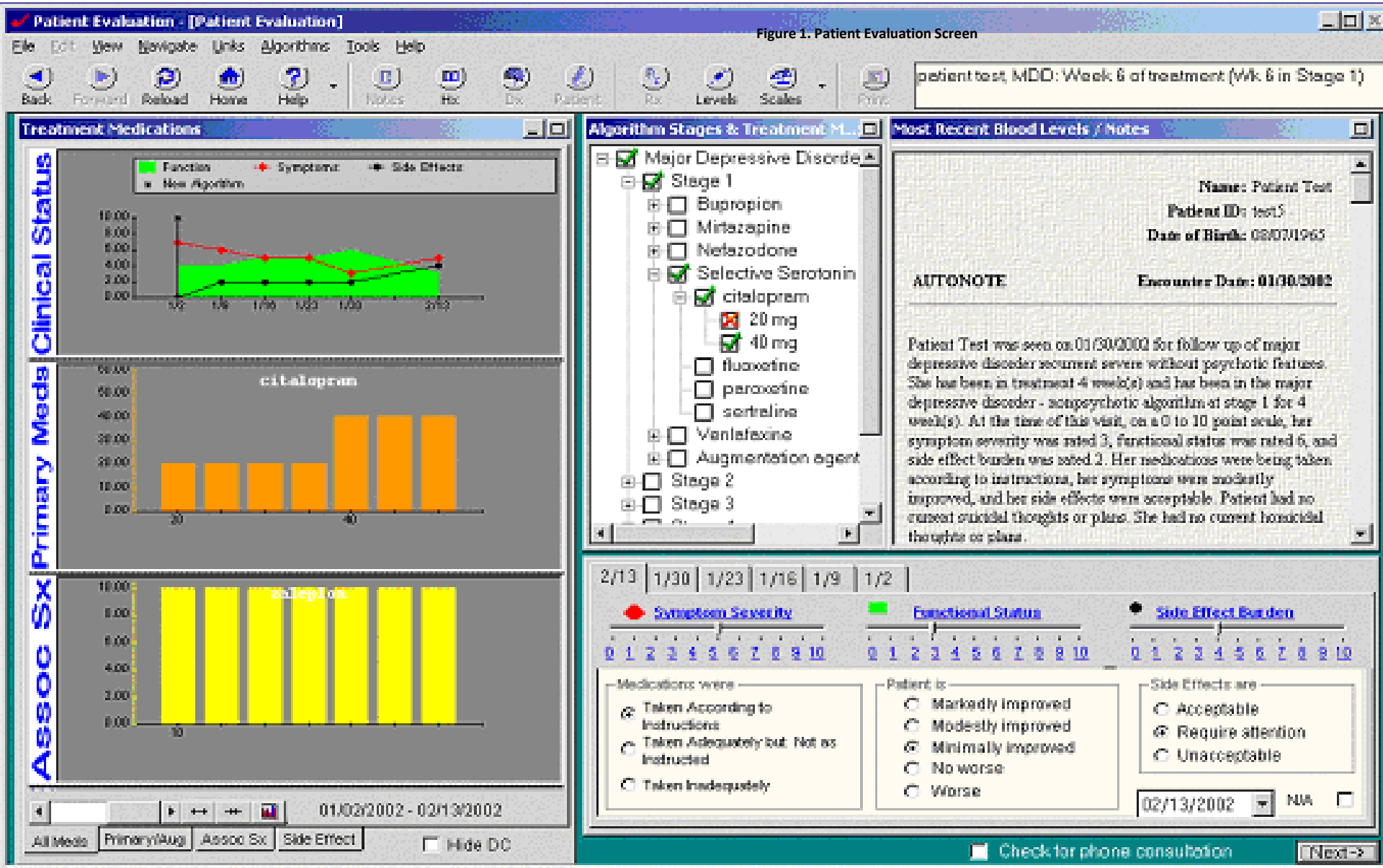
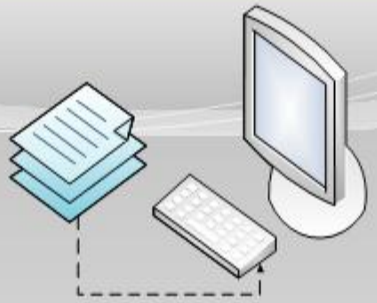


Figure 1. Patient Evaluation Screen

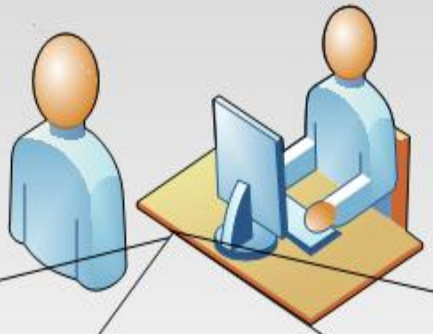
Patient Visit Flow Diagram

RA Visit Flow



Patient checks in → Front desk receptionist notifies RA → RA enters: New patient info, Medical History Form, Labs & Vitals, Opens Patient SR Form → Once Patient SR form is entered in computer, patient is ready to see doctor

Prescriber Visit Flow



Doctor assesses patient & completes the Clinician Rating Form online → Doctor & Patient discuss priorities for treatment and exercise shared decision making → Doctor reviews messages from decision support and selects treatment → Doctor finalizes visit on the Finishing Up screen & completes the visit

Patient Self Report Form

RAISE amhc	Self Report Questions	
	Patient Initials:	Visit Week: 0
Version 11/02/09 Self Eval: addressed	Patient ID:	Date 4/6/2010

Question	Answers
How have you been doing in the last month? Have you had problems keeping up with what you need to do for work, home, school or friends?	○ Yes, I have had problems If Yes what are they: ◉ No, I haven't had any problems
1 Since your last visit, have you been feeling depressed, sad or down?	○ Yes, I have felt depressed, sad or down ◉ No, I have not felt depressed, sad or down
2 Since your last visit, have you been feeling anxious, worried or nervous?	◉ Yes, I have been feeling anxious, worried or nervous ○ No, I have not been feeling anxious, worried or nervous
3 Since your last visit, have you been thinking about death or have you had any feelings that you would be better off dead?	○ Yes, I have been thinking about death or I have felt that I would be better off dead ◉ No, I have not been thinking about death and I have not had any feelings that I would be better off dead
4 Since your last visit, have you been feeling particularly good?	○ Yes, I have been feeling particularly good ○ No, I have not been feeling particularly good
5 Since your last visit, have you been feeling annoyed, angry, or resentful (whether you showed it or not)?	○ Yes, I have been feeling annoyed, angry or resentful ○ No, I have not been feeling annoyed, angry or resentful

Little red boxes indicate items not yet addressed

Clinician Rated Form Includes Information From Patient Self-Rated Form On Corresponding Items And Adjusts The Prompt Questions Accordingly

1. Depressed Mood

Sadness, grief, or discouragement (do not rate emotional indifference or empty mood here - only mood which is associated with a painful, sorrowful feeling).

Patient did not endorse depressed mood on self-report:

You said on the questionnaire that you have not had any problems recently feeling depressed, sad, or down.
Any problems not being interested in things you usually enjoy? (If yes, probe for the presence of depressed mood).

Rating

- ○ **Not reported**
- ○ **Very Mild:** occasionally feels sad or "down"; of questionable clinical significanc
- ○ **Mild:** occasionally feels moderately depressed or often feels sad or "down"
- ○ **Moderate**: occasionally feels very depressed or often feels moderately depress
- ○ **Moderately Severe:** often feels very depressed
- ○ **Severe:** feels very depressed most of the time
- ○ **Very Severe:** constant extremely painful feelings of depression
- ◉ **Unable to assess** (e.g. subject uncooperative or incoher

This item includes prompt question for a patient who *did not* endorse depressed mood on the Self-Report Form

Prompt question for patient who *did* endorse anxious mood

2. Anxiety / Worry

Subjective experience of worry, apprehension; over-concern fo mptom should be rated (e.g. the subject feels anxious because of a belief that h

Patient endorsed anxious mood on self-report:

You said on the questionnaire that you have been feeling anxious, worried or nervous.
Tell me about what you have been experiencing. What are some things you worry about or that make your nervous? How often did it happen? Does it come and go? How bad is the feeling?

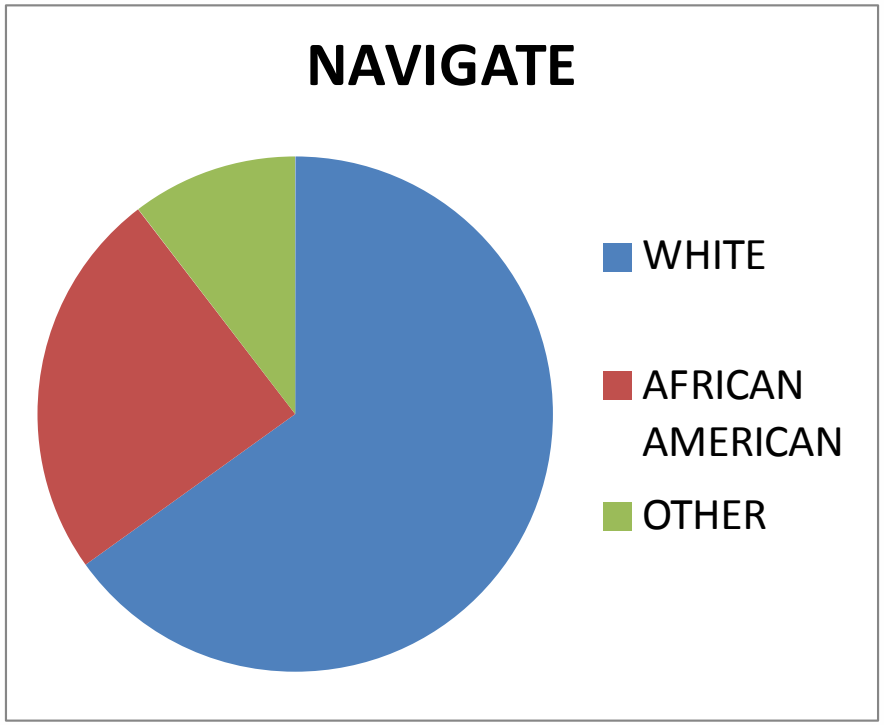
Clients' Baseline Characteristics

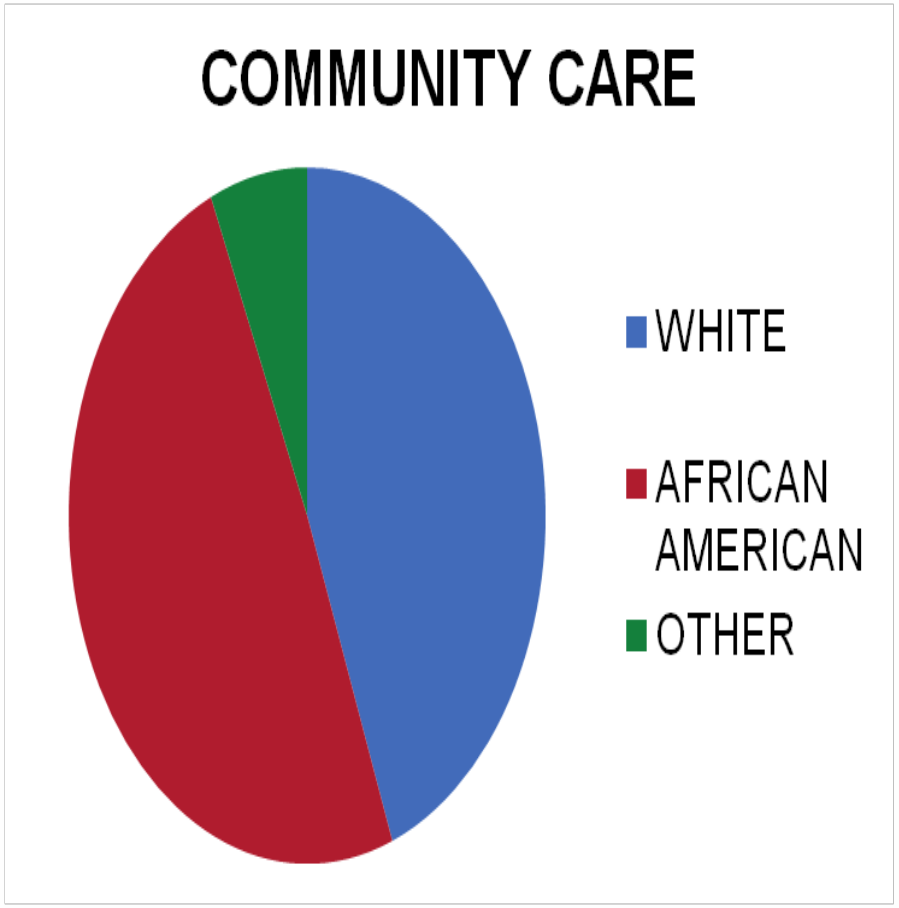
Demographics

Adjusted for Cluster Design

	NAVIGATE	Community Care	p-value
Age and Gender			
Age (mean)	23.5	23.2	
Males (%)	77.6	66.2	.05
Race			
White (%)	65.9	49.9	
African American (%)	25.4	44.1	
Other (%)	8.7	6.0	
Role Functioning			
In school (%)	14.9	25.5	.03
Working (%)	12.6	16.6	
Prior Hospitalization (%)	76.2	81.6	.05

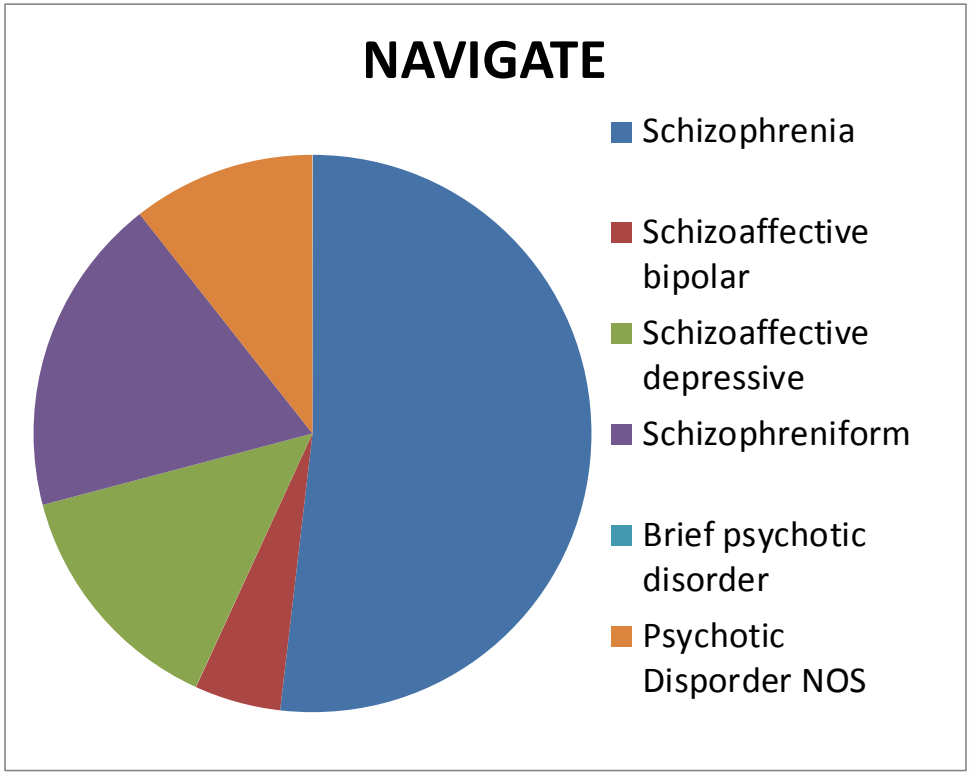
RAISE ETP Demographics – RACE (p<0.0001)

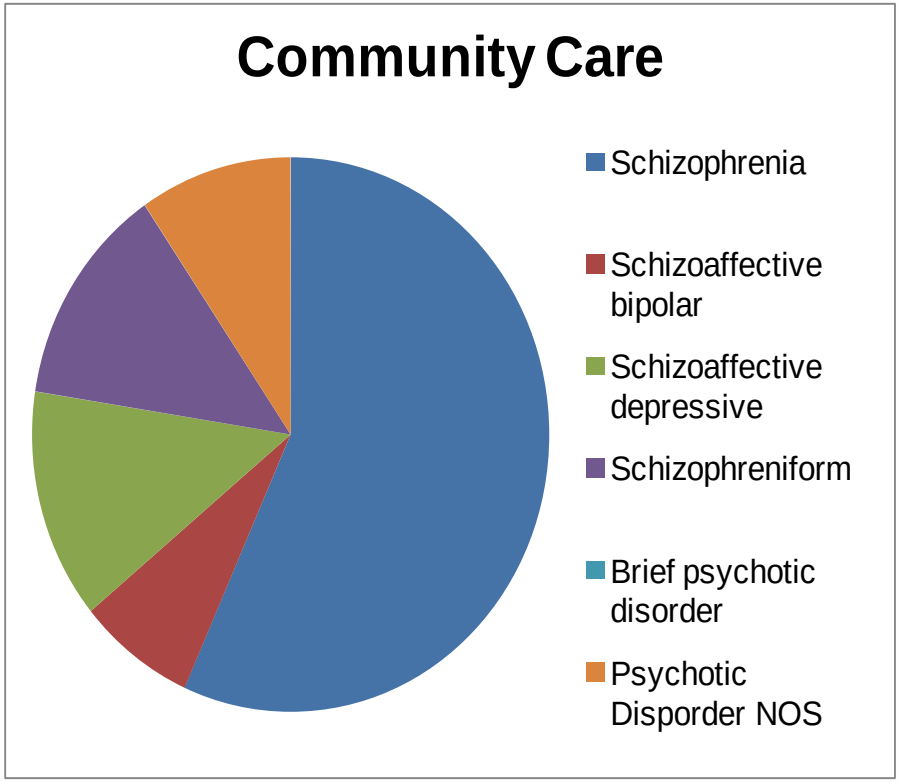




Baseline Diagnoses

Adjusted for Cluster Design





404 Subjects Entered the RAISE-ETP Study

- We examined their medication prescriptions at the time of study entry before any influence of treatment by study guidelines or procedures

- We identified 159 (39.4%) subjects who might have benefitted from one or more changes in their psychotropic prescriptions

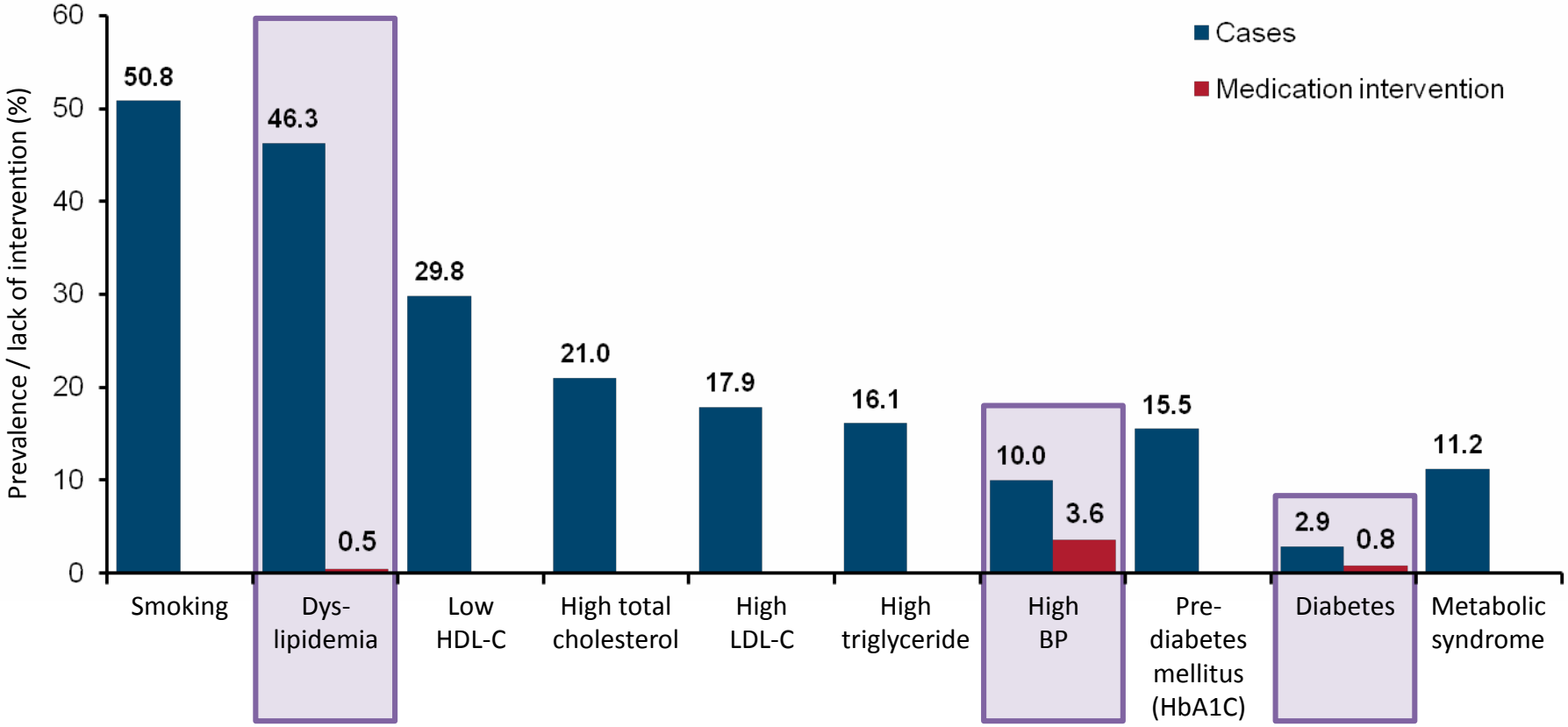
ETP=early treatment program
Robinson et al. Am J Psychiatry 2015

Of these 159 subjects…

- 14 (8.8%) were prescribed recommended antipsychotics at higher than recommended doses
- 51 (32.1%) were prescribed olanzapine (often at high doses)
- 37 (23.3%) were prescribed more than one antipsychotic
- 58 (36.5%) were prescribed an antipsychotic, but, also an antidepressant, without a clear indication
- 16 (10.1%) were prescribed psychotropic medications without an antipsychotic
- 5 (1.2%) were prescribed stimulants

Robinson et al Am J Psychiatry 2015

RAISE: smoking, lipid abnormalities, hypertension diabetes + metabolic syndrome with related drug treatment



After 47 days average lifetime antipsychotic treatment, olanzapine and quetiapine were related to higher metabolic values; dyslipidemia: TC ≥200 mg/dL or TG ≥150 mg/dL, or low HDL;
TC=total cholesterol; TG=triglyceride; HDL=high-density lipoprotein; LDL=low-density lipoprotein

Correll et al. JAMA Psychiatry 2015

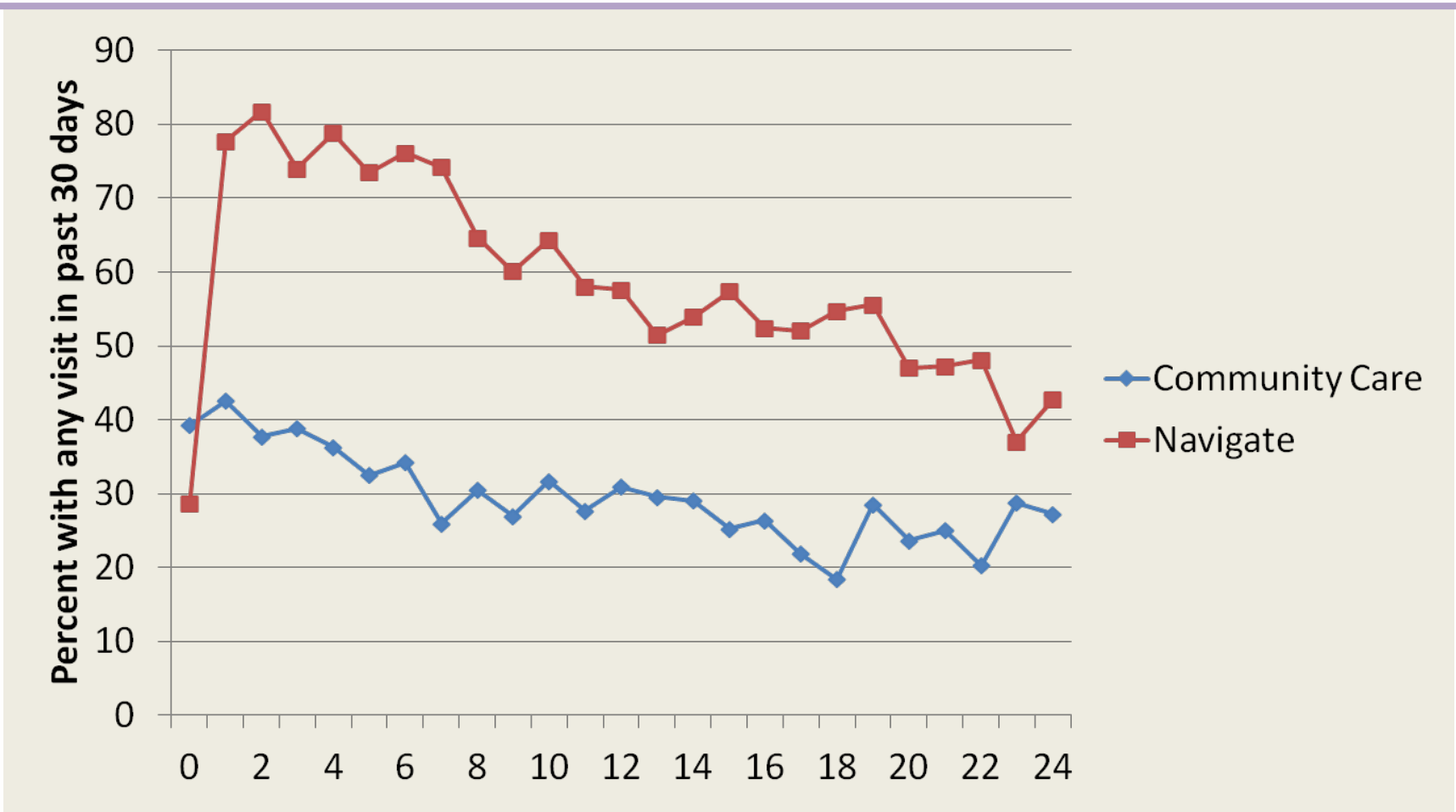
Smoking at Study Entry

- 51.2% of subjects reported smoking cigarettes at the time of study entry
- No subject was being prescribed nicotine replacement or varenicline
- Only 11 subjects (7 currently smoking) were prescribed bupropion (indication for bupropion not recorded)

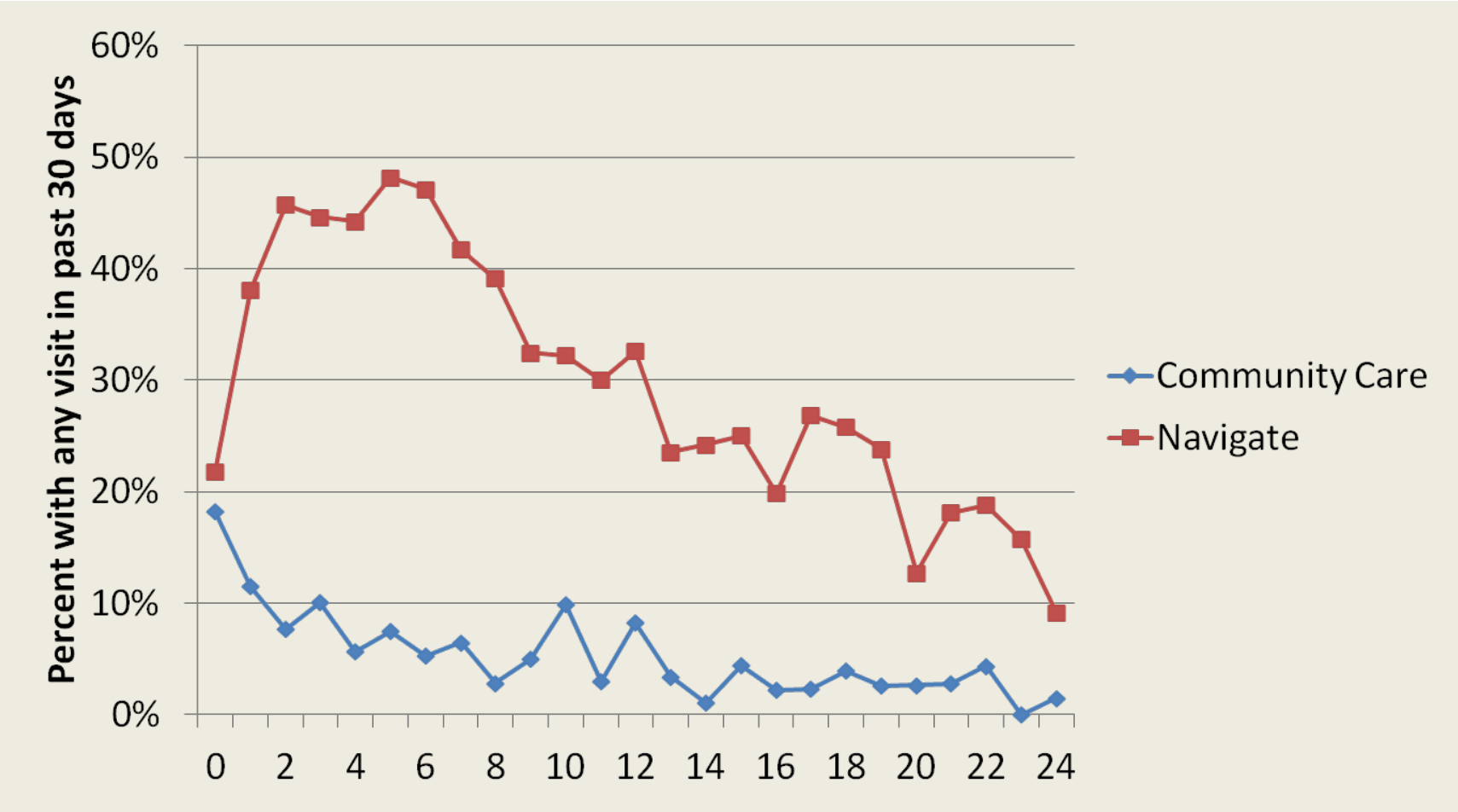
Robinson et al. Manuscript under review

Clients' Perceptions of Treatment

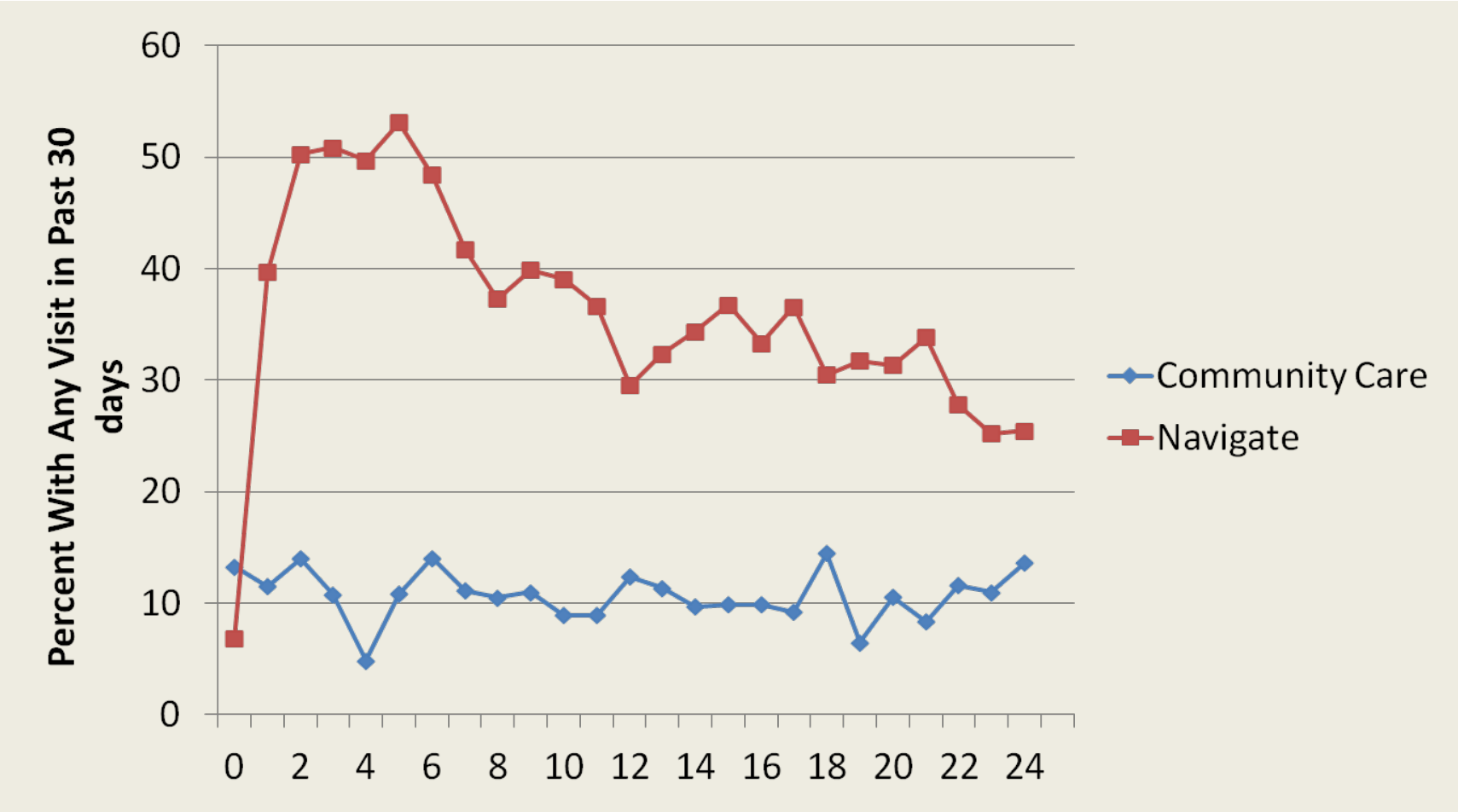
Have You Had Individual Sessions With a Mental Health Provider Who Helps You Work on Your Goals and Look Positively Towards the Future? (%)



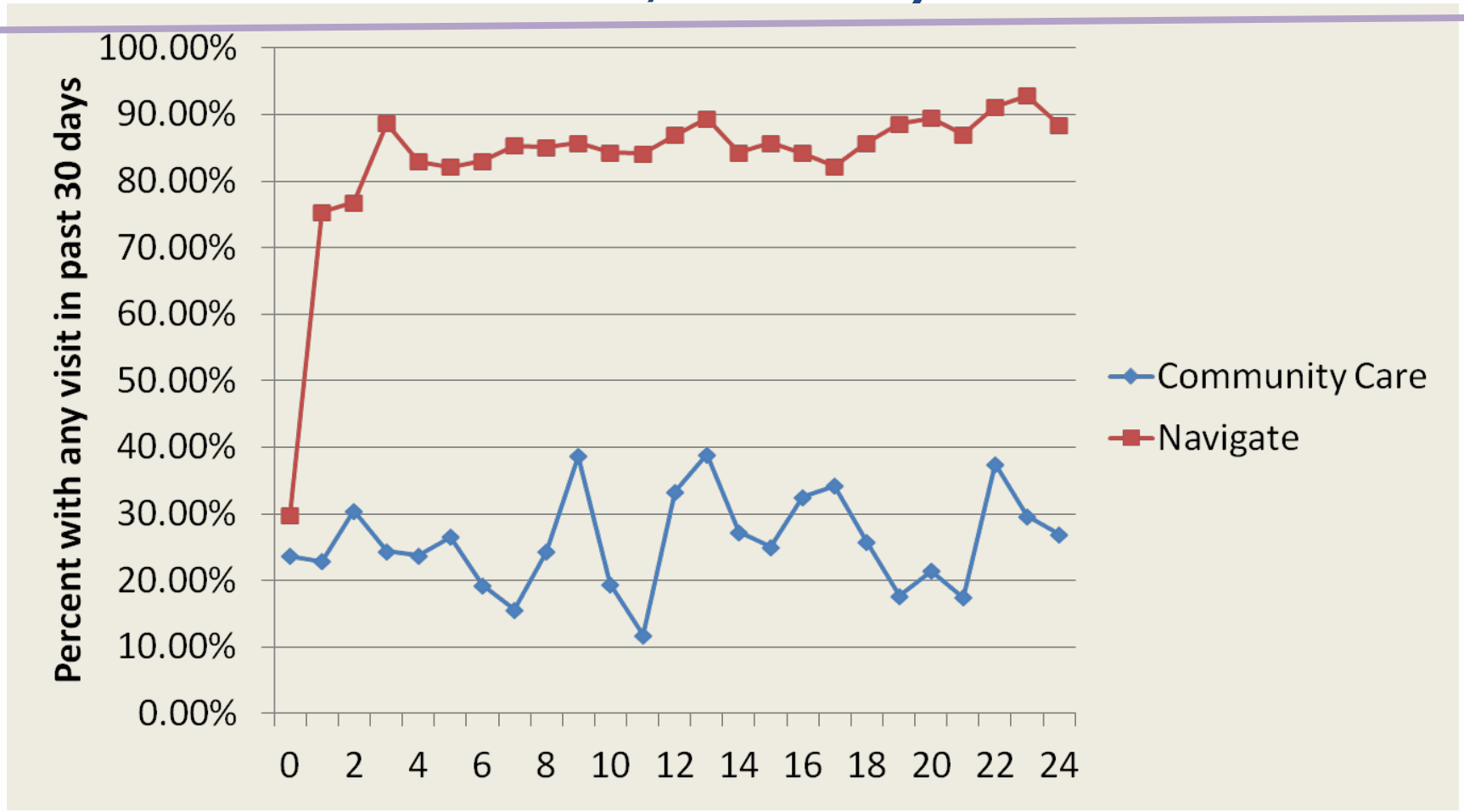
Has Your Family Met With a Mental Health Provider to Help Them Understand and Address Your Situation? (%)



Have You Met With a Person Who is Helping You Get a Job in the Community or Furthering Your Education? (%)



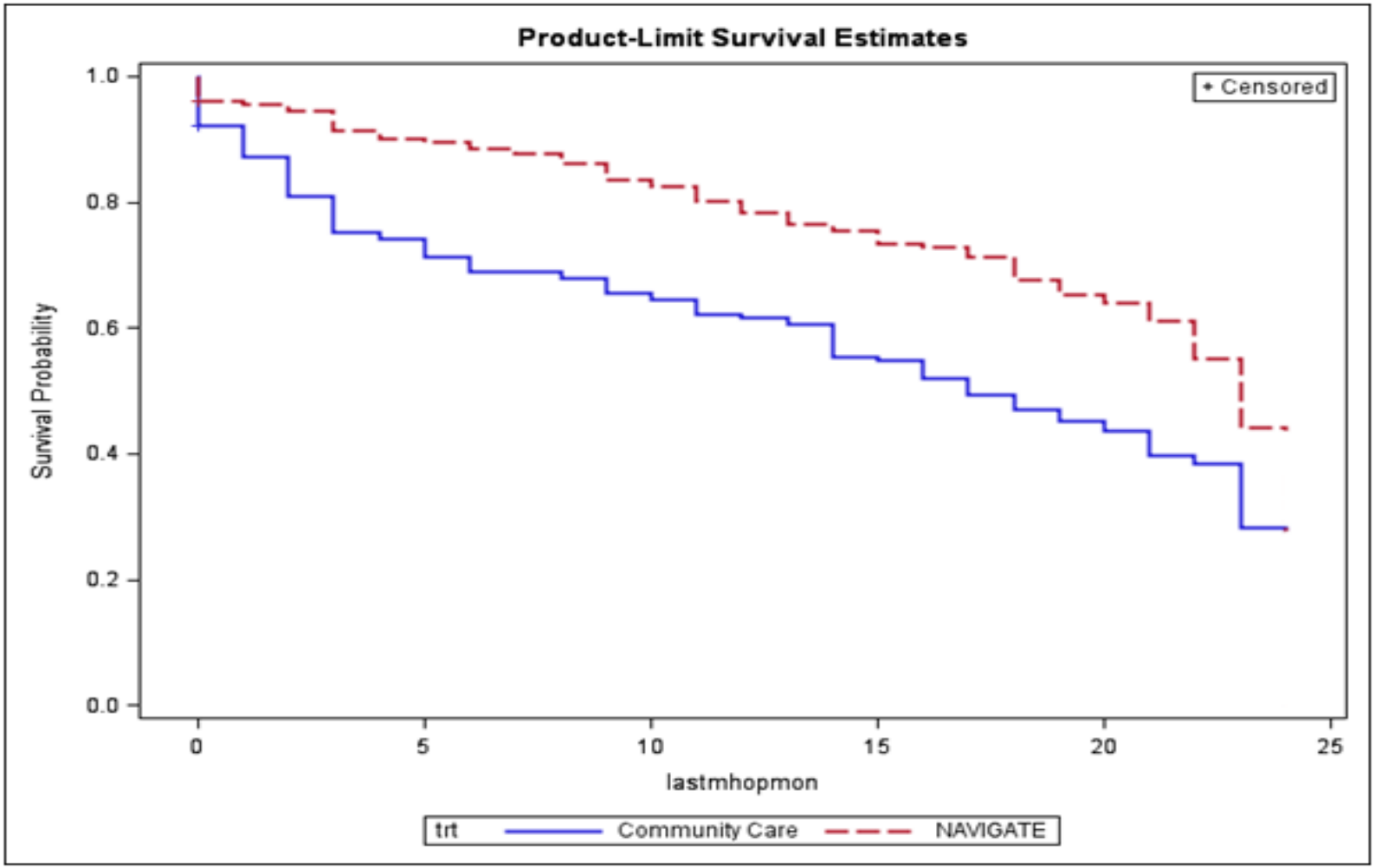
Were You Asked to Record Your Symptoms and Side Effects Before You Met With Your Psychiatrist or Nurse Practitioner? (% among responders: 44% in CC, 65% in N)



Major Study Outcomes

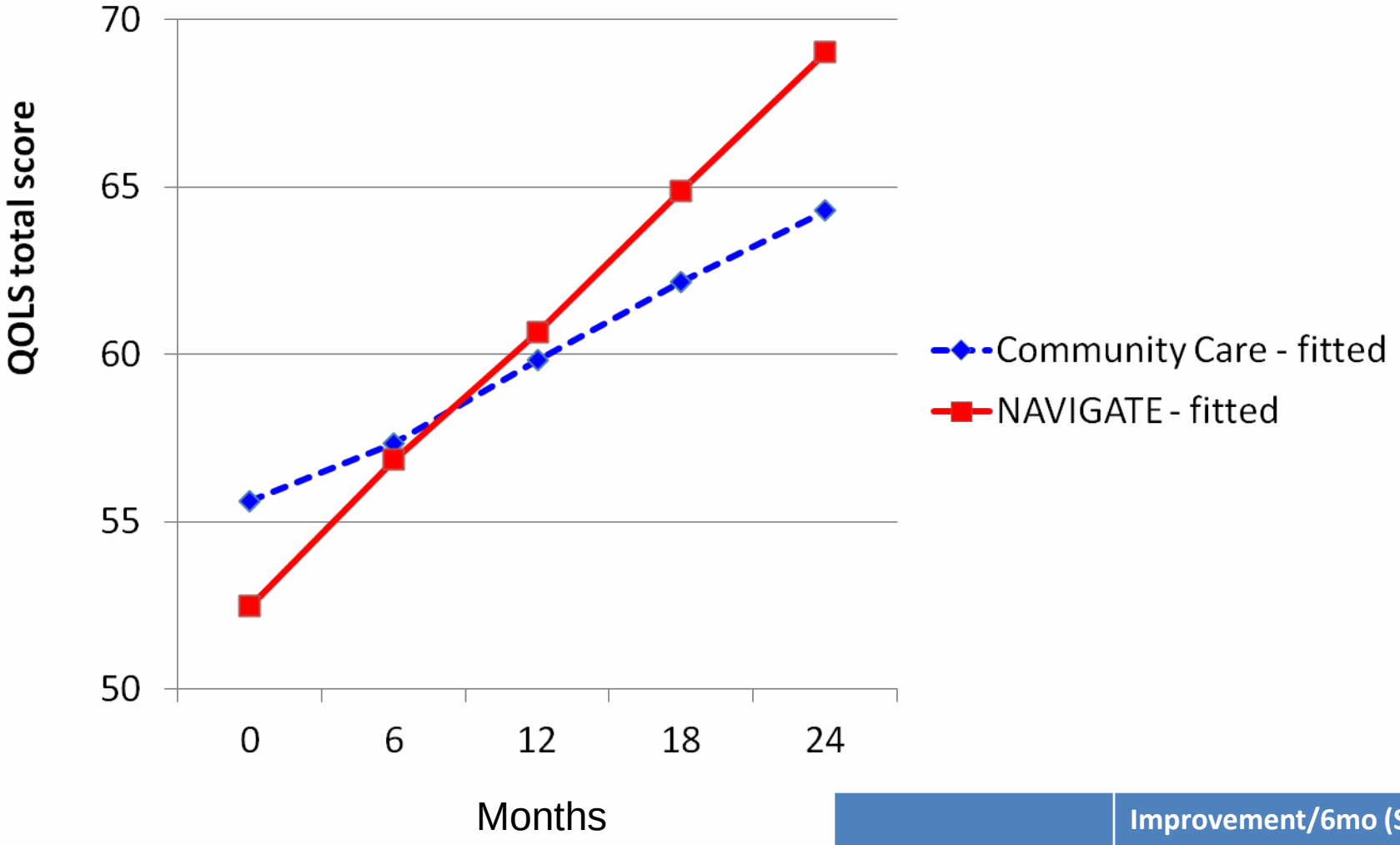
NAVIGATE Participants Stayed in Treatment Longer

Time to Last Mental Health Visit
(Difference between treatments, p=0.009)



Quality of Life Scale Fitted Model

Group by time interaction (p= 0.046)

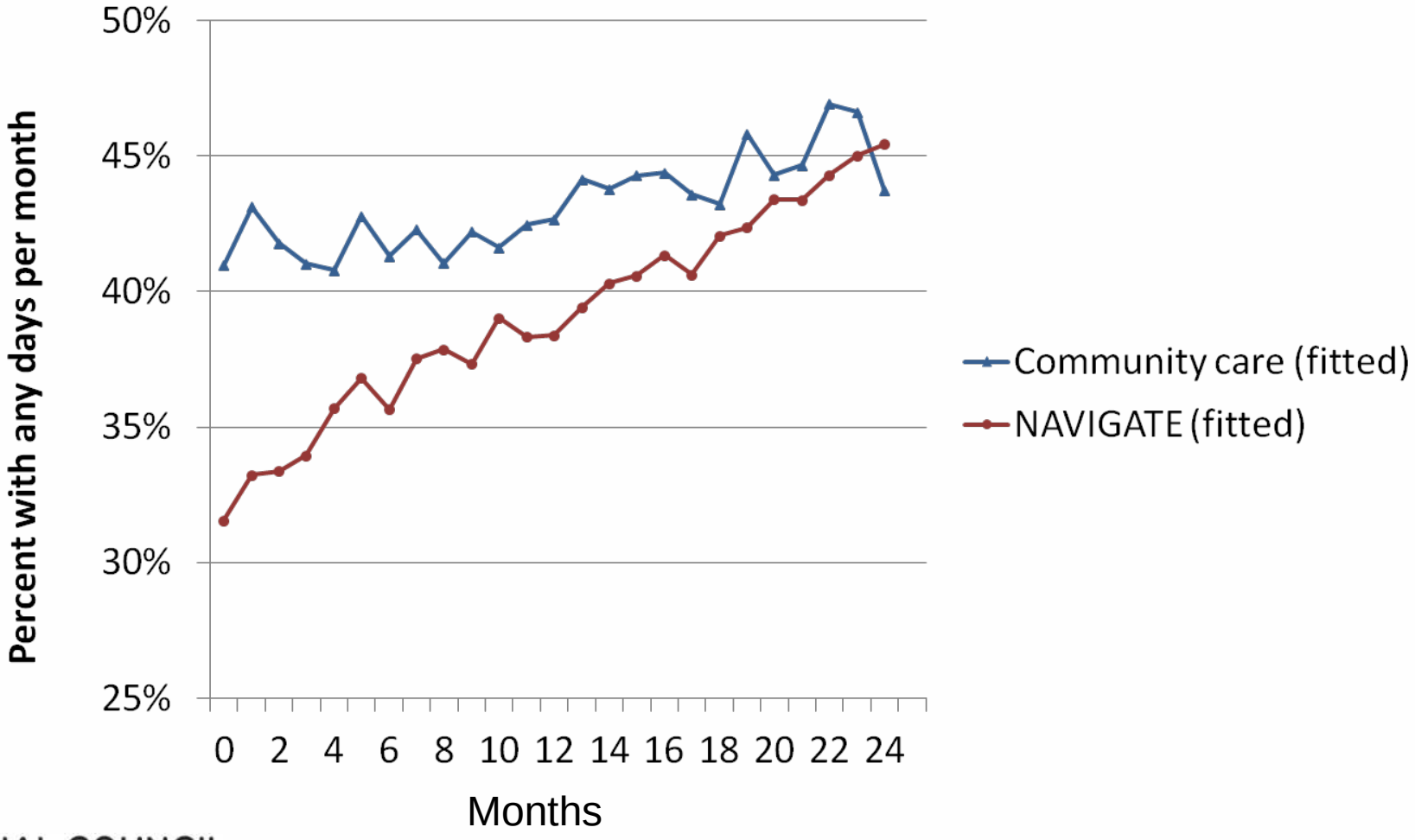


Cohen's d = 0.257

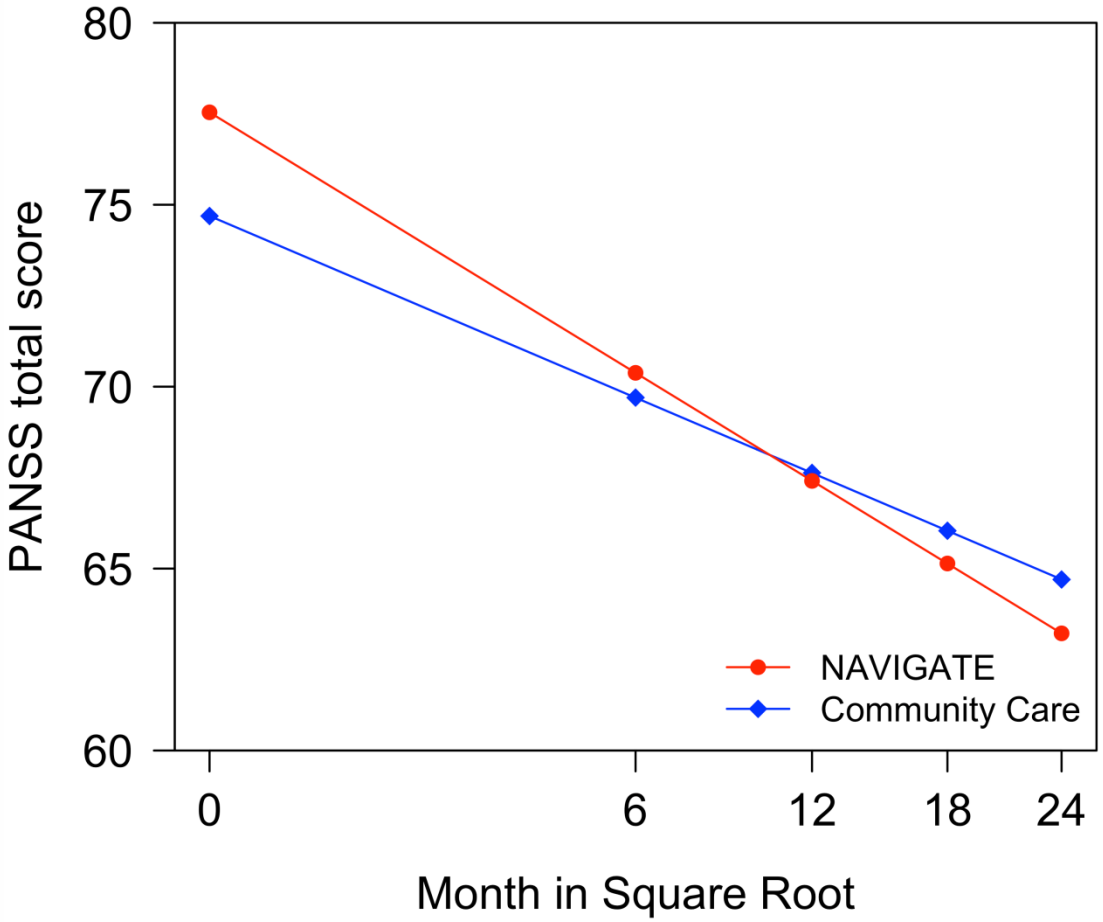
	Improvement/6mo (SE)
Community Care	2.359 (0.473)
NAVIGATE	3.565 (0.379)
Difference	1.206 (0.606)

Percent With Any Work or School Days per Month

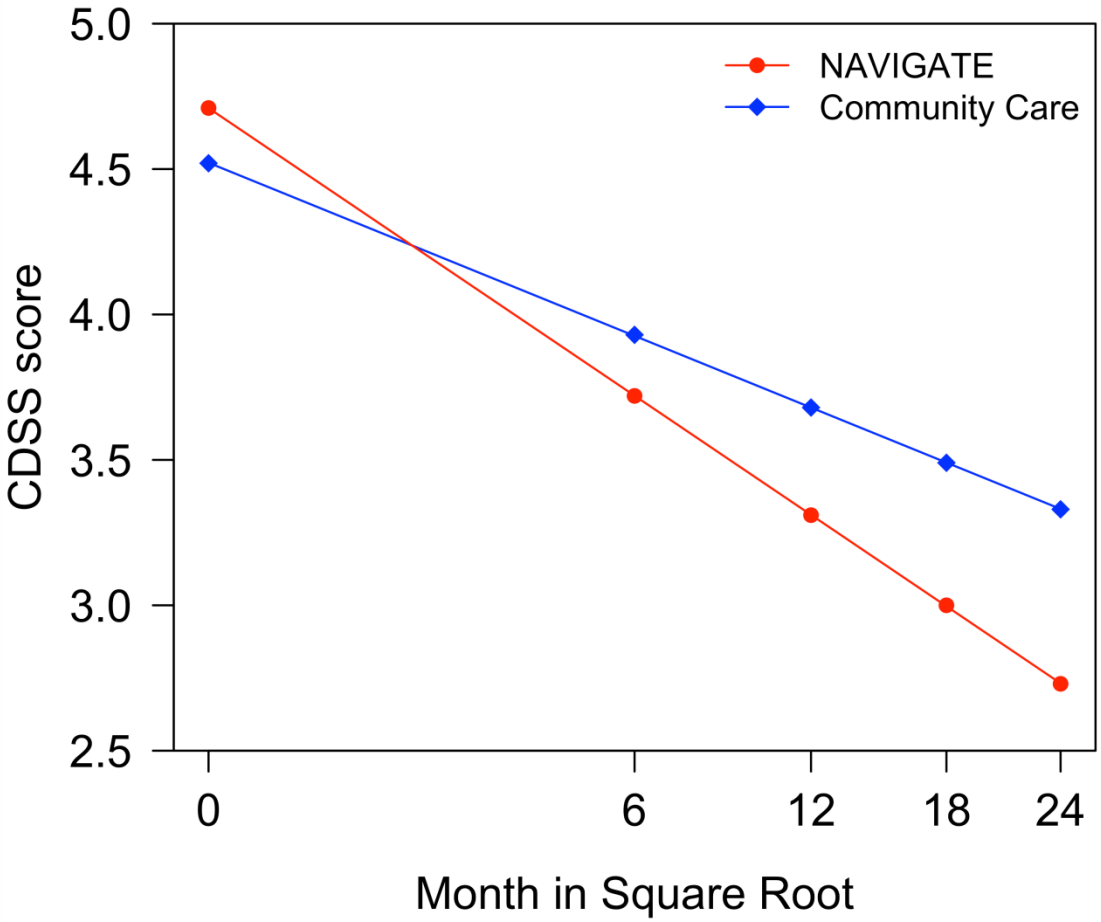
(Group by time interaction: p=0.044)



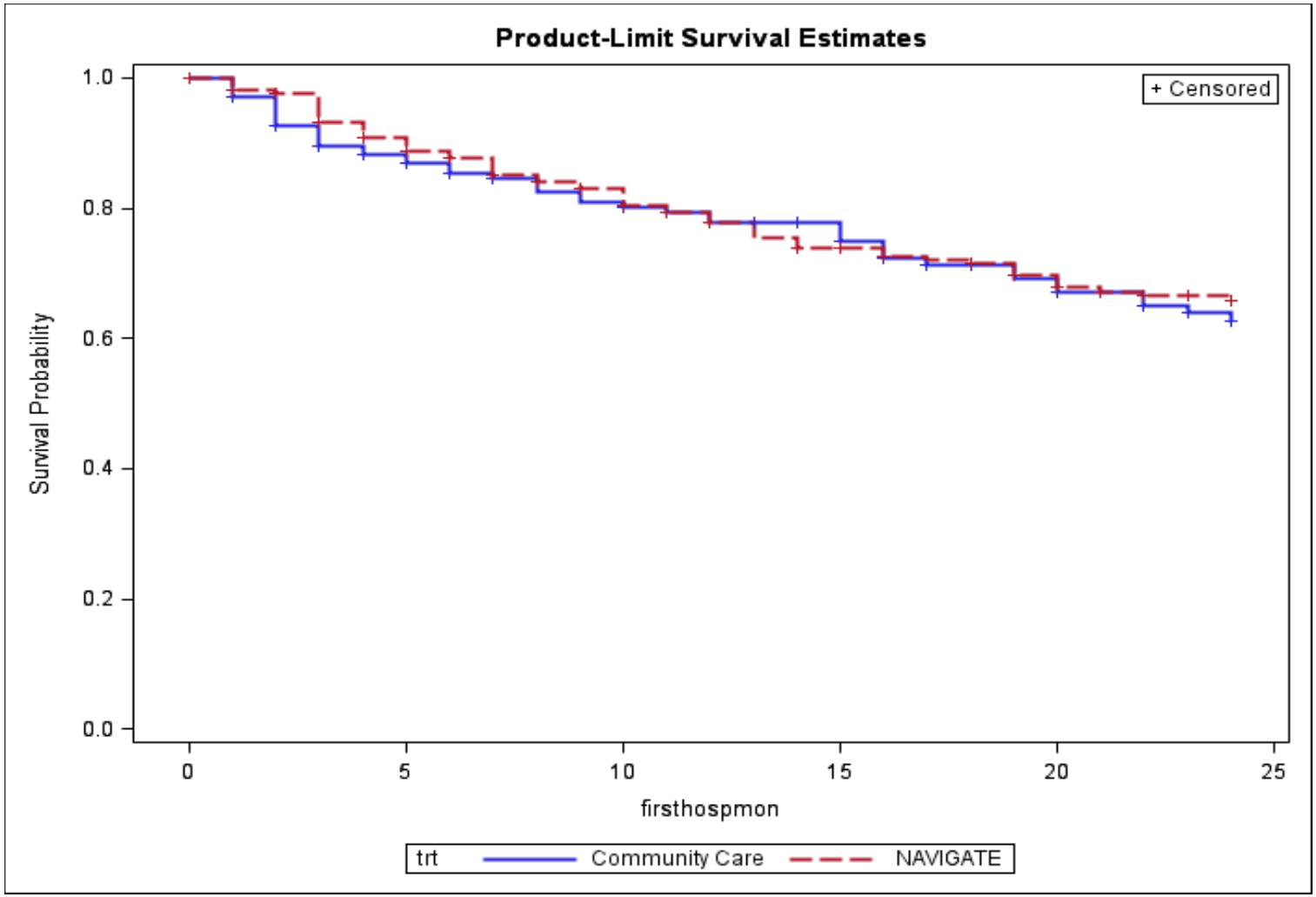
PANSS Total Score (p<0.02)



CDSS Score (p<0.04)

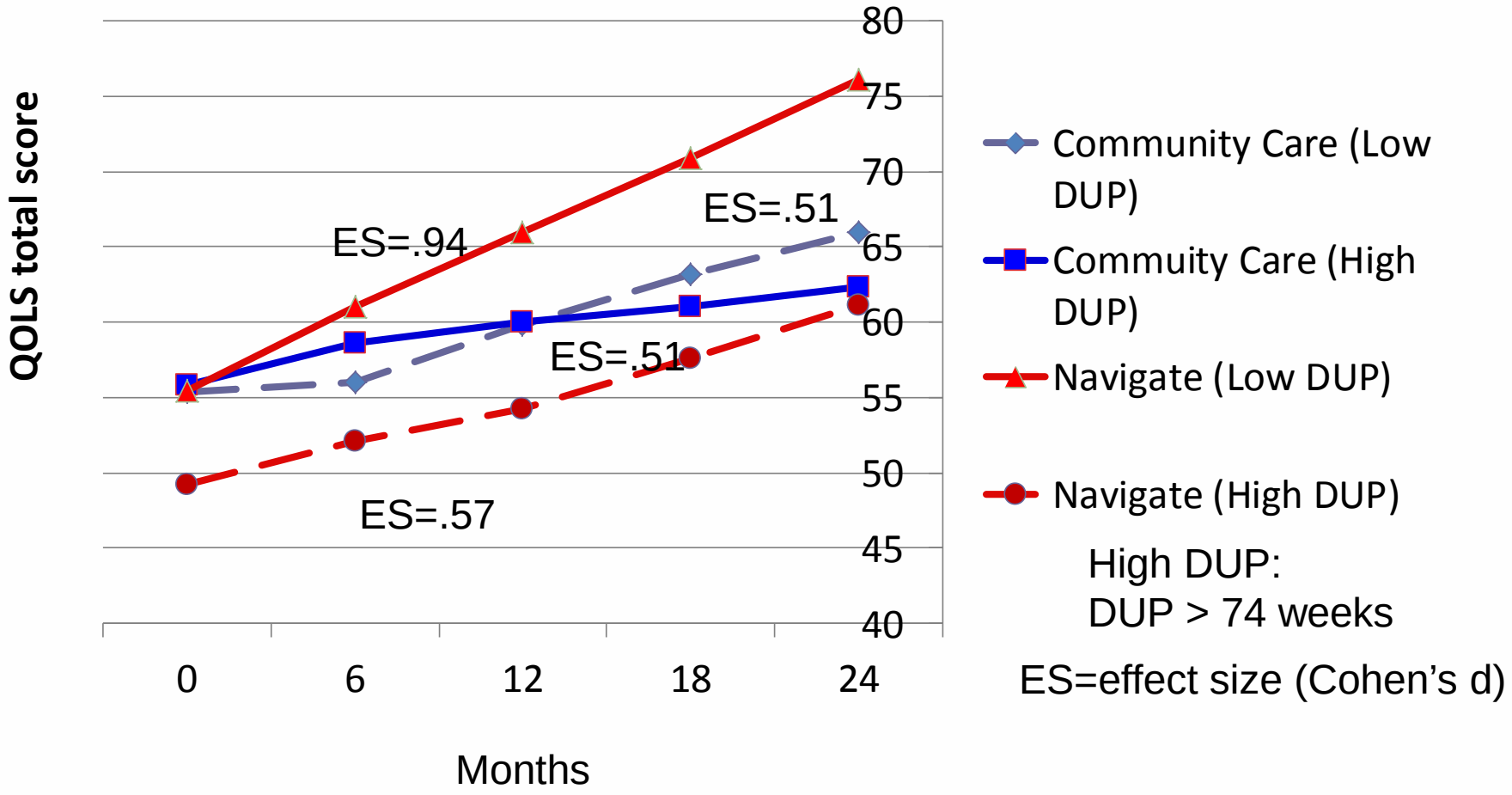


Time to First Psychiatric Hospitalization (Difference between treatments, p=0.75)

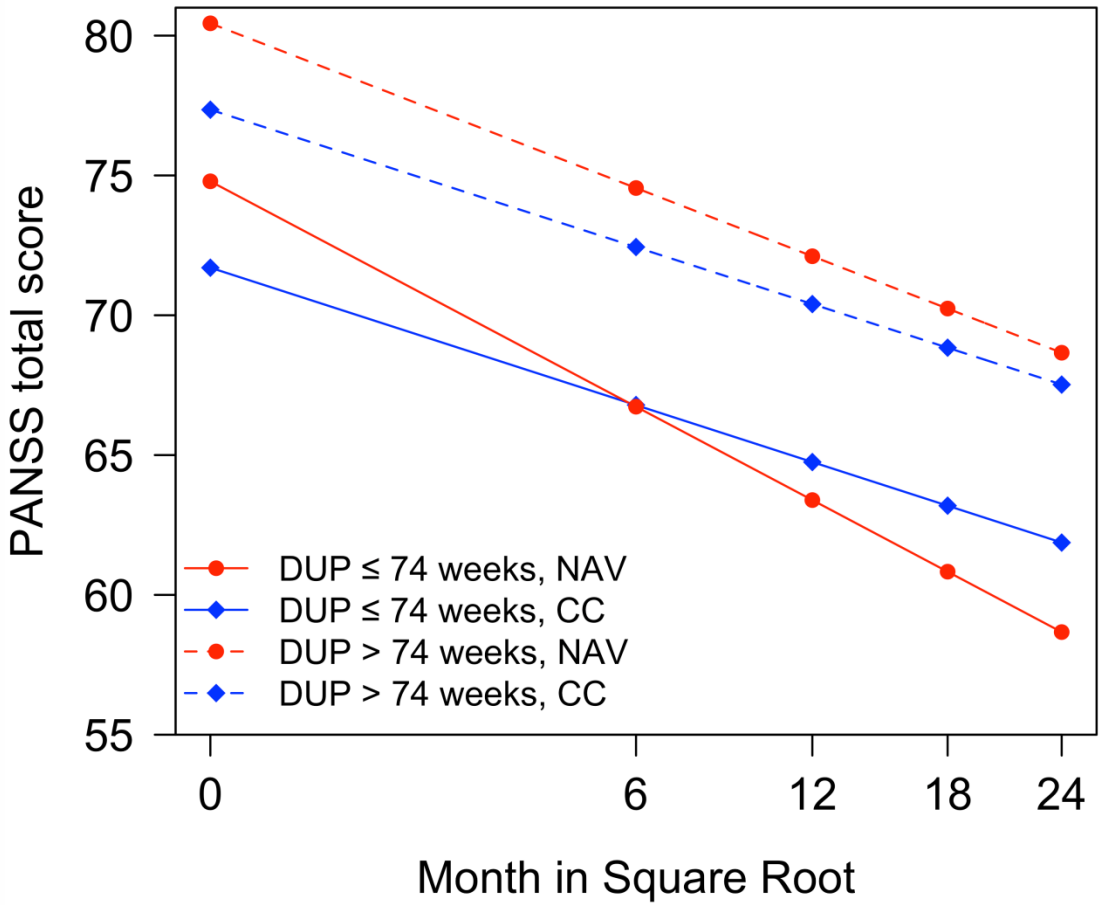


Predictors of Outcome

Quality of Life Scale: Effects of Shorter vs Longer Duration of Untreated Psychosis (DUP; p< 0.03)



Moderation of PANSS Total Score by DUP



DUP moderation
P-value 0.0426

Acknowledgements

We are grateful to all of our core collaborators and consultants.

We thank and acknowledge the terrific work of many clinicians, research assistants and administrators at the participating sites.

We are very grateful for the participation of the hundreds of patients and families who made the study possible with their time, trust and commitment.

With Thanks to Our 34 Sites: Clinicians and Participants

Burrell Behavioral Health- Springfield
Burrell Behavioral Health- Columbia
Catholic Social Services of Washtenaw County (CSSW)
Cobb County
Places for People
Community Mental Health Center, Inc.
Eyerly Ball
Grady Health System
Greater Nashua Mental Health Center @ Community Council
Henderson Behavioral Health
Howard Center
Human Development Center
Lehigh Valley Hospital
Life Management Center of Northwest Florida
Mental Health Center of Denver
The Mental Health Center of Greater Manchester

Community Mental Helath Center of Lancaster County
Clinton-Eaton-Ingham Community Mental Health Authority
North Point Health and Wellness
Park Center
PeaceHealth Oregon
Pine Belt Mental Health Center
The Providence Center
River Parish Mental Health Center
St. Clare's Hospital
South Shore Mental Health Center
Terrebonne Mental Health Center
Cherry Street Health Services
UMKC School of Pharmacy
Santa Clarita Mental Health Center
San Fernando Mental Health Center
United Services
Center for Rural and Community Behavior Health New Mexico
Staten Island University Hospital

Conclusions

- Recipients of NAVIGATE were significantly more likely to remain in treatment and experienced significantly greater improvement in the primary outcome measure (i.e., quality of life).
- They were more likely to be working or going to school.
- NAVIGATE participants showed a significantly greater degree of symptom improvement on PANSS and CDSS.
- DUP appears to be an important moderator of NAVIGATE effectiveness.
- These results show that a coordinated specialty care model can be implemented in a diverse range of community clinics and that the quality of life of first episode patients can be improved.