Clinical Conclusions from the CORE Studies

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Outline

I. ECT Background

II. CORE Studies I & II

III. PRIDE Phase I and Phase II Data

IV. Conclusions

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On the significance of elektroconvulsive therapy in the treatment of severe mental diseases

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Summary

Background Quite a few patients with severe mental diseases do not respond sufficiently to psychopharmacology as a last resort but in an evidence-based way. Patients should be informed timely and adequately about the therapeutic option.

aspects.

Results Due to its excellent efficacy, ECT is an important option in the treatment of severe mental disease. Technological innovations and continued development in the psychiatric environment determined the evolution from the electroshock of the 1930s to the ECT of today. This process led to reduced side effects and a stronger patient-oriented praxis.

Conclusions ECT is a modern, highly effective and safe treatment of severe mental diseases with compara-

superior efficacy, ECT has remained an important treatment option for patients with severe psychiatric disorders. It can be easily combined with other treatment methods and should be applied within the frame of an overall treatment plan, which considers psychopharmacological, psychotherapeutic, socio-psychiatric, trialogical as well as juridical aspects. Despite positive scientific evidence, the therapy is often approached with reserve that cannot be explained rationally. With this article, we aim at providing a compact and practically oriented overview of ECT

"Despite positive scientific evidence, the therapy is often approached with reserve that cannot be explained rationally."

FDA "Cleared Indications for Use" ECT Devices

1. Depression (unipolar and bipolar)
2. Schizophrenia
3. Bipolar manic (and mixed) states
4. Schizoaffective disorder
5. Schizophreniform disorder
6. Catatonia

ECT's Shortcomings

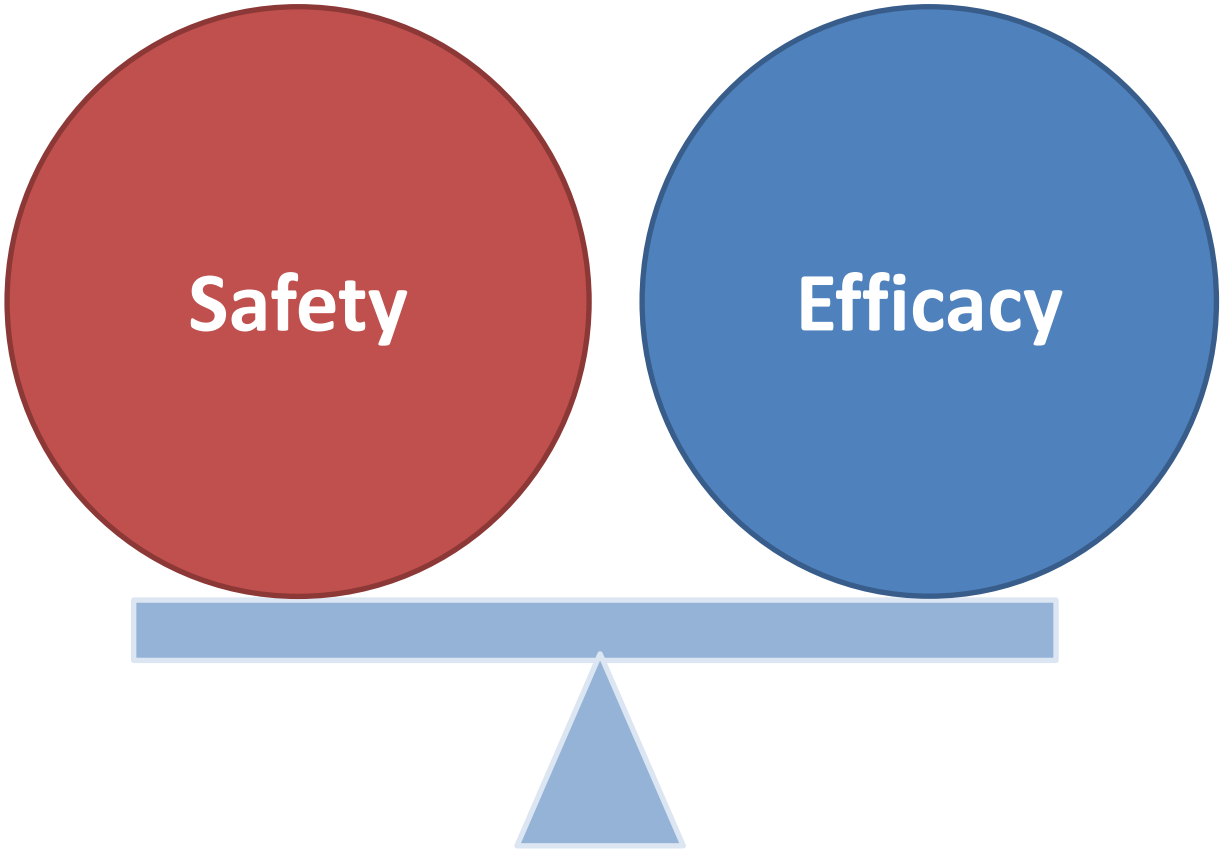
- Medical risks (safety)
  - risk of general anesthesia (death in 1/10,000)
- Cognitive effects (tolerability)
  - retrograde amnesia
- Does not prevent future episodes (unless use maintenance ECT)
- Post-ECT relapse rates higher in the modern era

Safety/Tolerability

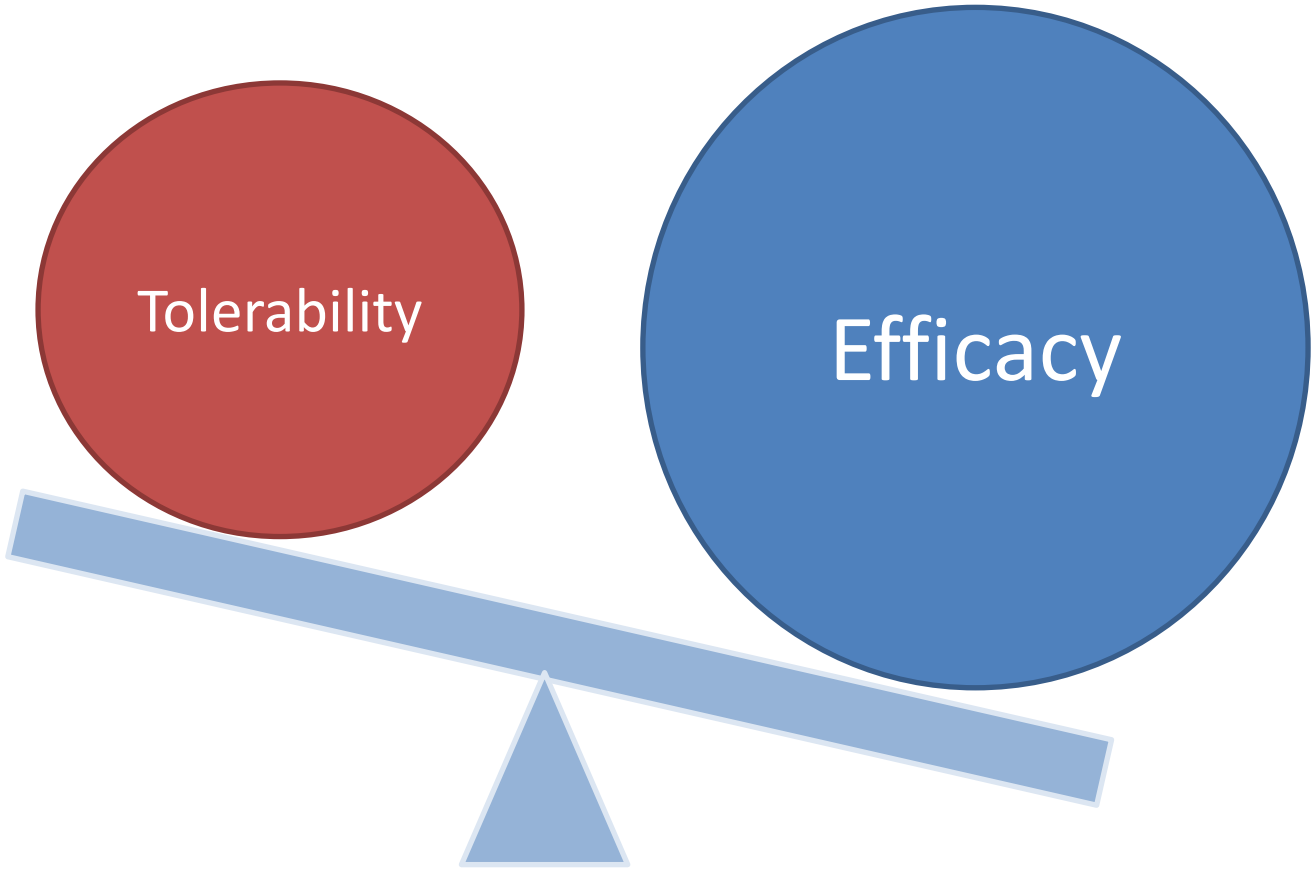
- Safety = Risk of physical injury or death

- Tolerability = Side effect burden

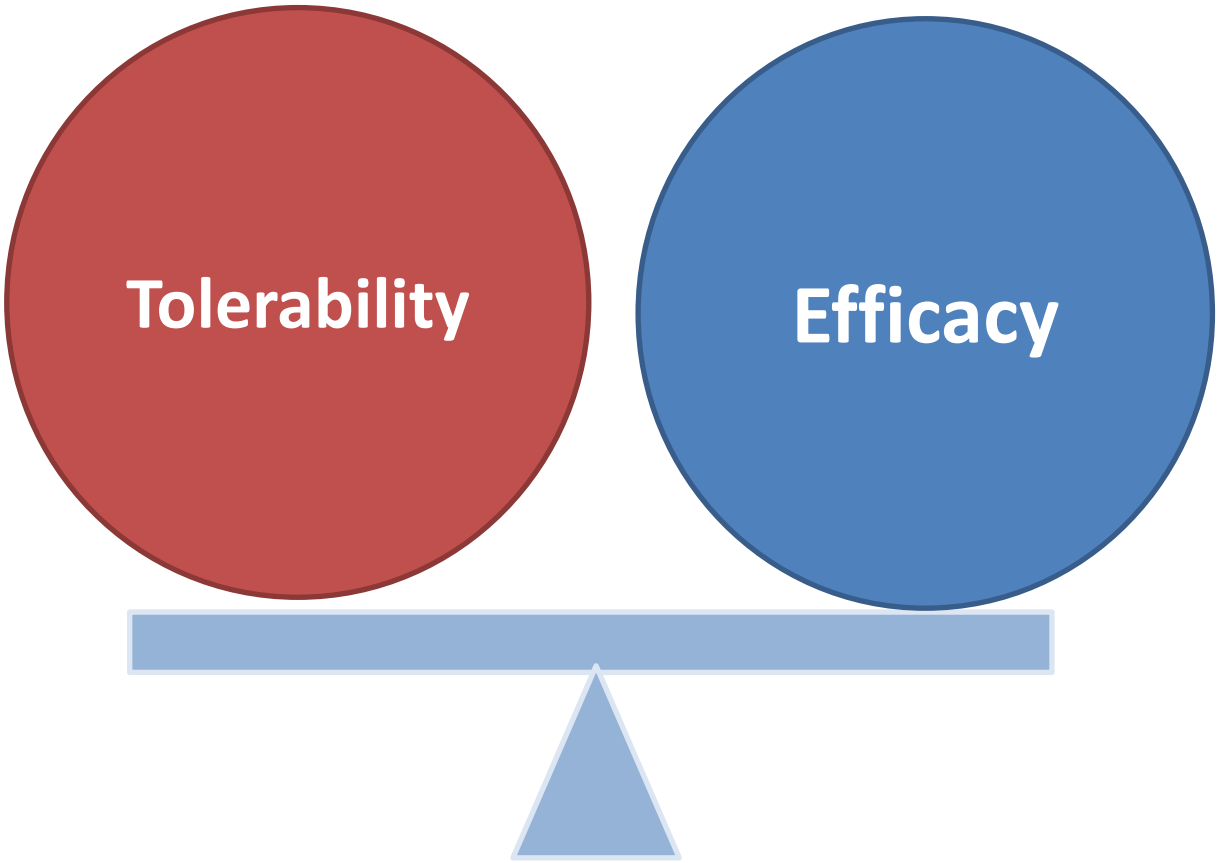
ECT



ECT



ECT (Optimized)



C.O.R.E.

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(1997-2017)

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Rebecca Knapp, Martina Mueller

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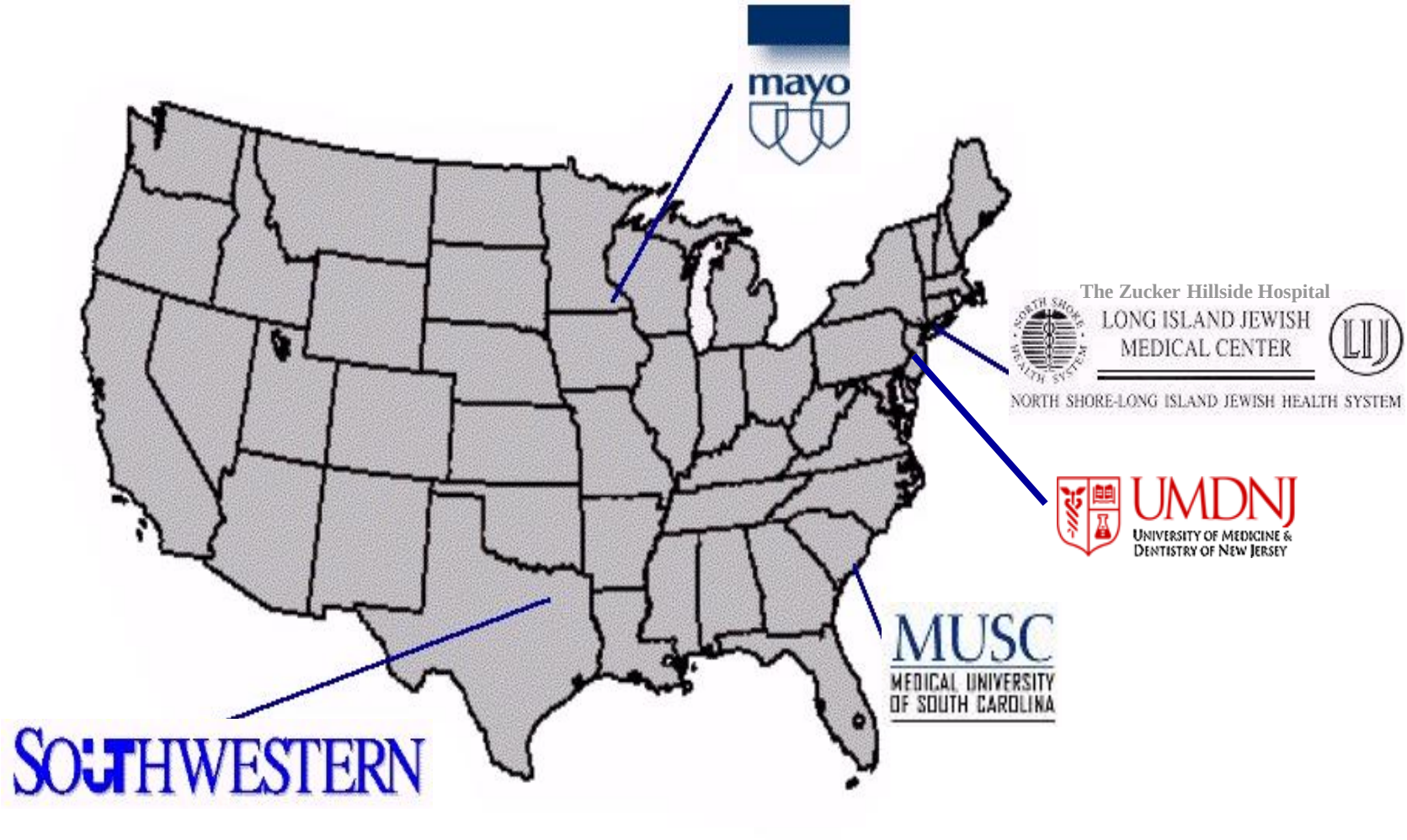
MUSC

CORE Studies I-II



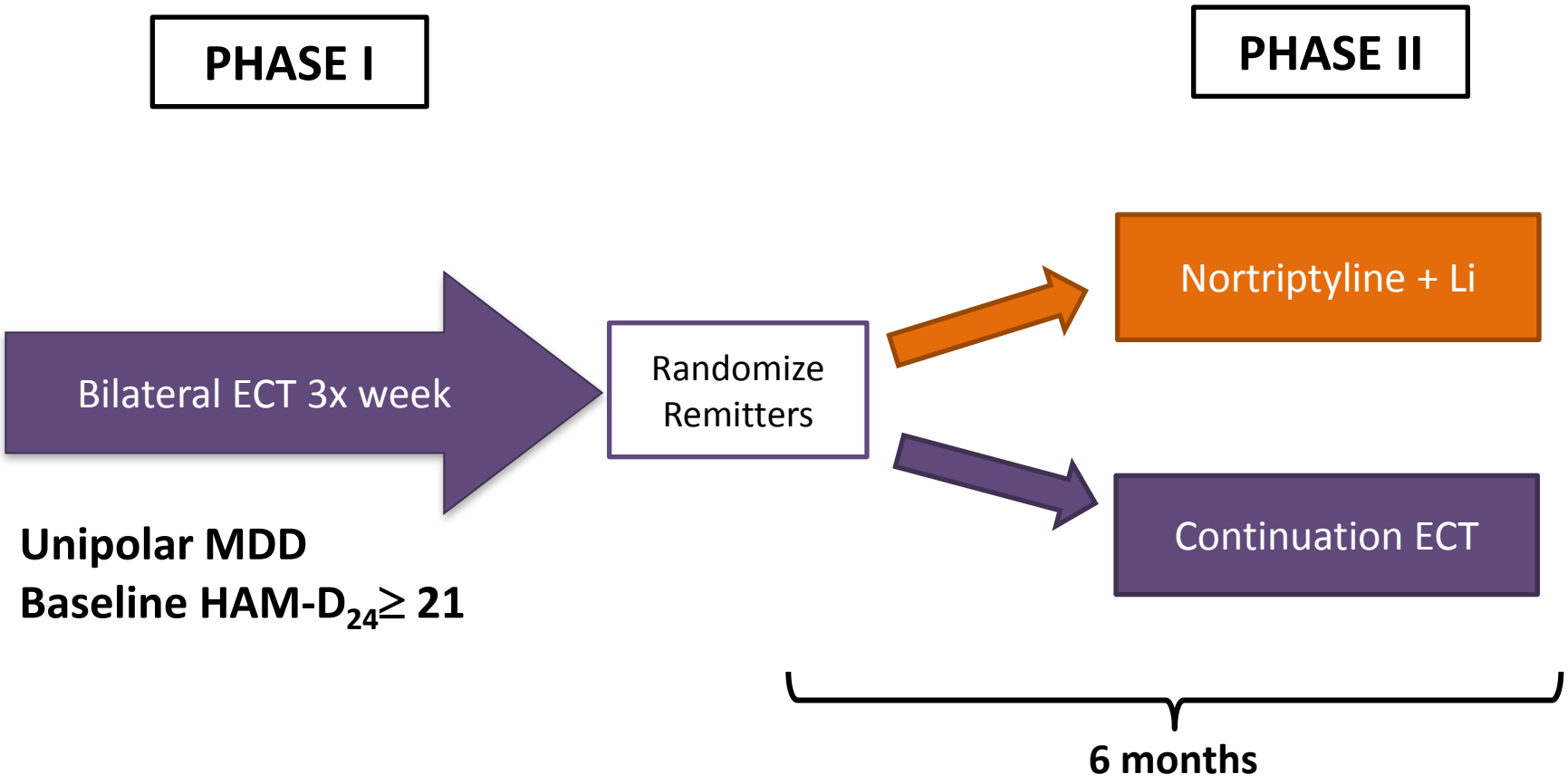
CORE
Data Coordinating Center

Charleston, SC

MUSC Institute of Psychiatry

NIH, Bethesda, Maryland

CORE I:
Continuation ECT vs Pharmacotherapy



Kellner CH, et al., Arch Gen Psychiatry. 2006 Dec;63(12):1337-44.

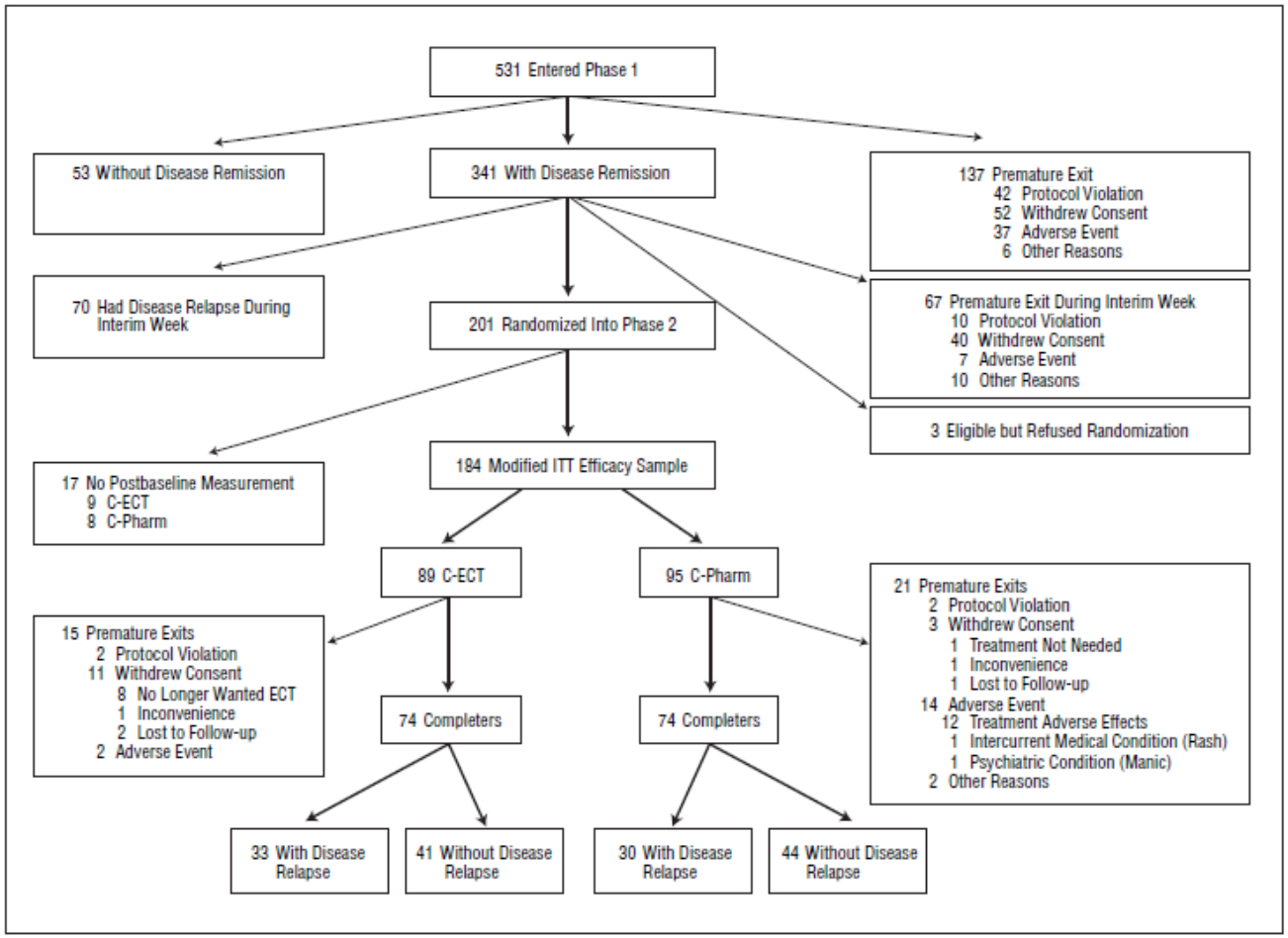
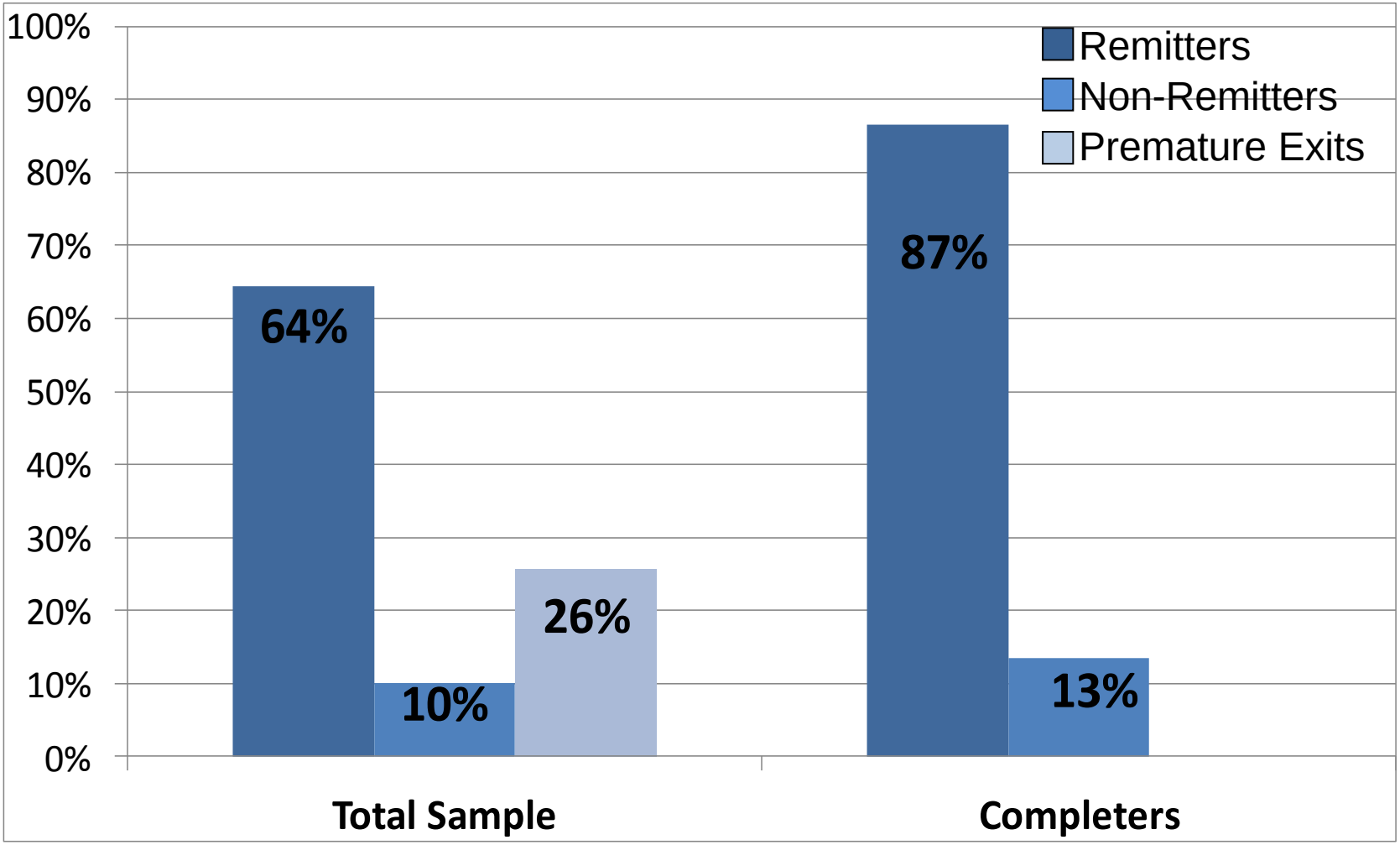


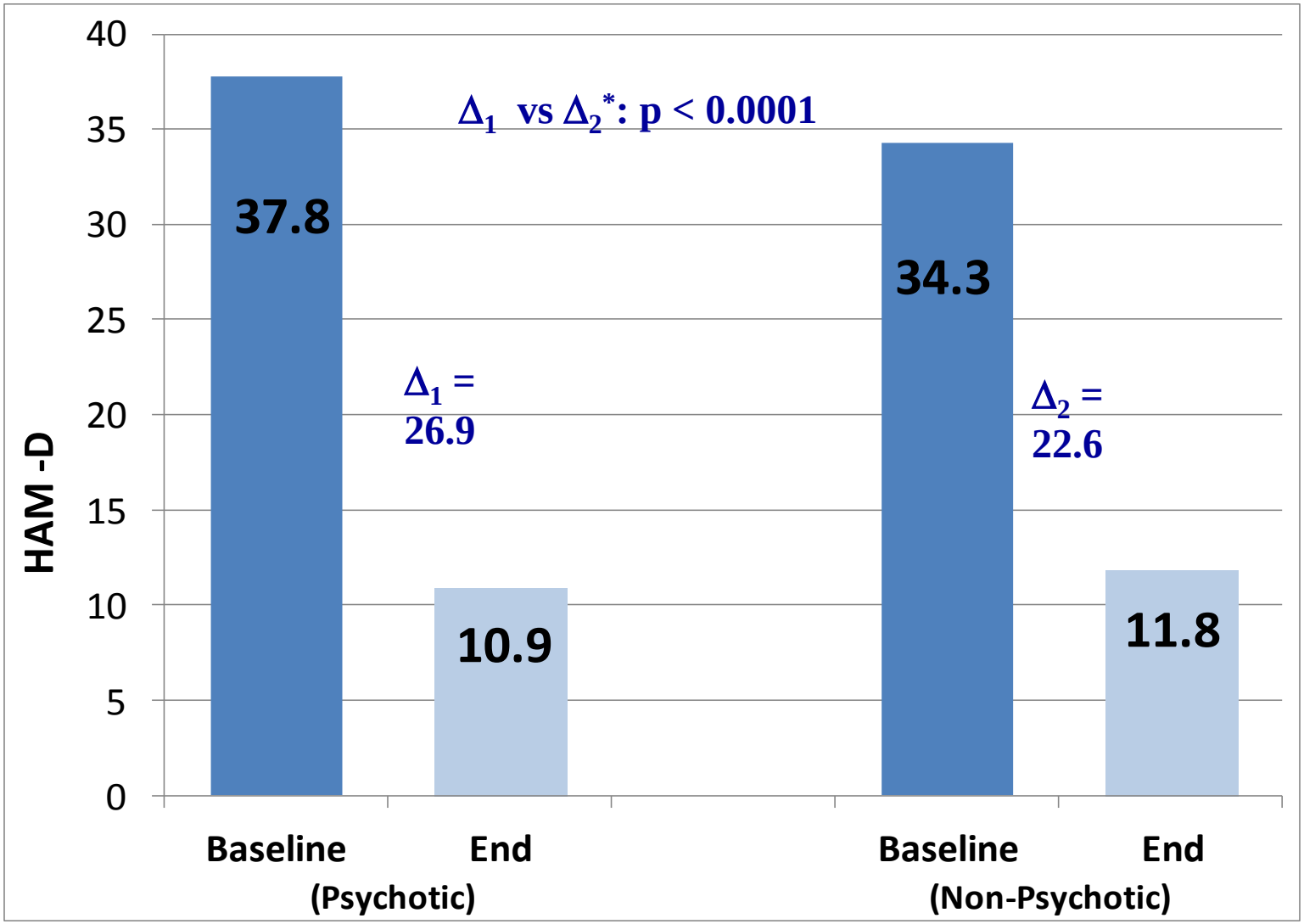
Figure 1. Participant flow for acute electroconvulsive therapy (ECT) phase (phase 1) and randomized continuation phase (phase 2). C-ECT indicates continuation ECT; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.

Remitter Status for Patients Entering Phase I and for Patients Completing Phase I (N=530)



Kellner CH, et al., Arch Gen Psychiatry. 2006 Dec;63(12):1337-44.

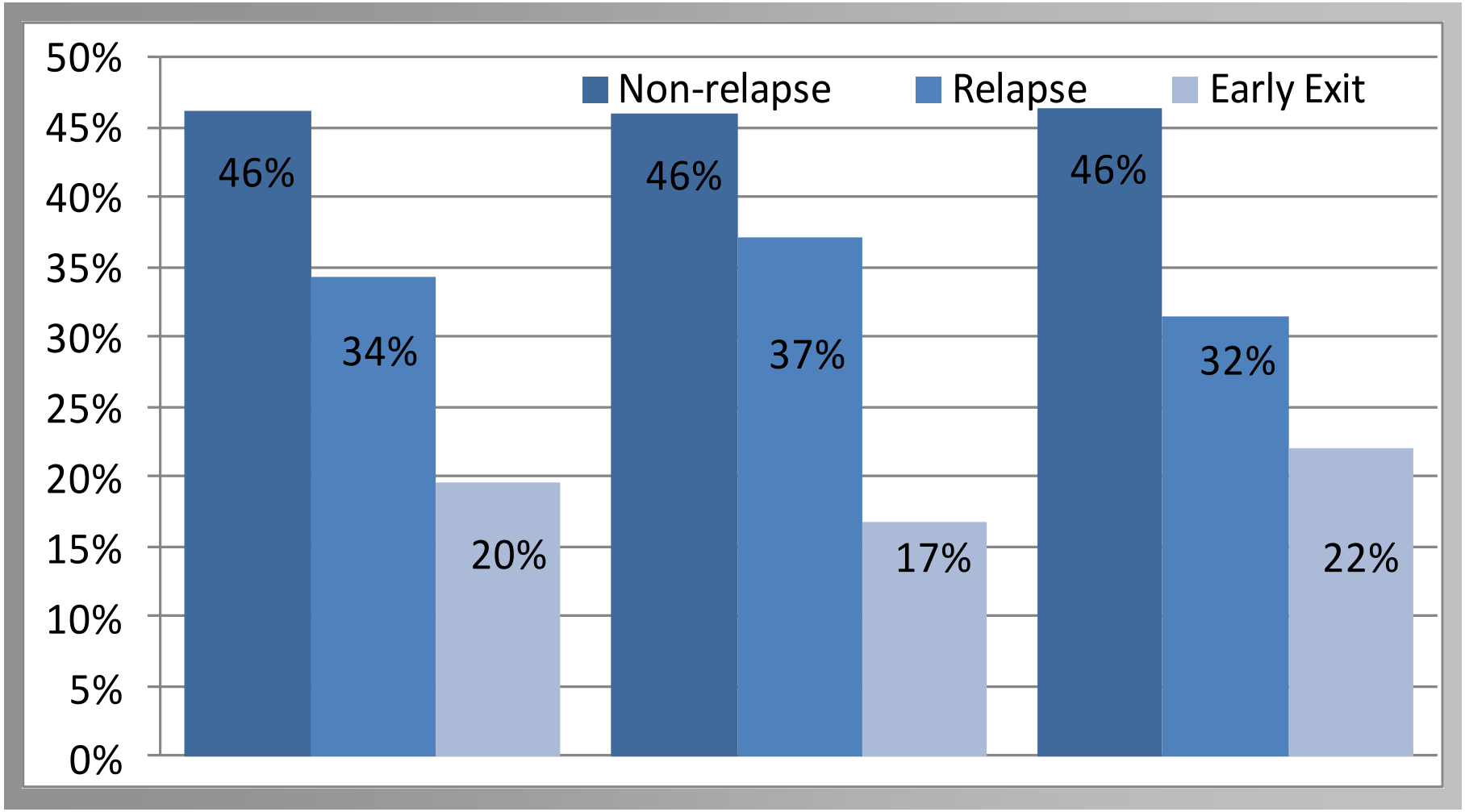
Depression Ratings by Psychosis Status
Phase I (n = 530)



*: pooled t-test

Kellner CH, et al., Arch Gen Psychiatry. 2006 Dec;63(12):1337-44.

CORE I: Relapse Status at 6 Months

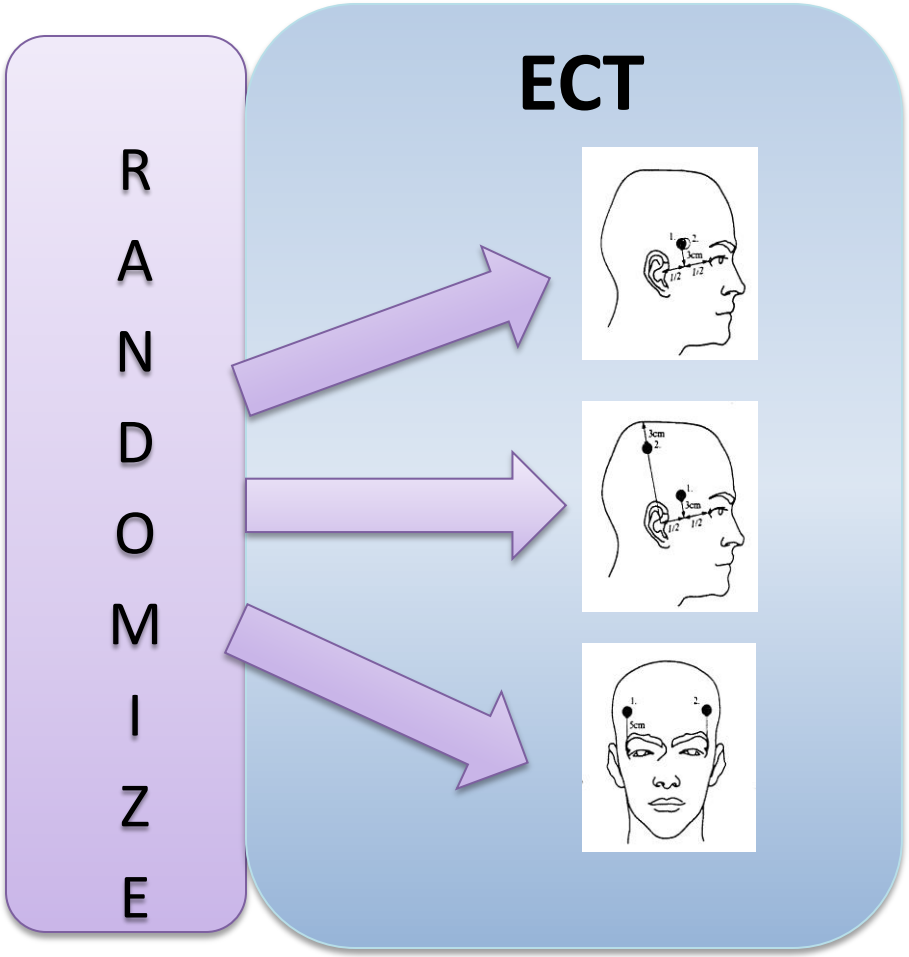


Kellner CH, et al., Arch Gen Psychiatry. 2006 Dec;63(12):1337-44.

Conclusions from the First Core Study

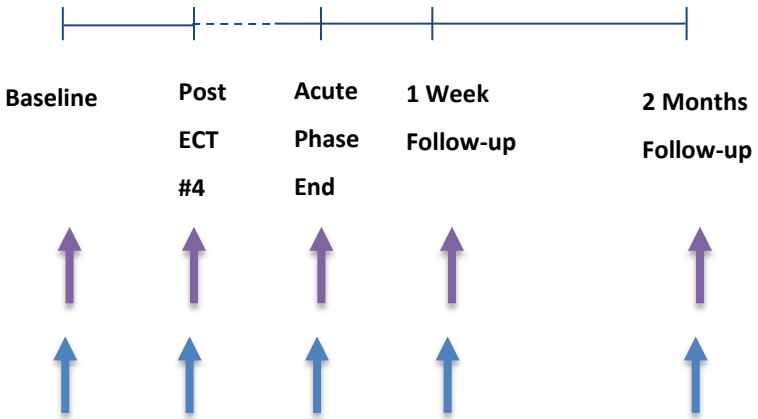
- Standard Bilateral ECT confirmed as an excellent antidepressant. (Phase I)
- Replication of superior response of psychotic depression. (Phase I)
- Fixed schedule of monomodality C-ECT as protective as drug combination. (Phase II)

CORE II: Three Electrode Placement

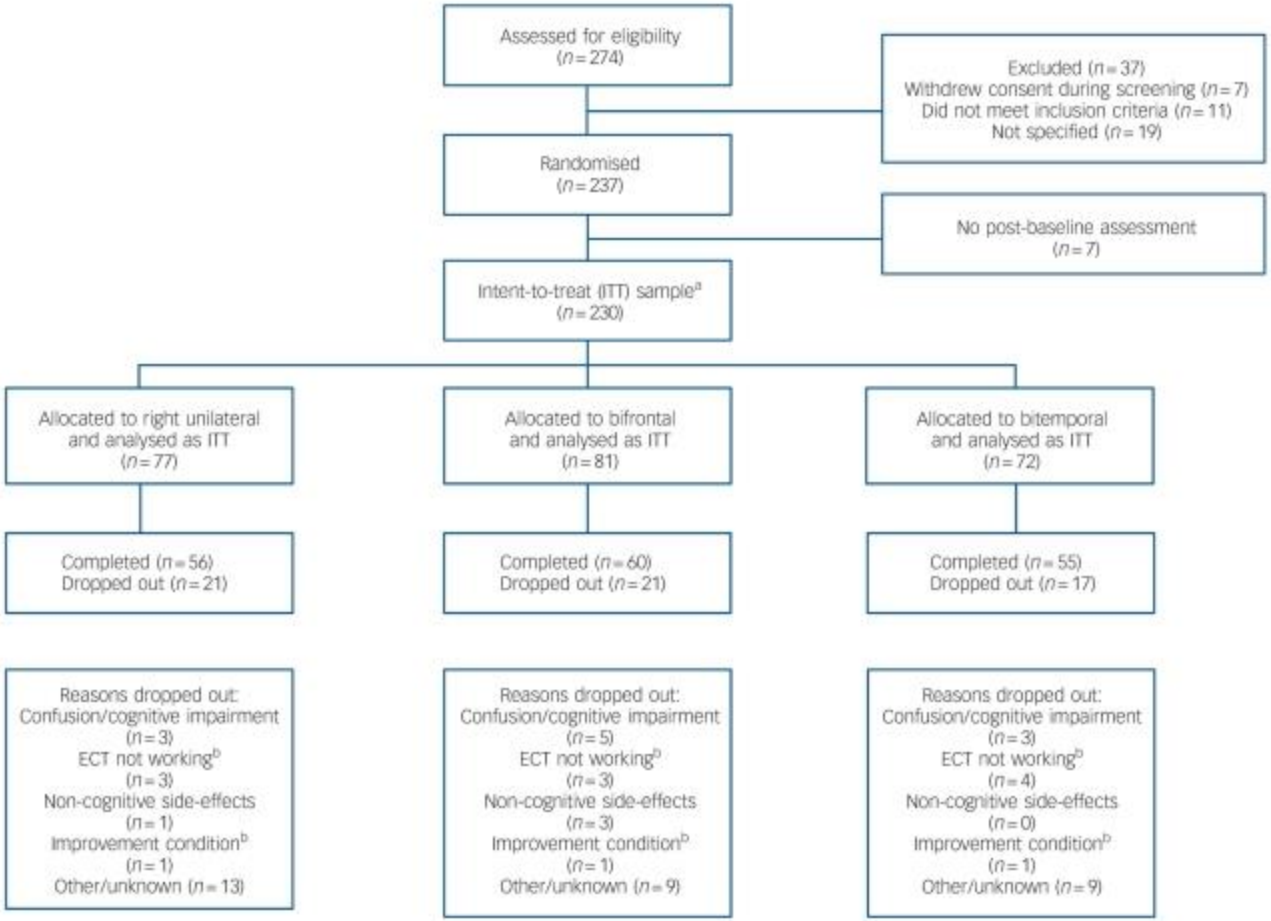


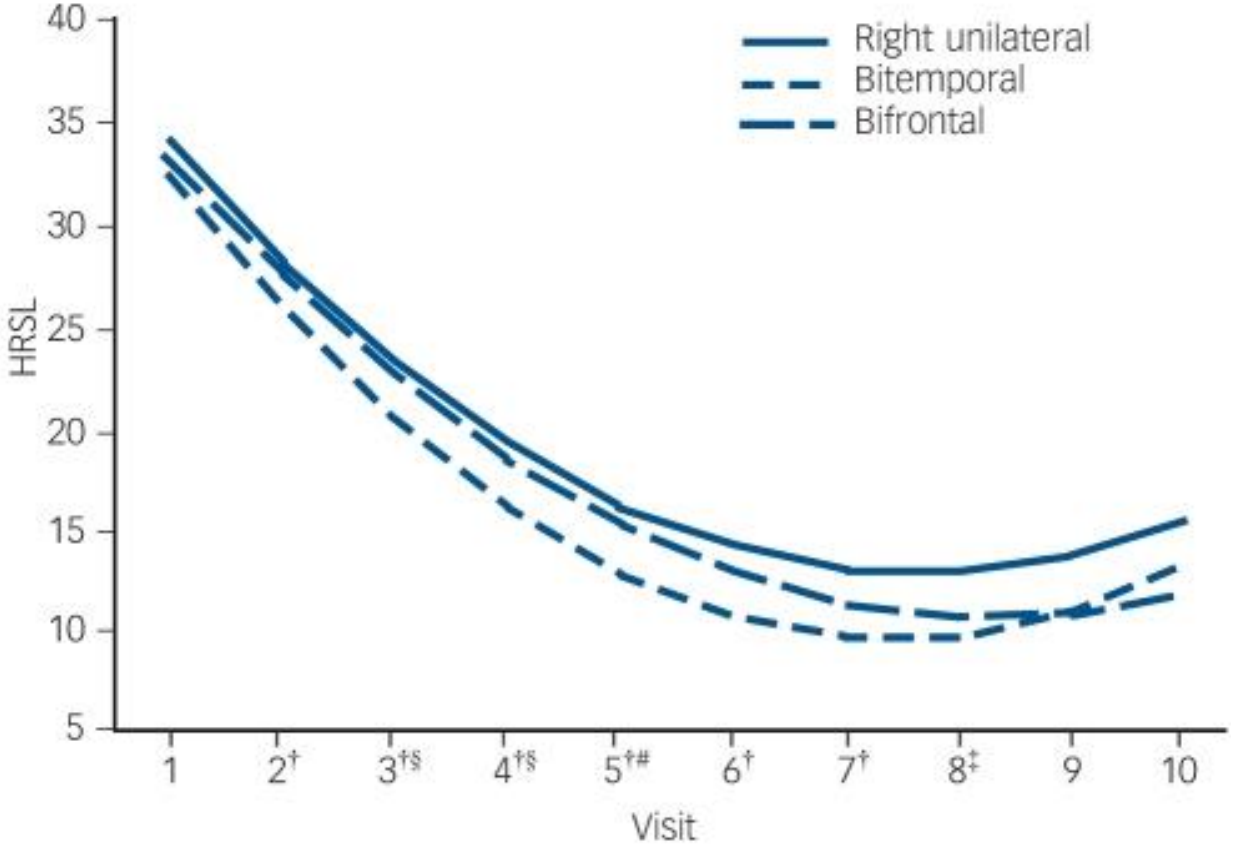
HAM-D_{24}
(acute phase: 3x/week)

Neuropsych. battery

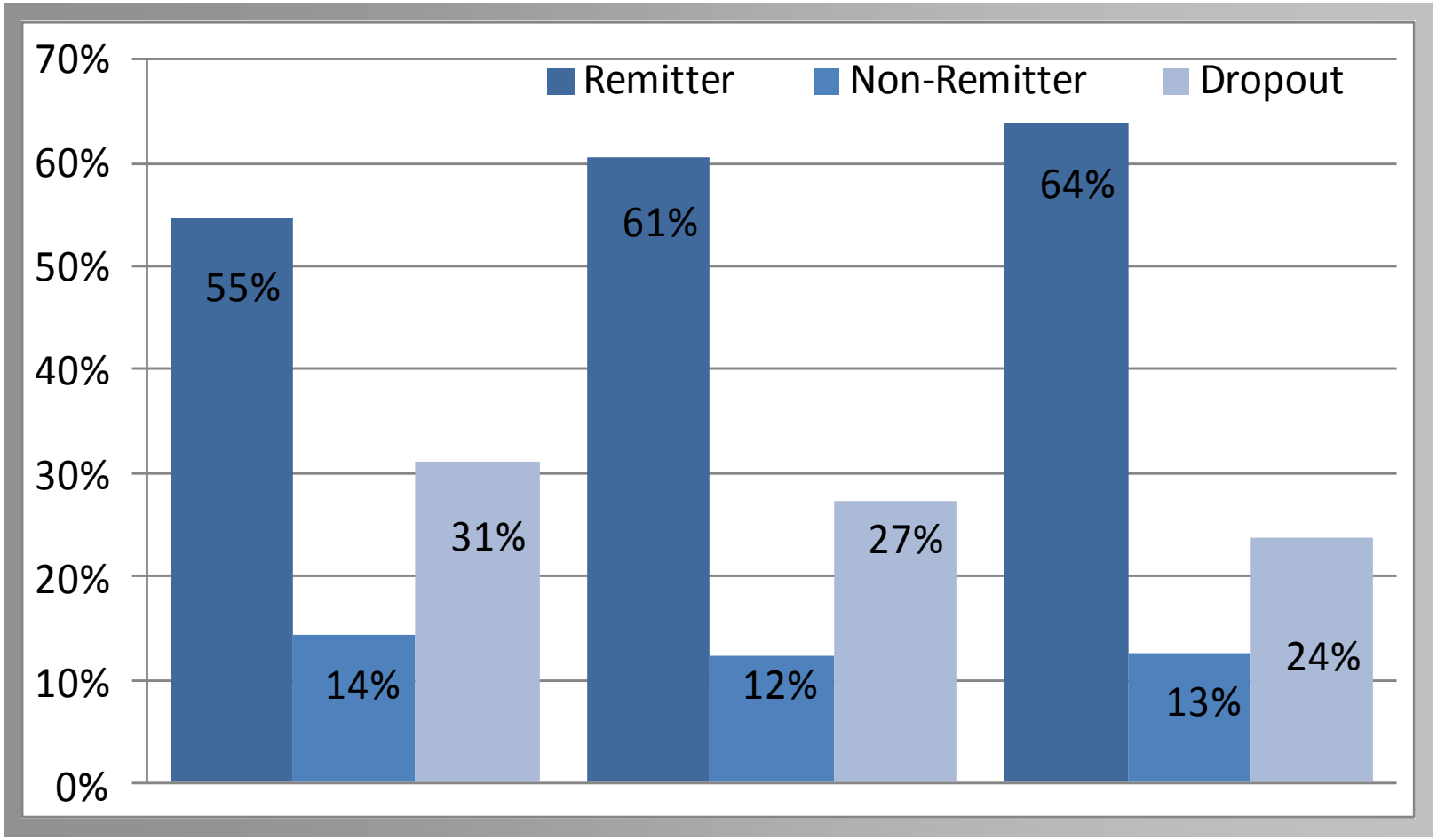


- Unipolar **or** Bipolar Major Depression
- Baseline HAM-$D_{24} \geq 21$
- 3x/week


Assessed for eligibility (n = 274)
Excluded (n = 37)
Withdrew consent during screening (n = 7)
Did not meet inclusion criteria (n = 11)
Not specified (n = 19)
Randomised (n = 237)
No post-baseline assessment (n = 7)
Intent-to-treat (ITT) sample[a] (n = 230)
Allocated to right unilateral and analysed as ITT (n = 77)
Allocated to bifrontal and analysed as ITT (n = 81)
Allocated to bitemporal and analysed as ITT (n = 72)
Completed (n = 56)
Dropped out (n = 21)
Completed (n = 60)
Dropped out (n = 21)
Completed (n = 55)
Dropped out (n = 17)
Reasons dropped out:
Confusion/cognitive impairment (n = 3)
ECT not working[b] (n = 3)
Non-cognitive side-effects (n = 1)
Improvement condition[b] (n = 1)
Other/unknown (n = 13)
Reasons dropped out:
Confusion/cognitive impairment (n = 5)
ECT not working[b] (n = 3)
Non-cognitive side-effects (n = 3)
Improvement condition[b] (n = 1)
Other/unknown (n = 9)
Reasons dropped out:
Confusion/cognitive impairment (n = 3)
ECT not working[b] (n = 4)
Non-cognitive side-effects (n = 0)
Improvement condition[b] (n = 1)
Other/unknown (n = 9)

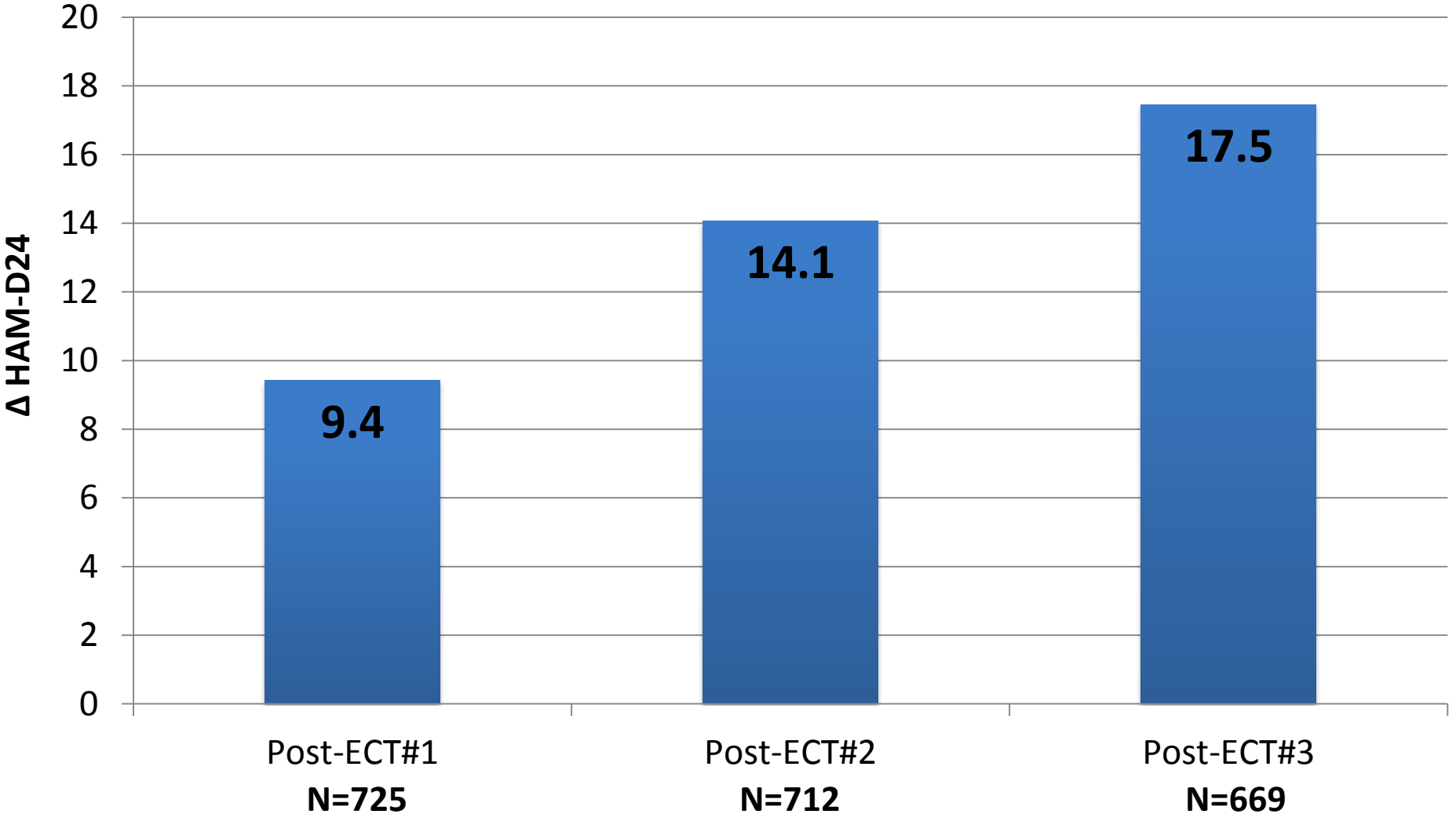

Right unilateral
Bitemporal
Bifrontal
HRSL
40
35
30
25
20
15
10
5
1
2†
3†§
4†§
5†#
6†
7†
8‡
9
10
Visit

CORE II: Remission Outcome by EP



Kellner et al., Br J Psychiatry. 2010 Mar;196(3):226-34.

CORE I, II Pooled:
Decrease in HAM-D_{24} after first 3 ECT

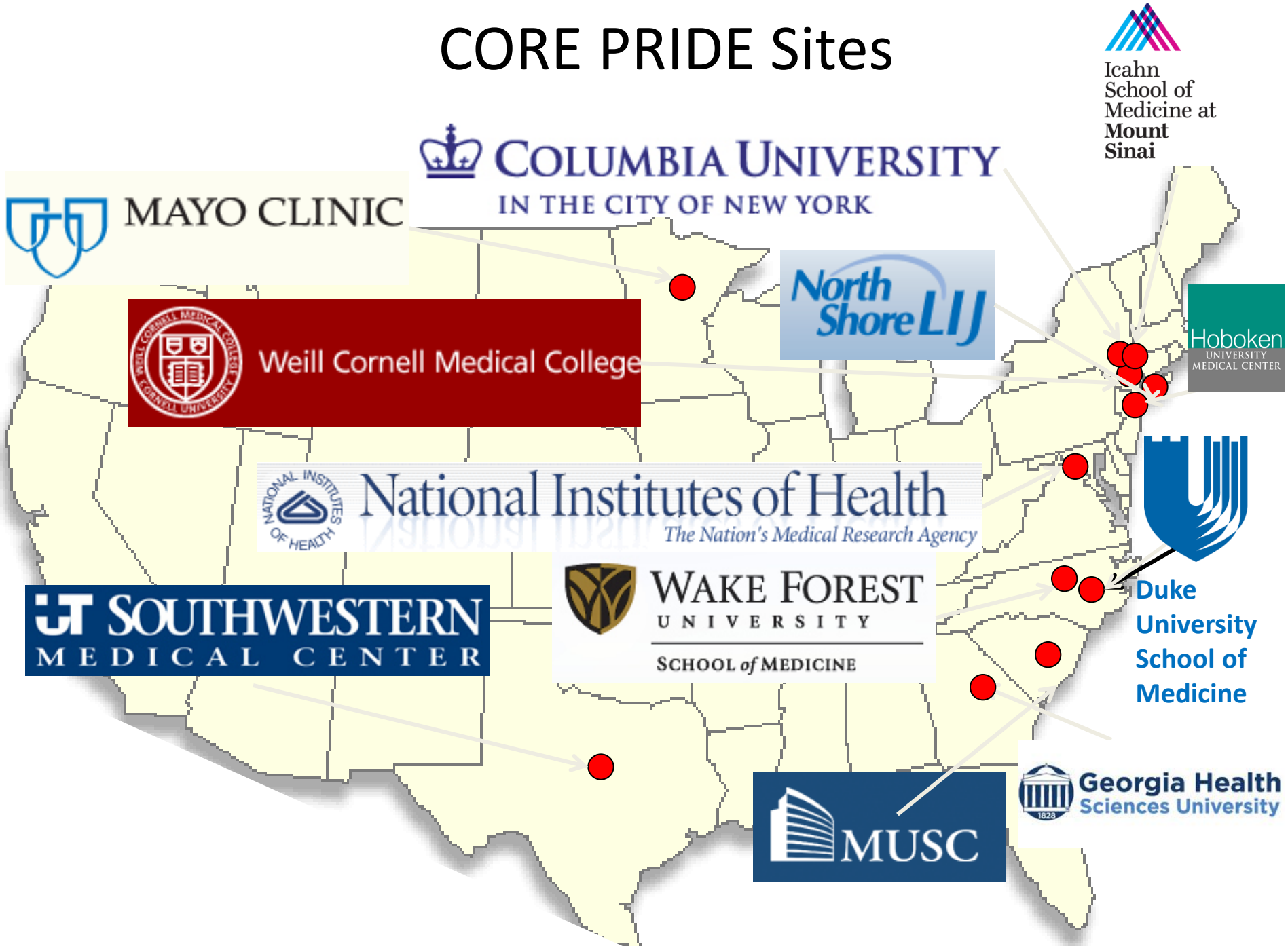


CORE data: combined C-ECT-3EP data set, unpublished

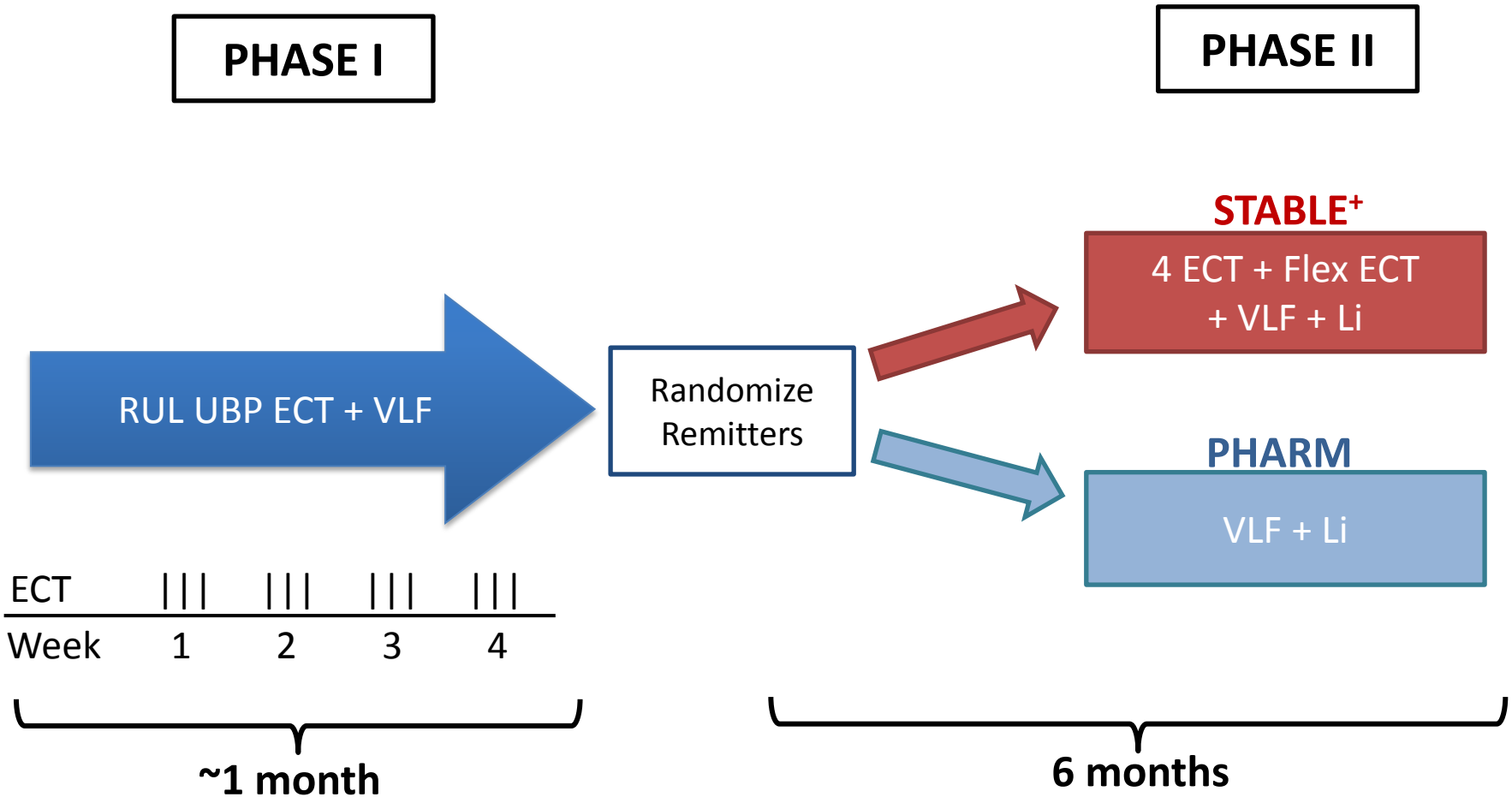
Conclusions from the Second Core Study

- RUL, BF and BT electrode placements all effective antidepressant techniques.
- BT has faster antidepressant effect.
- Be careful not to confuse group data with individual patient experience (a substantial minority of patients will need switch to BL electrode placement).

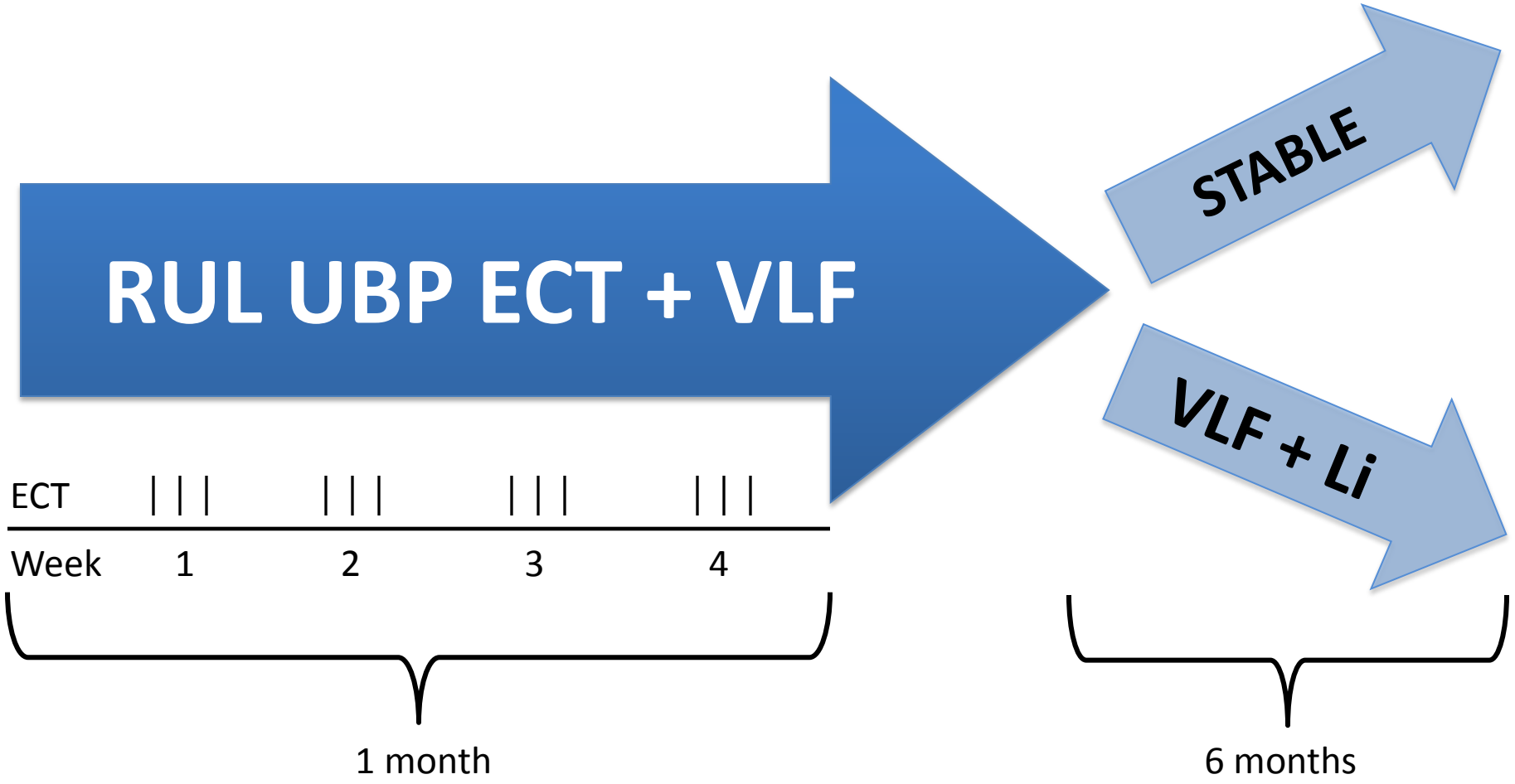
CORE PRIDE Sites



Prolonging Remission in Depressed Elderly (PRIDE)



PRIDE Phase I



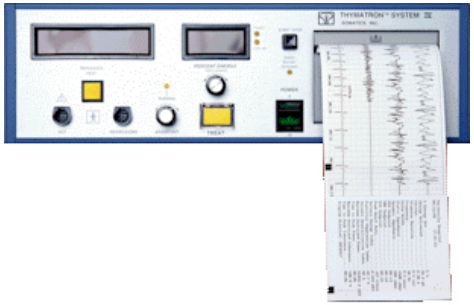
PRIDE Selection Criteria

- **Inclusion**
  - ≥60 yr, MDE, Unipolar (MINI)
  - Baseline HRSD≥21 (24-item)
  - ECT clinically indicated, competent to give consent
- **Exclusion**
  - bipolar disorder, schizophrenia, schizoaffective disorder, mental retardation
  - delirium, dementia, or substance abuse/dependence in past 6 months
  - general medical condition or CNS disease that may affect cognition or response to treatment.
  - medical condition contraindicating Li or VLF
  - Failure to respond to adequate trial of Li + VLF, or ECT, in the current episode, or history of intolerance to Li or VLF.

PRIDE Medication Procedures

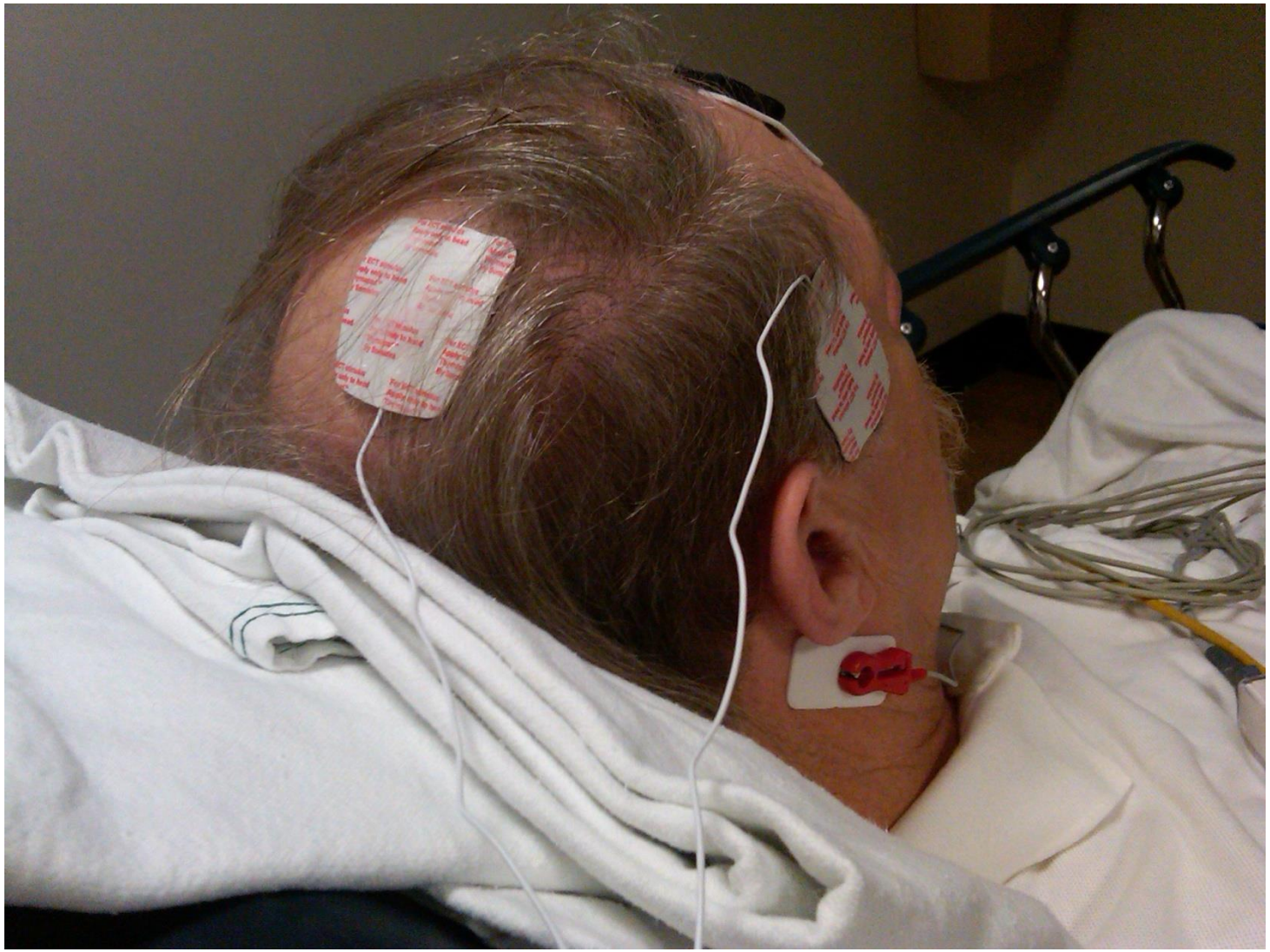
- Washout
  - 1 week pre Phase 1 ECT
- Venlafaxine
  - started 1-5 days prior to ECT at 37.5 mg, increase by 37.5 mg q3D in AM to target 225 mg
- Rescue Meds
  - lorazepam up to 3 mg qD

PRIDE ECT Procedures

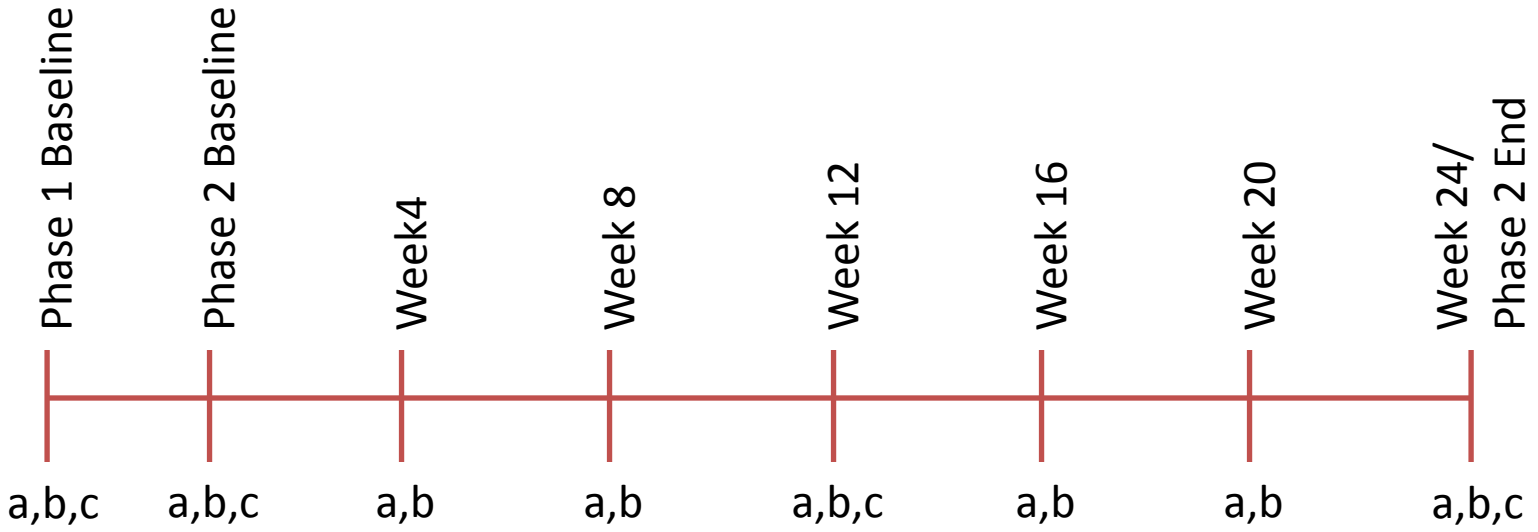


- Dose Titration (5, 10, 15, 20 %)
- 6x Seizure Threshold RUL (0.25 ms) ECT 3/wk
- Anesthesia
  - Glycopyrrolate (0.2 mg IV) (first procedure only)
  - Methohexital (0.75 mg/kg)
  - Succinylcholine (0.75 mg/kg)
- Adequate seizure ≥15s motor
- Midcourse dose increase if response plateaus

RUL Electrode Placement

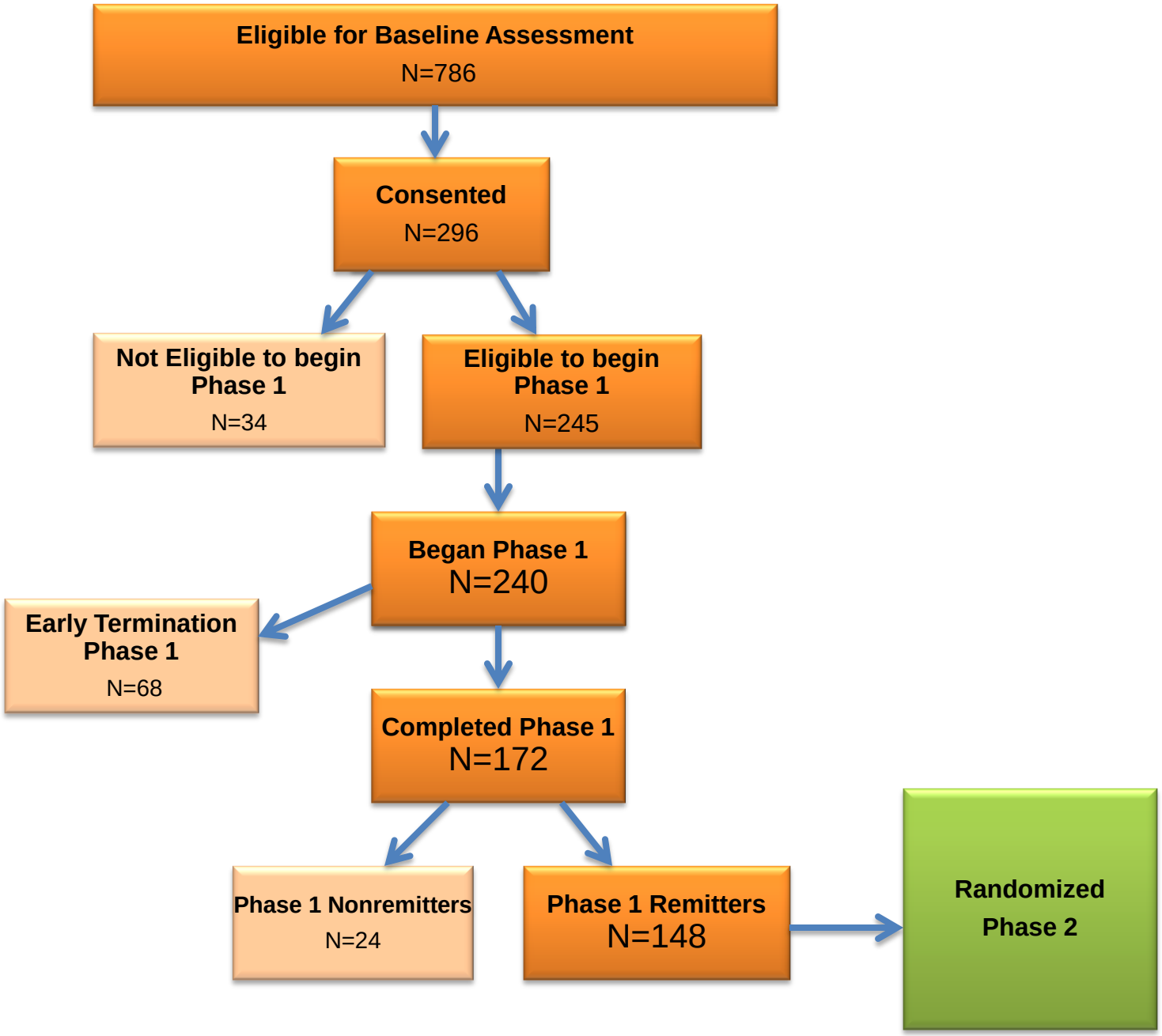


Neuropsychological Testing



Assessment "a": Orientation/Global Status	Assessment "b": Memory	Assessment "c": Executive Function
•Mini-Mental State Examination (MMSE)	•California Verbal Learning Test (CVLT-II) •Autobiographical memory interview-Short Form (AMI-SF)	•Trail Making Test A/B •Stroop •DRS-IP •D-KEFS Verbal Fluency Test

PRIDE Phase I Consort Chart



PRIDE Phase I Baseline Data (n = 240)

- Age (mean): **69.9**
- HAM-D_{24} (mean): **31.2**
- Psychosis: **11.7%**

Seizure Threshold Data

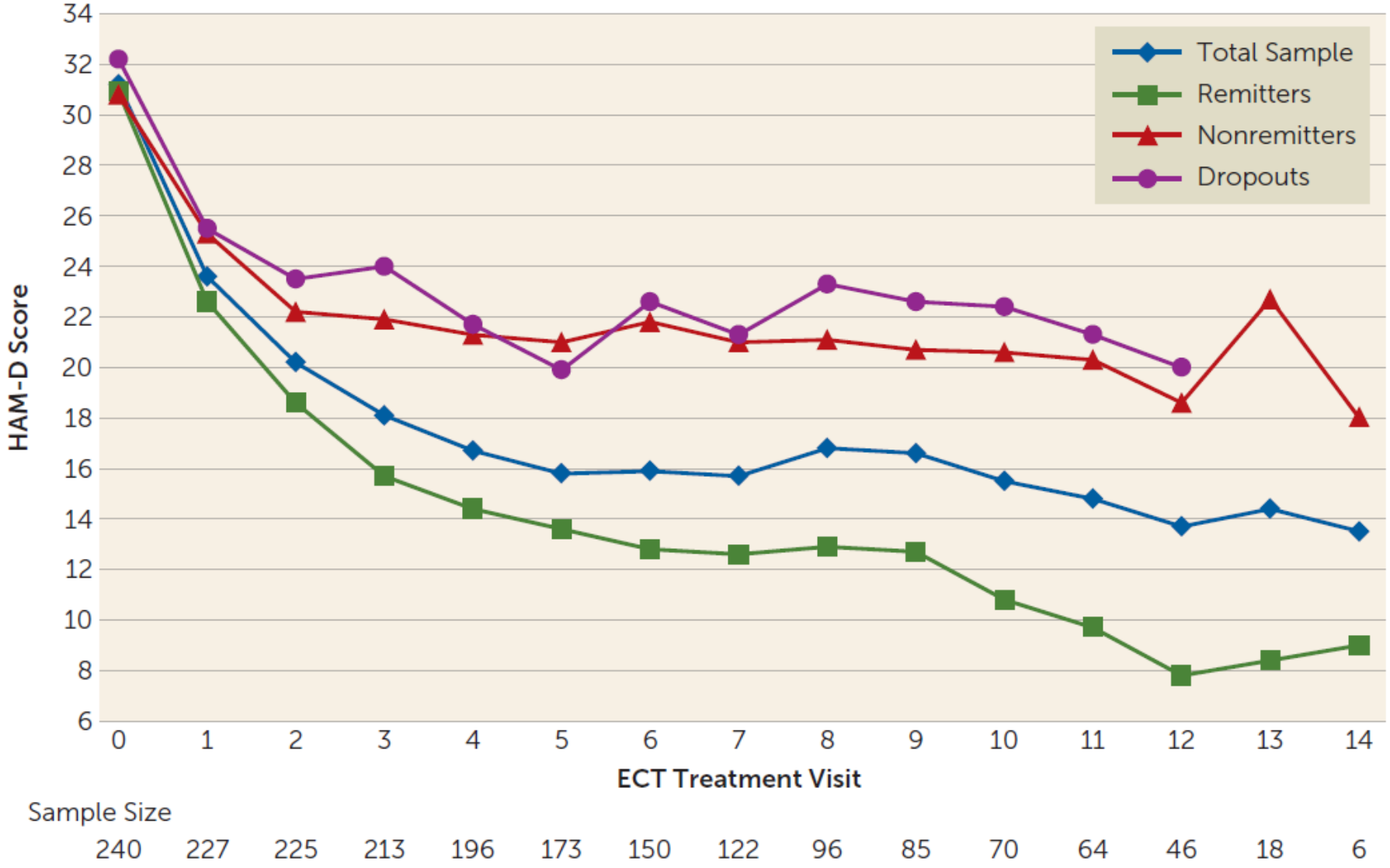
Baseline Seizure Threshold (mC), n=238

	Mean	Range
Total	30.5	19.0 - 150.0

Total number of Stimuli at Phase I Baseline

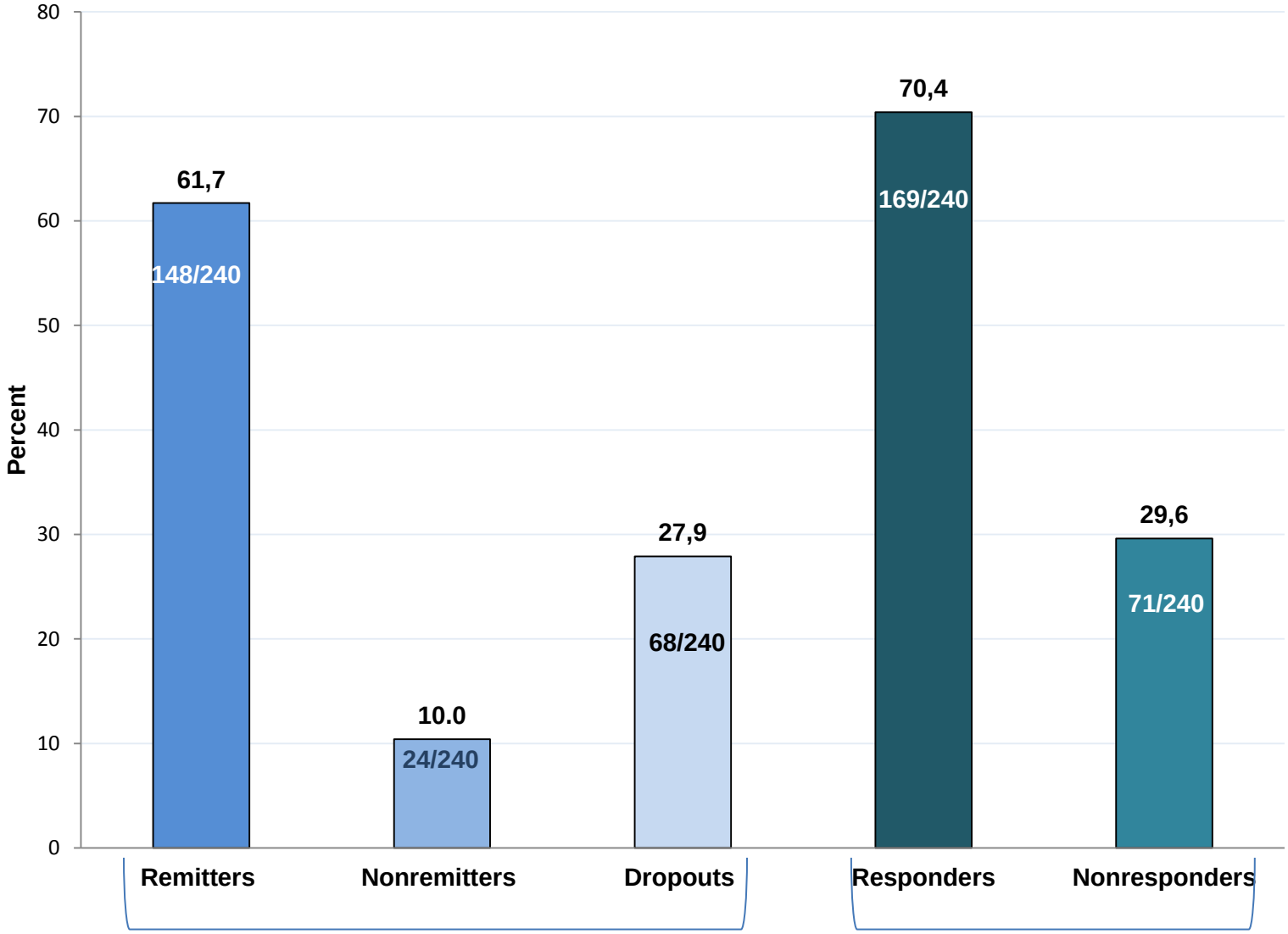
Number stimuli	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	201	83.75	201	83.75
2	34	14.17	235	97.92
3	2	0.83	237	98.75
4	3	1.25	240	100.00

FIGURE 2. Trajectory of Observed Mean Scores on the 24-Item Hamilton Depression Rating Scale (HAM-D), by Outcome Group, in a Study of ECT and Venlafaxine in Geriatric Depression[a]



[a] Visits 15–17 were omitted because of small sample sizes (N=3, 2, 1, respectively), resulting in unstable means.

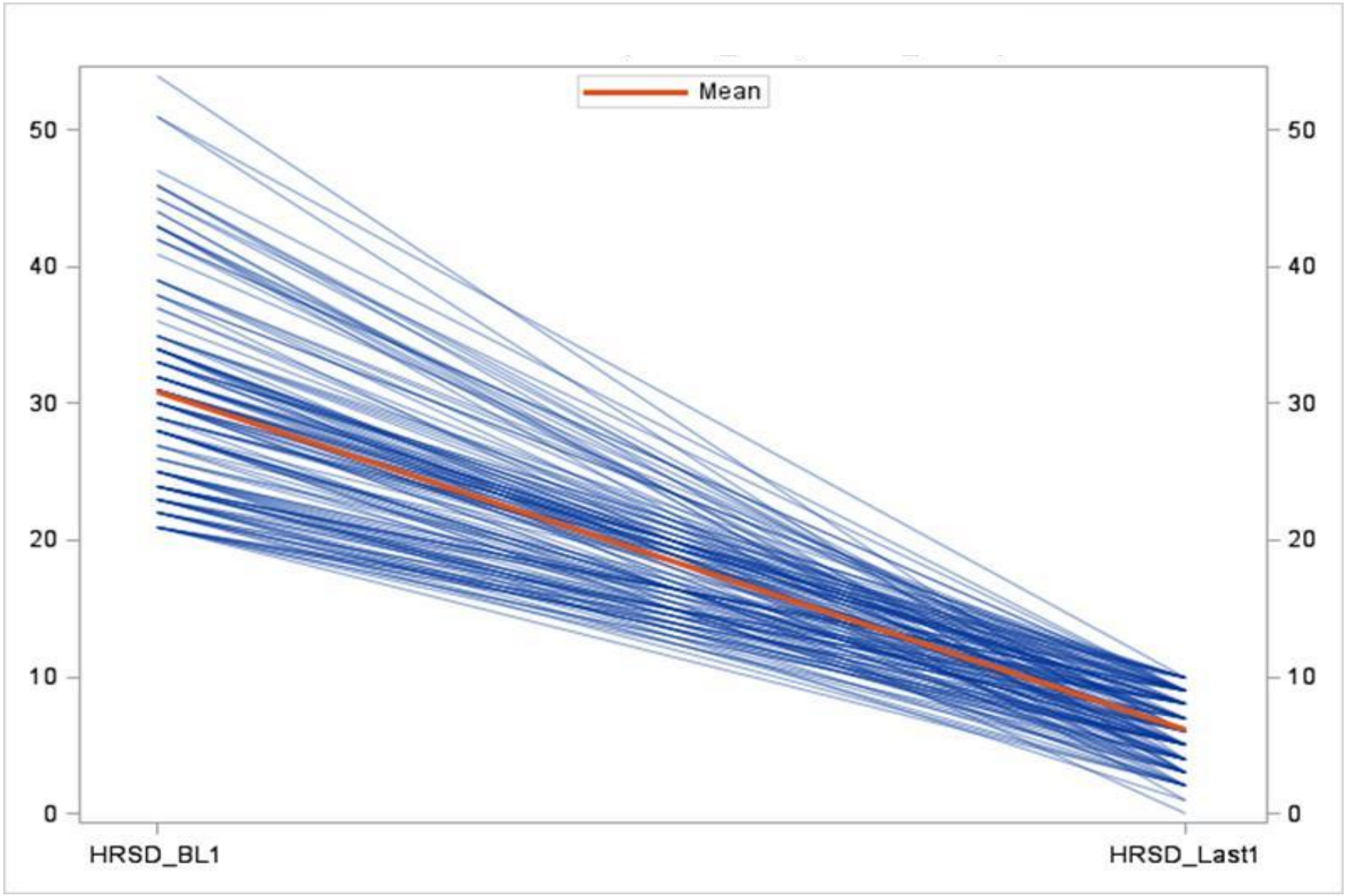
PRIDE Phase I Remission[1] and Response Proportions[2]



[1]Remission: Last two $HRSD_{24} \leq 10$

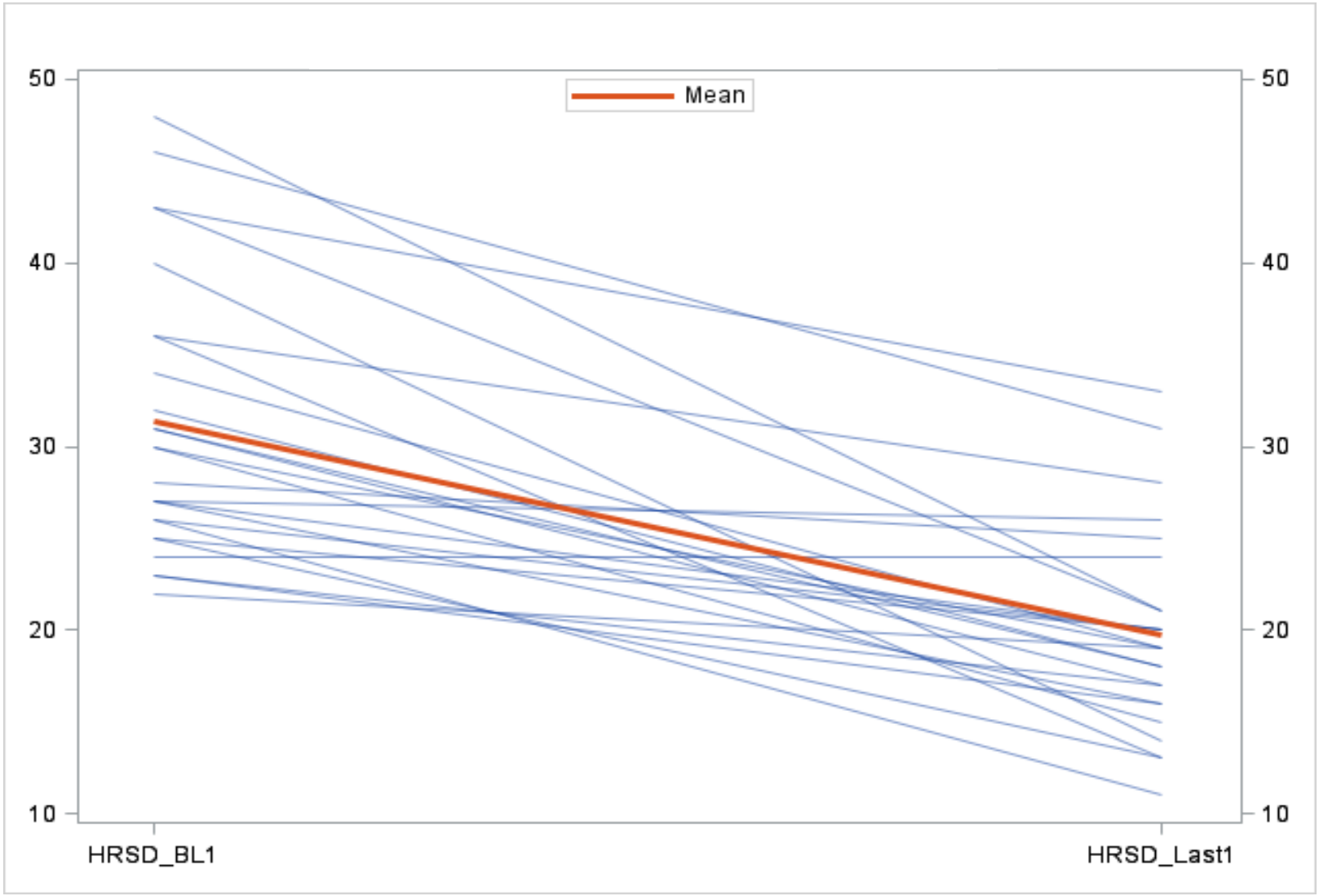
[2]Response: ≥ 50% decrease $HRSD_{24}$ (Baseline - Last)

PRIDE Phase I: Individual Patient HRSD Trajectories for Remitters (n=148)



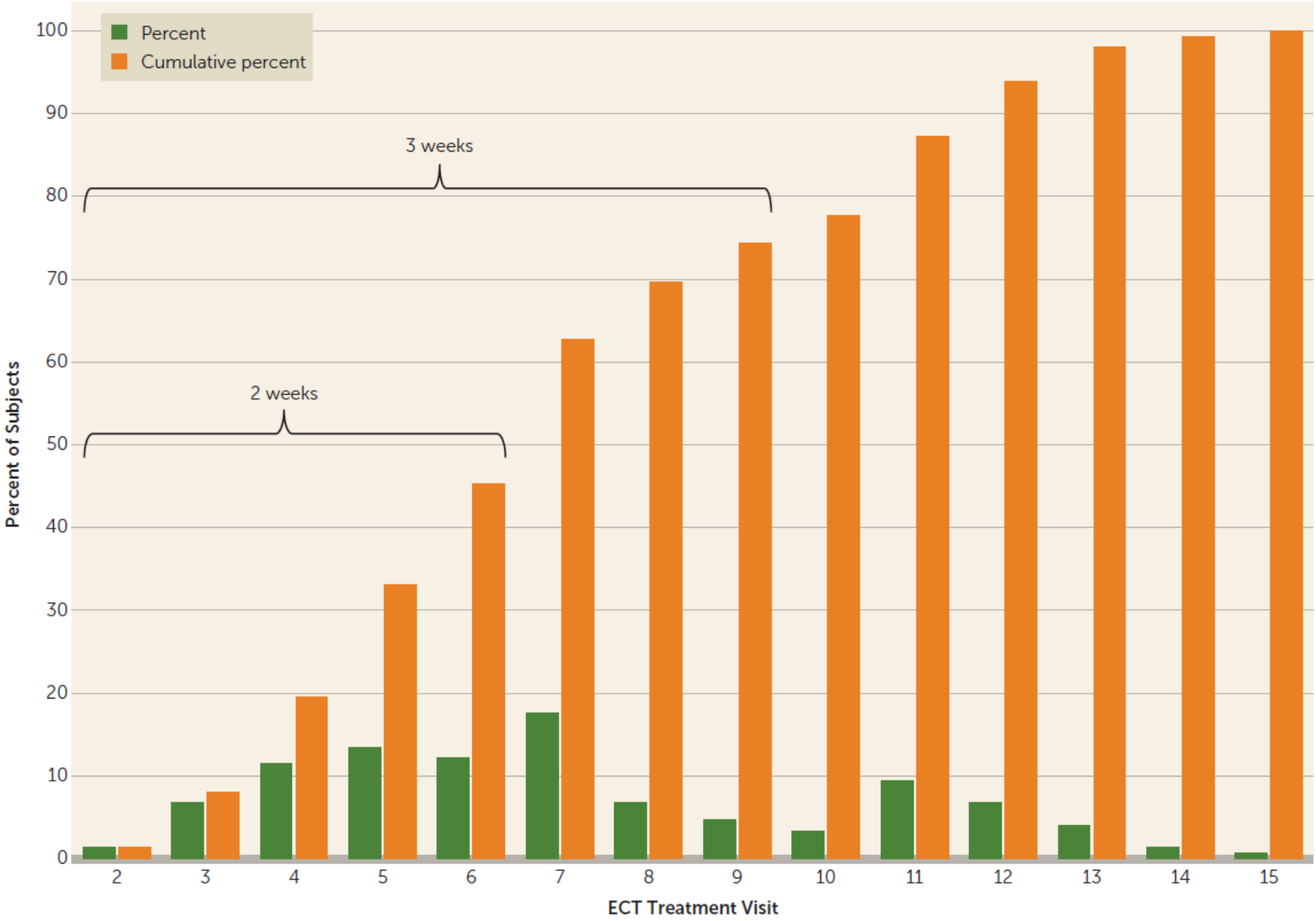
February 10, 2015 data

PRIDE Phase I: Individual Patient HRSD Trajectories for Non-Remitters (n=24)

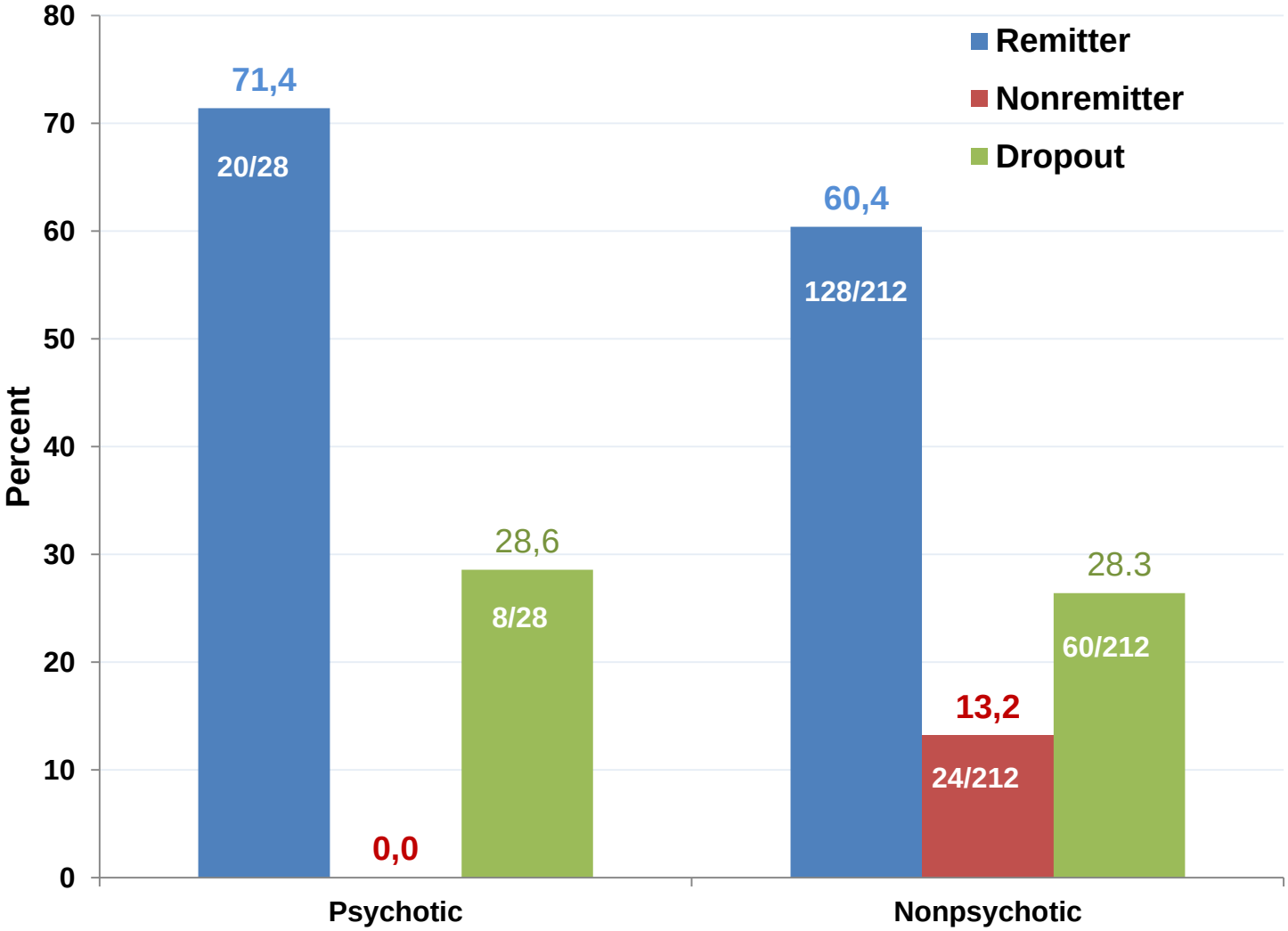


February 10, 2015 data

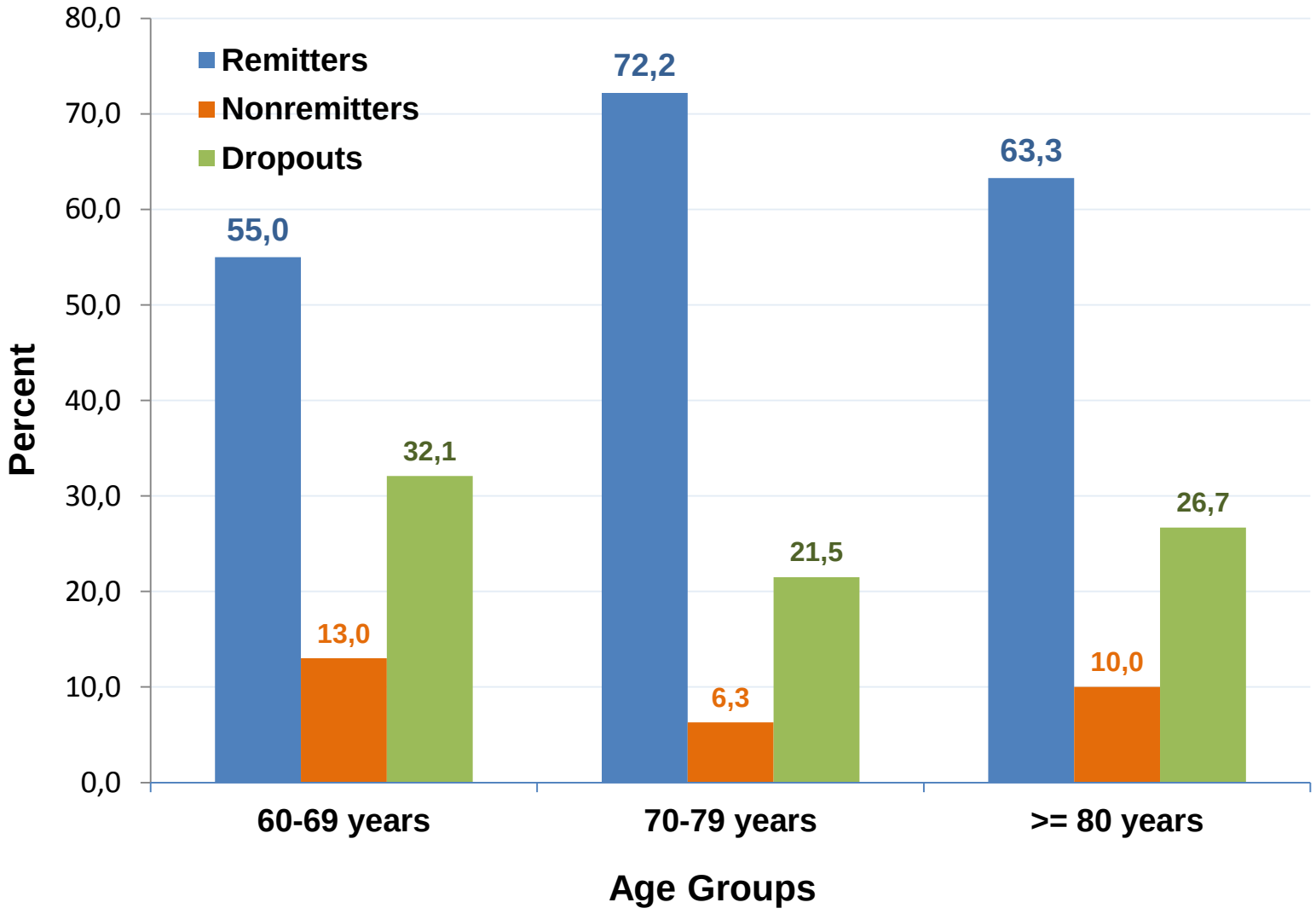
FIGURE 3. Speed of Remission Among Remitted Patients (N=148) in a Study of ECT and Venlafaxine in Geriatric Depression



PRIDE Phase I Outcome by Psychosis Status (n=240)



PRIDE Phase 1 Outcome by Age Category (n=240)

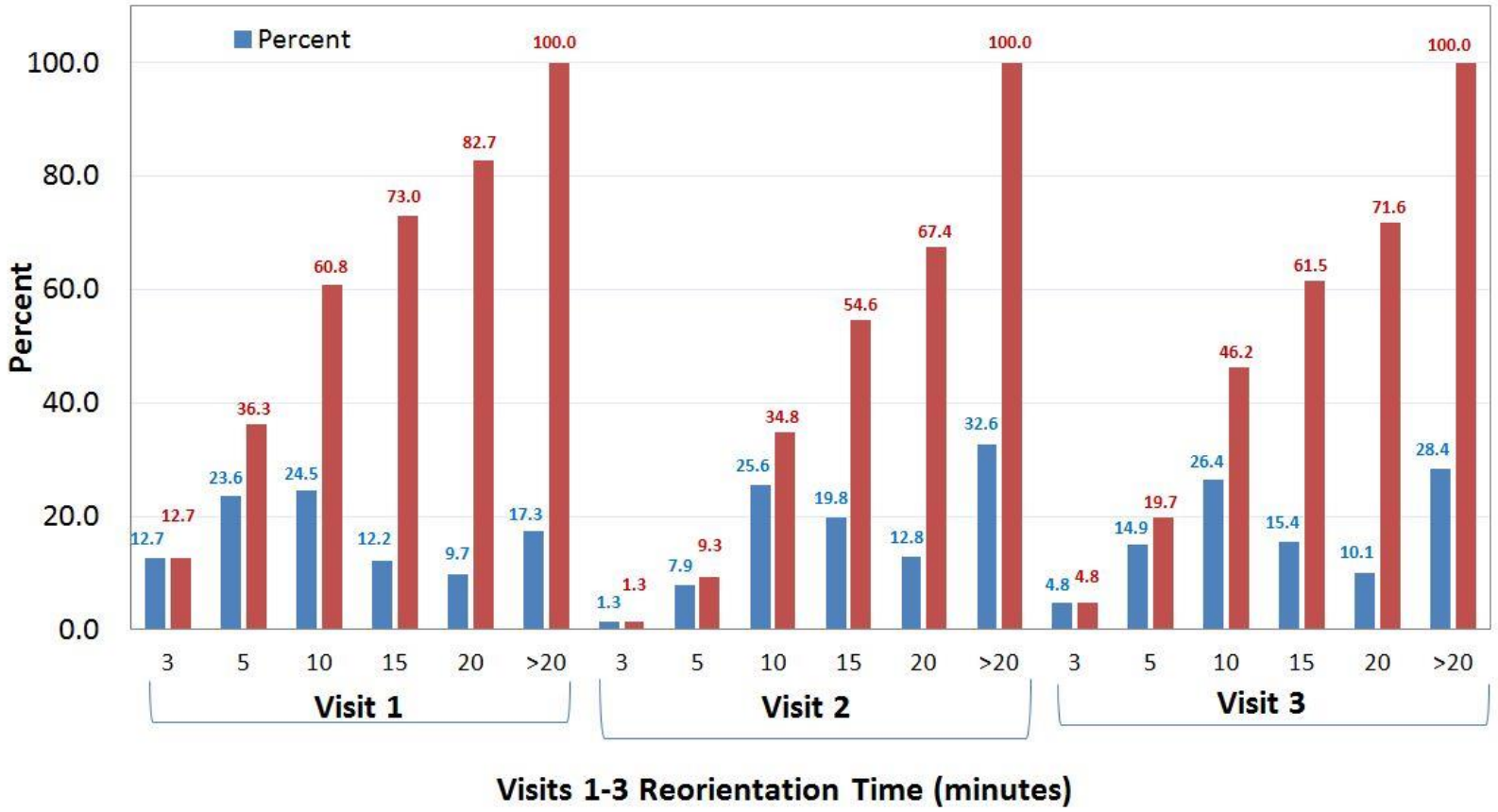


Number of ECT by Phase I Outcome

Outcome	Mean (sd, n)
Remitters	7.3 (3.1, 148)
Nonremitters	12.3 (1.1, 24)
Dropouts	5.0 (3.3,68)

Time to Reorientation

Figure S1: Phase1 (Visits 1-3) Frequency Distribution of Reorientation Time after Treatment

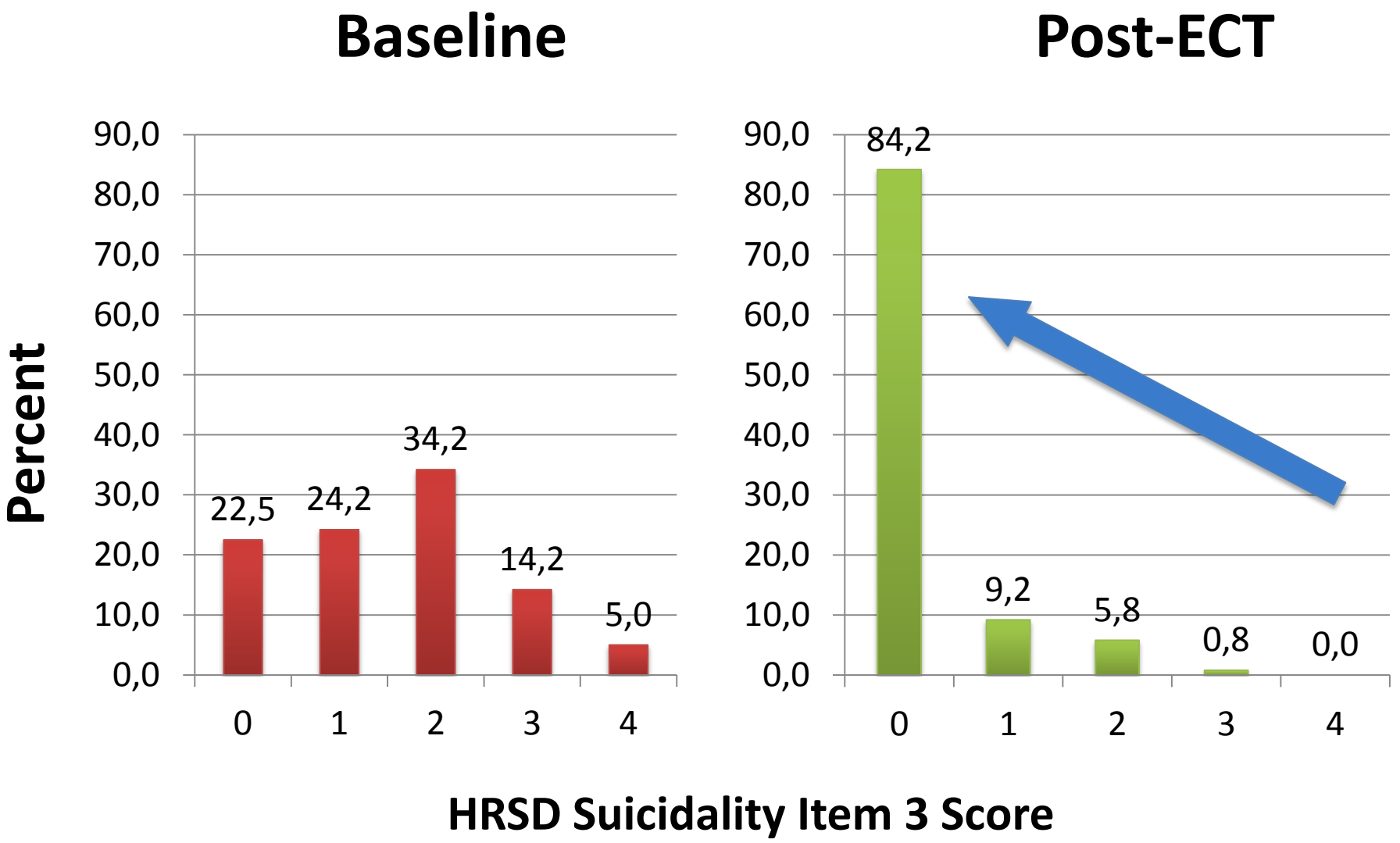


MMSE

- Baseline mean: **27.5** (sd=2.4, n=239)
- Post ECT mean: **27.6** (sd=2.6, n=238)

  p<0.562, paired t-test

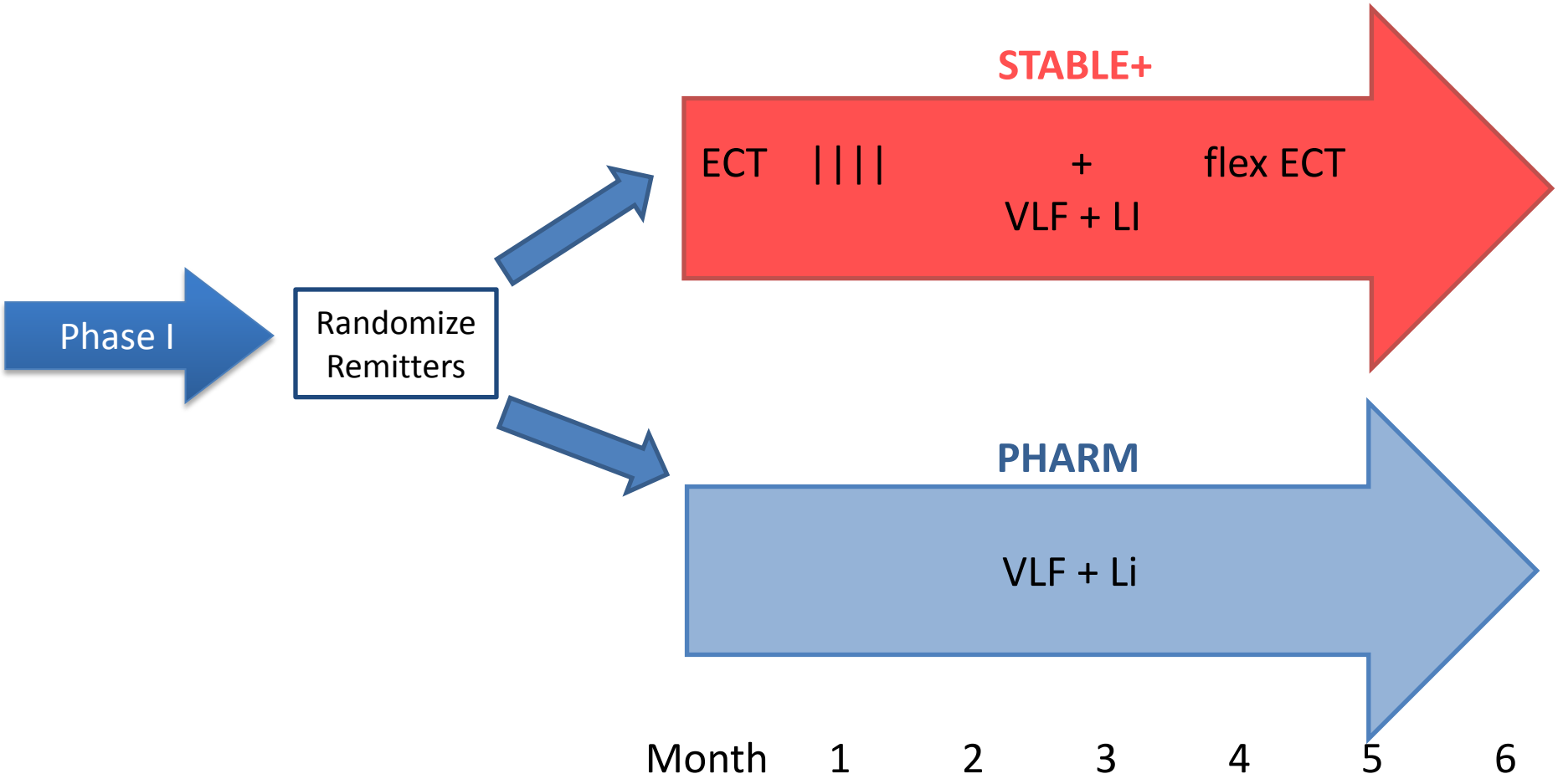
HRSD Suicidal Rating Data



Conclusions from PRIDE Phase I

- RUL-UBP ECT is a viable treatment technique for geriatric depression
- RUL-UBP is rapidly acting (including on suicidality)
- RUL-UBP is generally well-tolerated

PRIDE Phase II



Symptom-**T**itrated **A**lgorithm-**B**ased **L**ongitudinal **E**CT

STABLE

STABLE Algorithm

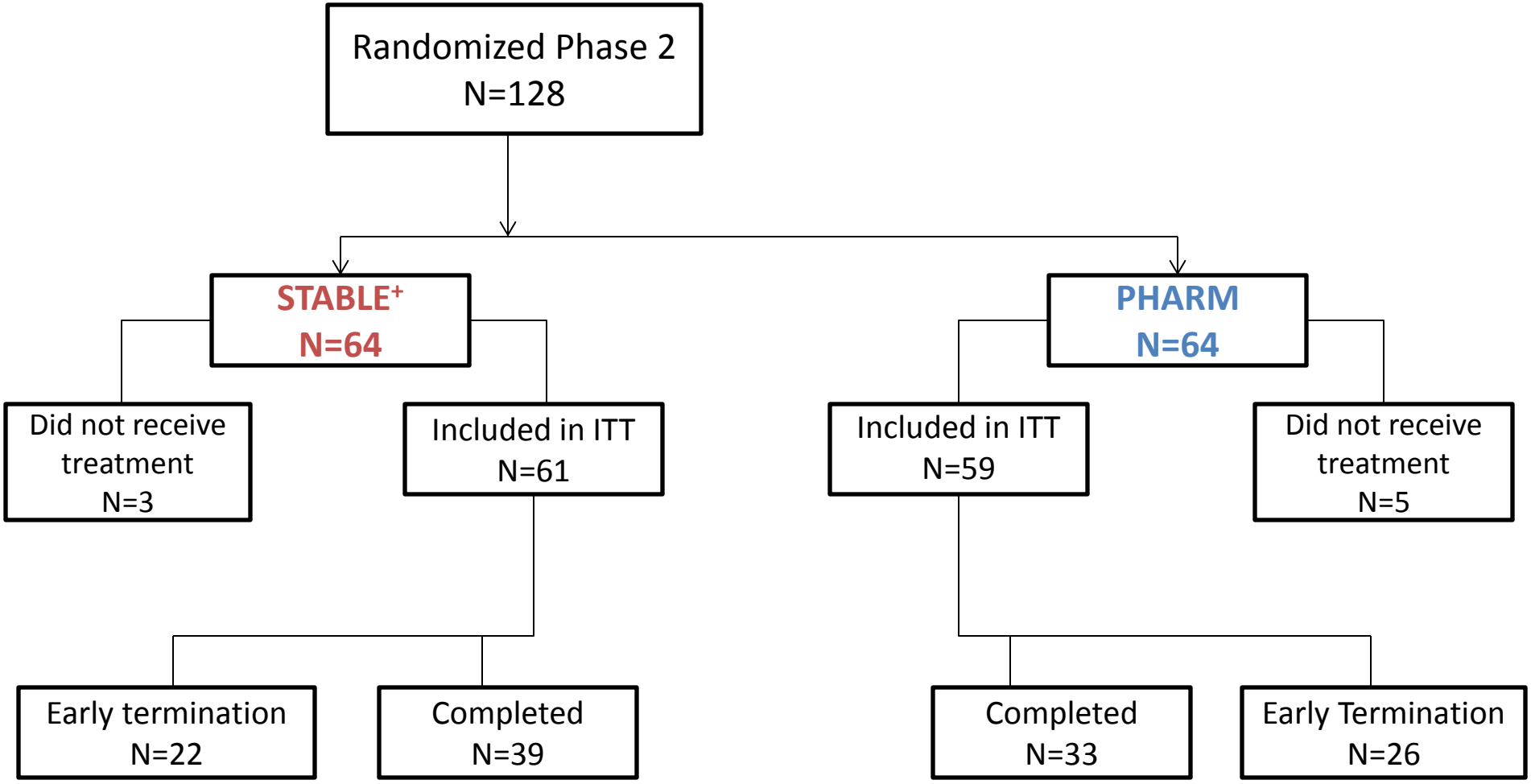
Phase 2: Weeks 1-4: Fixed ECT Schedule: 1 ECT 2-5 days after randomization, 1 ECT 7-12 days after randomization, 1 ECT 14-19 days after randomization, 1 ECT 23- 28 after randomization (Total = 4 ECT in one month

Phase 2: Weeks 5-24: Symptom Titrated Schedule

Number ECT per week	Description	Corresponding HAM-D Condition	Relapse potential
0	**Current symptomology level very low**, *or*	HAM-$D_C \leq 6$, *or*	Low
	Current symptomology level low to moderate, with only small drift from baseline level, *or*	$7 \leq$ HAM-$D_C \leq 12$ *and* HAM-D_C-HAM-$D_B \leq 2$, *or*	Low
	Last 2 HAM-D in remitted range with flat trajectory (remission stable with less than 2 point change from previous)	$7 \leq$HAM-$D_C \leq 10$ *and* $5 \leq$HAM-$D_P \leq 10$ *and* (HAM-D_C-HAM-D_P) ≤ 2	Low
2	**Current symptomology level very high**, *or*	HAM-$D_C \geq 16$, *or*	High
	Current symptomology level moderate to high, with trajectory increasing rapidly and large drift from baseline	$11 \leq$ HAM-$D_C \leq 15$, *and* (HAM-D_C-HAM-D_P) ≥ 3, *and* ($HRSD_C$-$HRSD_B$) ≥ 8	High
1	**Patients not requiring 0 or 2 received 1 ECT**	HAM-D_C intermediate between criteria for "low" or "high" relapse potential	Moderate
Discontinue study	HAM-D_C *and* HAM-$D_P \geq 21$, or patient suicidal, or patient requires psychiatric hospitalization		

[a]HAM-D_B= baseline HAM-D; HAM-D_C=current visit HAM-D; HAM-D_P= previous visit HAM-D (visit preceding current visit)

PRIDE Phase II Consort Chart

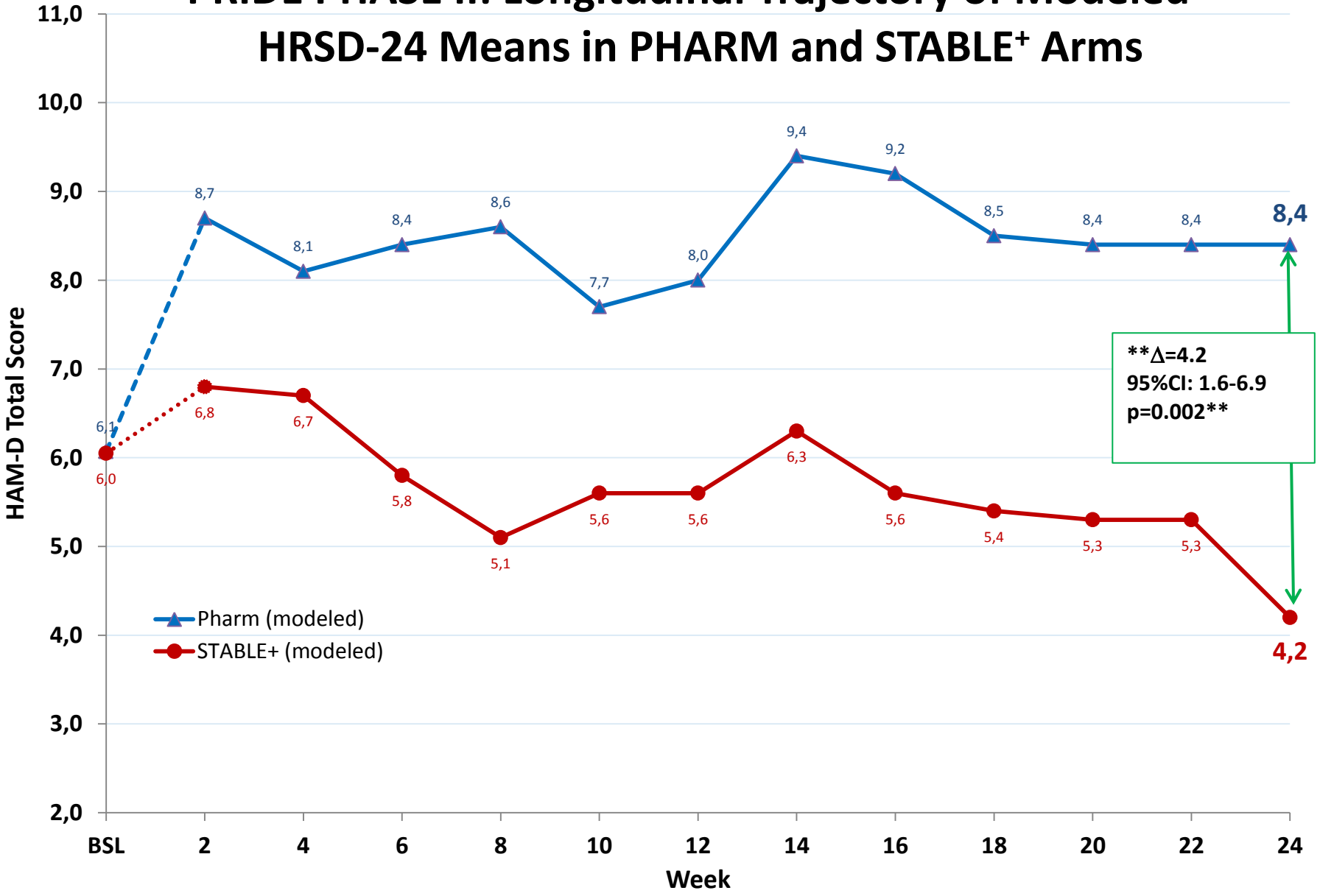


Li and VLF in Phase II

- VLF dose (mean): 192 mg (no difference between arms)

- Li level (mean): 0.53 mEq/l (PHARM)
- Li Level (mean): 0.36 mEq/l (STABLE^{+})

PRIDE PHASE II: Longitudinal Trajectory of Modeled* HRSD-24 Means in PHARM and STABLE+ Arms



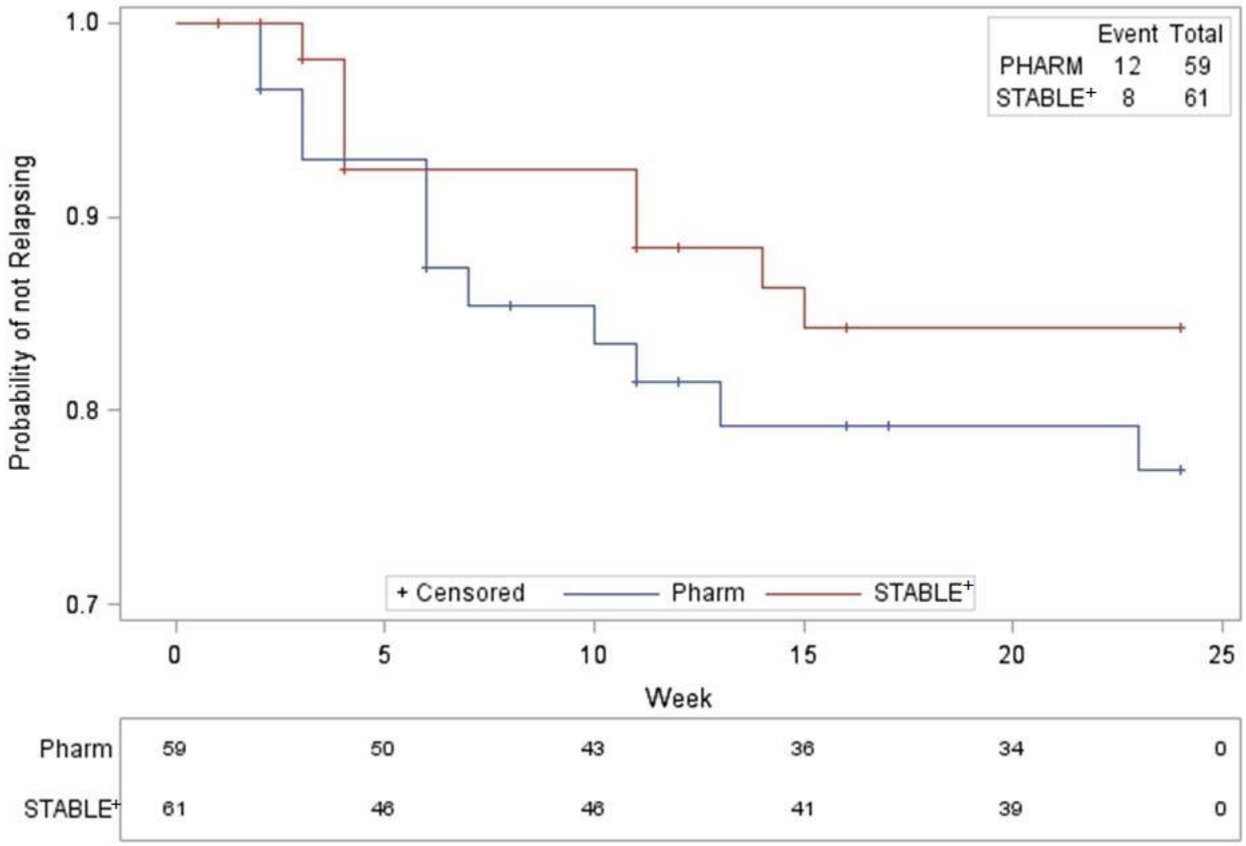
*Model contains treatment, time, treatment-by-time with HRSD baseline, site, psychosis as adjustment covariables

** Δ=4.2 is difference in baseline, site, psychosis adjusted least squares means for STABLE+ vs PHARM

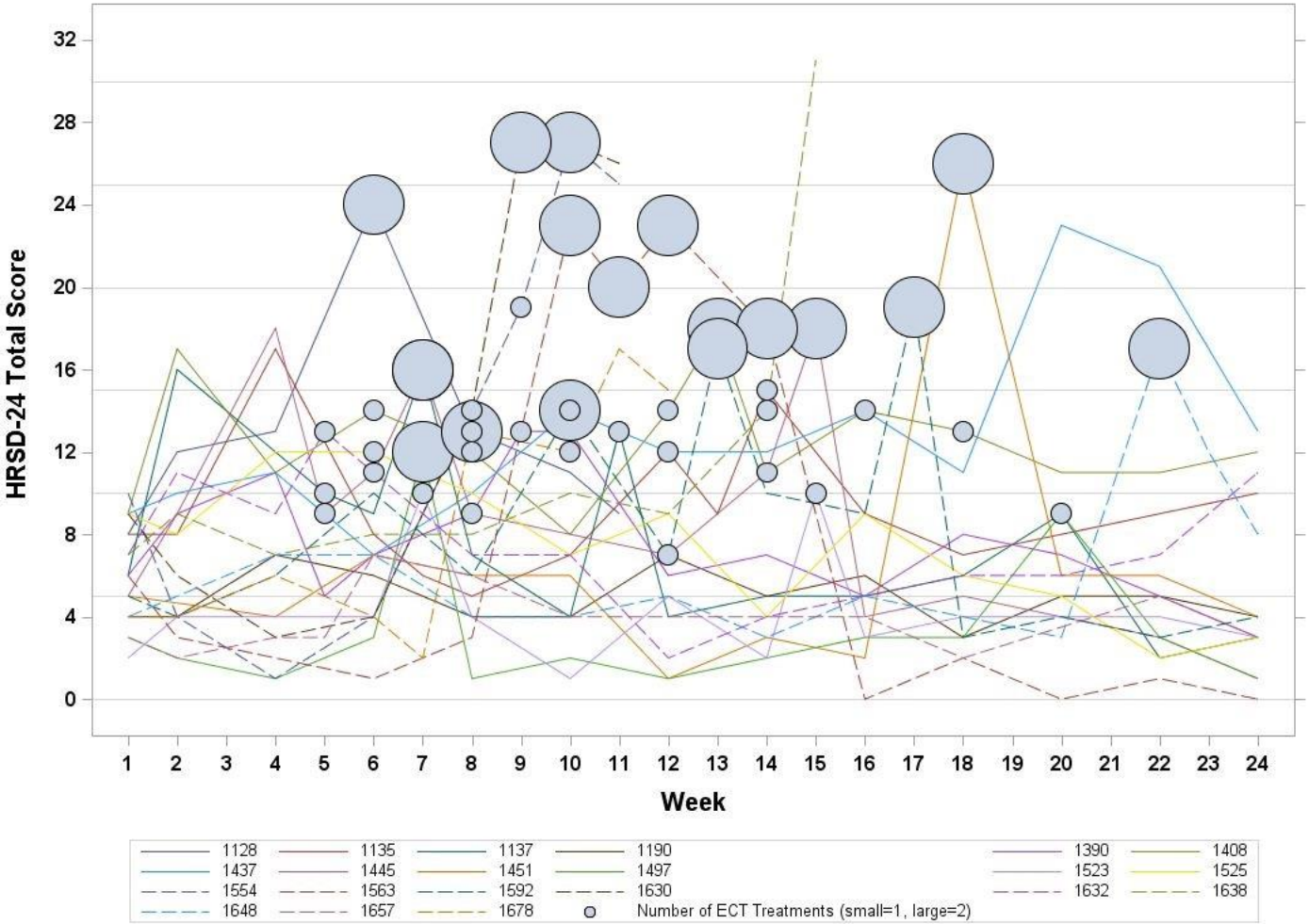
PRIDE Phase II Results

- At 6 month study endpoint, mean HRSD-24 score for STABLE^{+} = 4.2 vs PHARM = 8.4 (p=0.002)
- CGI-S: odds of being rated “not at all ill” were 5.2 times greater for STABLE^{+} vs PHARM
- Odds of relapsing 1.7 times higher for PHARM vs STABLE^{+}
- 34.4% (21/61) of STABLE^{+} patients received at least one additional ECT in weeks 5-24

PRIDE PHASE II: Time to relapse for patients in STABLE^{+} and PHARM treatment arms



PRIDE PHASE II: The effect of additional ECT



Relapse* by Treatment Group

- Overall Relapse Rate: 16.7%

- PHARM Relapse Rate: 20.3%
- STABLE+ Relapse Rate: 13.1%

*Relapse defined as when a patient was removed from the study for safety because of worsening of MDD requiring alternative treatment (2 consecutive $HRSD_{24} \geq 21$, or patient required psychiatric hospitalization, or patient became suicidal).

PRIDE Quality of Life Data (Methods)

- Medical Outcomes Study Short Form 36 (SF36)
- Phase I: 240 patients, pre- and post ECT
- Phase II: 120 remitters, measured q 4 weeks

(McCall WV et al. J Affect Disord 2017;209:39-45, J Psychiatr Res 2018; 97:65-69)

PRIDE Quality of Life Data (Results)

- Phase I: Remitters showed significant improvement in every dimension of QOL
- Phase II: STABLE group had significantly higher QOL scores at week 24
- Changes in QOL with ECT best explained by mood improvement; cognitive variables play only minor role

(McCall WV et al. J Affect Disord 2017;209:39-45, J Psychiatr Res 2018; 97:65-69)

Conclusions from PRIDE PHASE II

- STABLE^{+} was superior to PHARM in maintaining low depression symptom severity for 6 months after remission.
- RUL UBP was safe and well tolerated.
- Practitioners should be liberal in prescribing additional ECT past the acute course (taper, continuation/maintenance).
- Aim is to prevent full syndromic relapse and its attendant catastrophic consequences.

The PRIDE Study and the Conduct of Electroconvulsive Therapy
Questions Answered and Unanswered

Keith G. Rasmussen, MD

Abstract: The recently published PRIDE study (prolonging remission in the depressed elderly) constitutes an important contribution to electroconvulsive therapy (ECT) technique, from the standpoint of both the index course to treat depressive symptoms and the post–remission continuation period to prevent relapse. This study was probably the last large, National Institute of Mental Health–funded, multisite ECT technical study for some time to come, so extracting clinically relevant recommendations is worthwhile. In this commentary, the author discusses evidence from this trial relevant to several important clinical index and continuation ECT technical issues and elaborates several unanswered questions deserving further consideration.

Key Words: electroconvulsive therapy, depression

(*J ECT* 2017;33: 225–228)

Rasmussen: PRIDE Q and A

- The PRIDE Study and Index ECT: Right Unilateral Ultrabrief Comes of Age
- Is Right Unilateral Ultrabrief to Be Recommended for all Depressed ECT Patients?
- What is the Best Electrical Dosing Method for unilateral Ultrabrief Pulse Width?

Rasmussen: PRIDE Q and A

- At What Point in a Course of Treatment with Right Unilateral Ultrabrief Should a Switch Be Undertaken to a More Intensive Treatment Method?
- What Should Be the Next-Step Technique for Patients Who Do Not Respond to Unilateral Ultrabrief?
- The PRIDE Study and Continuation ECT: To Use STABLE or Not to Use STABLE?

Rasmussen: PRIDE Q and A

- Should Continuation ECT Be Offered to All Depressed Patients Who Have Remitted With Index ECT?
- Should STABLE Be Considered the Standard of Care for Continuation ECT?
- How and When Should Lithium Be Intermixed With ECT?
- Do Responders, as well as Remitters, Benefit From Adding Continuation ECT to Pharmacotherapy?

Thomas F. Eagleton, 77, a Running Mate for 18 Days, Dies

By ADAM CLYMER

Thomas F. Eagleton, a former United States senator whose legislative accomplishments were overshadowed by his removal as the Democratic vice presidential candidate in 1972 after revelations of mental illness and electroshock therapy, died yesterday in Richmond Heights, Mo. He was 77 and lived outside St. Louis in Clayton, Mo.

Associated Press, 1972

Thomas F. Eagleton, left, and George McGovern in Miami Beach.

What *your* doctor may not know

Psychiatric Drug Facts

with Dr. Peter Breggin

RECENT HIGHLIGHTS OF DR. BREGGIN'S WORK:

$1.5 million jury award in child tardive dyskinesia (TD) 2014

$700,000 settlement in tardive dyskinesia (TD) case in Mass. 2014

$1.5 million jury award for suicide with antidepressant Paxil 2012

Free video series: "Simple Truths About Psychiatry" by Dr. Breggin

Upcoming: Our Best Empathic Therapy Conference--April 17-19, 2015 in Michigan.

HOME
RESUME
LEGAL CASES
BRIEF BIO
ACCOMPLISHMENTS
OUR ORGANIZATION
OUR CONFERENCES
FOR THERAPISTS
HuffingtonPost Blog
NaturalNews Blog
Homepage Blogs
LIVE TALK RADIO
Simple Truths Videos
TV/VIDEO ARCHIVES
BOOKS
FREE NEWSLETTER
SCIENTIFIC PAPERS
DRUG HAZARDS

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The dangers of electroconvulsive therapy

See Dr. Breggin's new

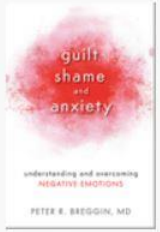
ECT Resources Center

with more than 125 annotated scientific articles, glossary of searchable terms and a brochure for patients and families.

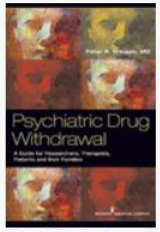
ECT (electroconvulsive treatment) damages the brain and mind. In many cases, it results in huge permanent gaps in memory for important life events, educational background, and professional skills. The individual may even lose his or her identity. Even when much less harm is done, individuals continue to suffer from ongoing cognitive difficulties with learning and remembering new things, and with unwanted changes in their personalities. Dr. Breggin has now created a free **ECT Resources Center** that includes (1) a brochure for patients, families, and advocates, (2) introductory scientific articles that cover the field of ECT-induced harm to the brain and mind, and (3) more than 125 articles about ECT with search terms such as "brain damage," "memory loss," "women," and "abuse." The ECT Resources Center will help introduce newcomers to the field and provide research materials for advanced researchers as well.

The most detailed recent publication about the harm associated with ECT is found in a chapter in Dr. Breggin's book,

search...



Guilt, Shame And Anxiety (New)



Psychiatric Drug Withdrawal

Conclusions

- **ECT is increasingly a vital treatment for our most severely ill patients.**
- Technical advances allow greatly improved tolerability.
- New research likely to lead to understanding of how ECT works, help elucidate etiology of psychiatric illness.
- **Stigma remains the biggest impediment to the appropriate prescription of ECT.**