Vagus Nerve Stimulation for Treatment-Resistant Depression 2025: update and unipolar RECOVER Trial Summary

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Disclosures

Scott T. Aaronson, MD

- **Receives grant/research support from:**
  - **LivaNova**
  - **Compass Pathways**
  - **MindMed**
- **Is a member of the Advisory Board for (company name) :**
  - **LivaNova**
  - **Neuronetics**
  - **GenoMind**

Faculty Disclosure: Charles Conway

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Equity Position*	*Ownership/ Employee*	*Other (please specify)*
LivaNova	**Limited***	**Limited***	-	-	-	-	-	**Research funded indirectly through WU Dept of Psychiatry**

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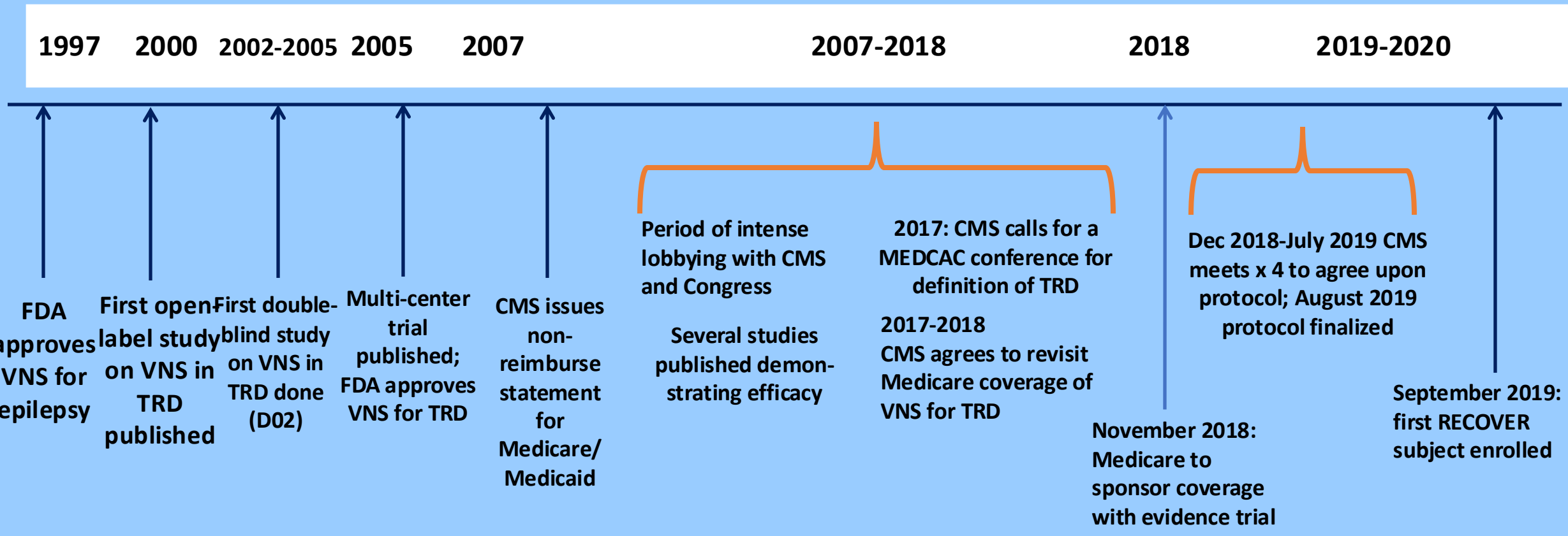
Off-Label Product Use

Will you be presenting or referencing off-label or investigational use of a therapeutic product?	
X	No

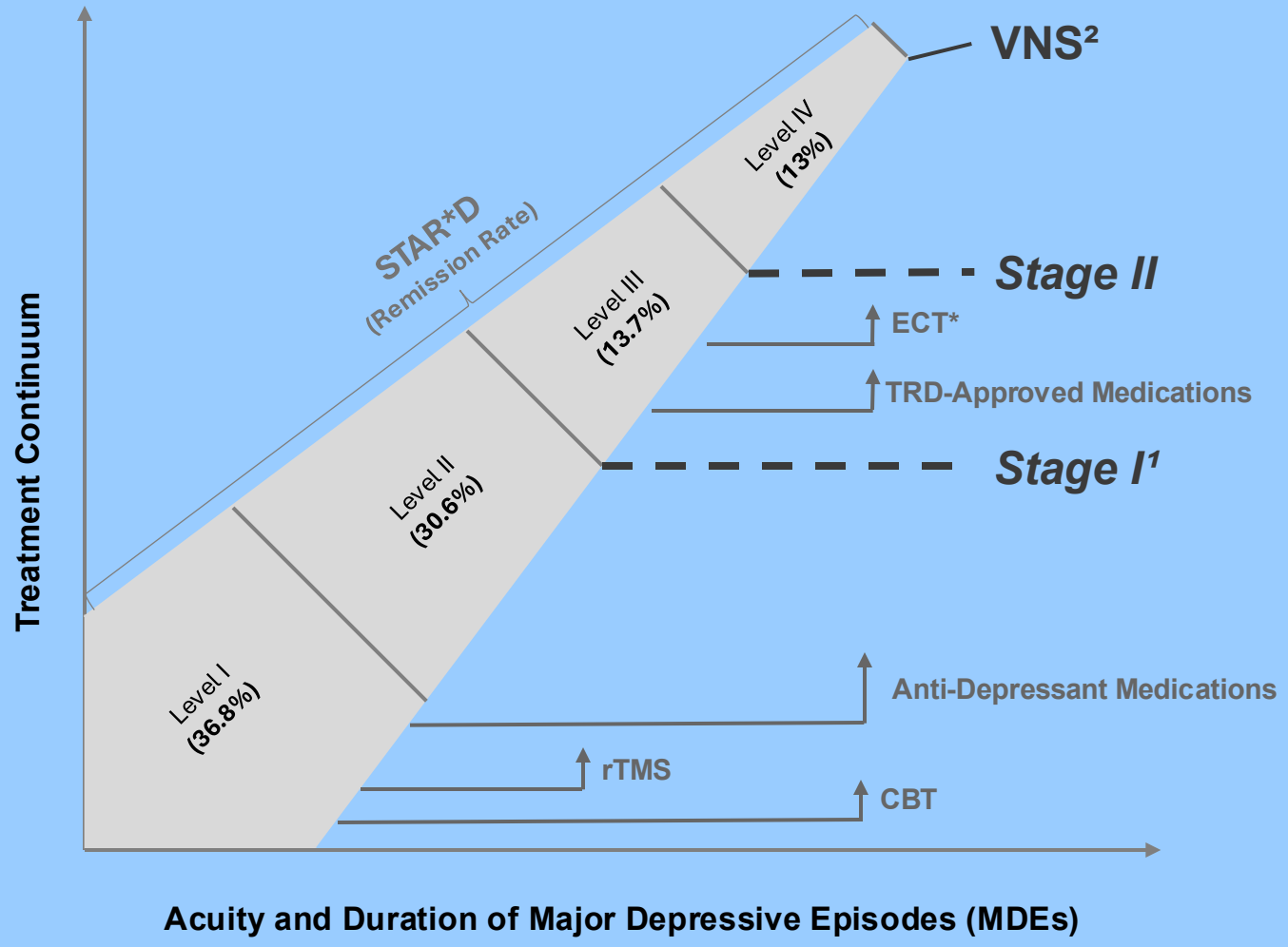
*Reviewed and approved by Washington University School of Medicine COI Committee

Long and winding road

Timeline for VNS for TRMD



Treatment Continuum for Major Depressive Disorders Provides Staged Approach to Defining TRD



KEY

STAR*D Staging Model

Proposed TRD Staging Model

**ECT should be considered at any point along continuum for acute, severe MDE*

VNS: Vagus Nerve Stimulation
ECT: Electroconvulsive Therapy
rTMS: Repetitive Transcranial Magnetic Stimulation
CBT: Cognitive Behavioral Therapy

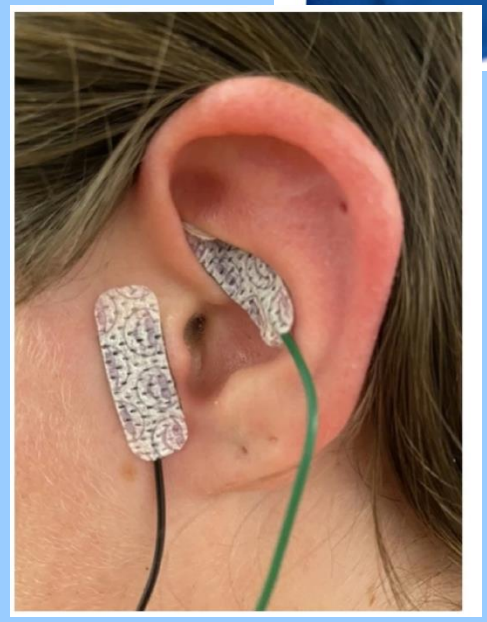
[1]**Studies:** Rizvi, 2014; Kubitz, 2013; Vieta & Colom, 2011; Albert, 2015
[1]**Guidelines:** VA/DoD, 2009; NICE, 2009; AHRQ, 2011; APA, 2010
[1]**Health Tech Assessments**: Oregon HERC, 2012; AHRQ, 2011; ICER-CEPAC, 2011
[2]**AHRQ**, 2011; APA, 2010

What Should Be Our Goal for Treatment

- **Current thought is the goal is management of acute depressive episodes, but this is a chronic, progressive, recurrent illness**
- **Our target is usually response or remission without much attention to durability**
- **With chronic depression even reliable small improvements are meaningful**
- **Which is a better target: 50% reduction in symptoms for 6 months or 25% reduction for 5 years?**

Vagus Nerve Stimulation (VNS)

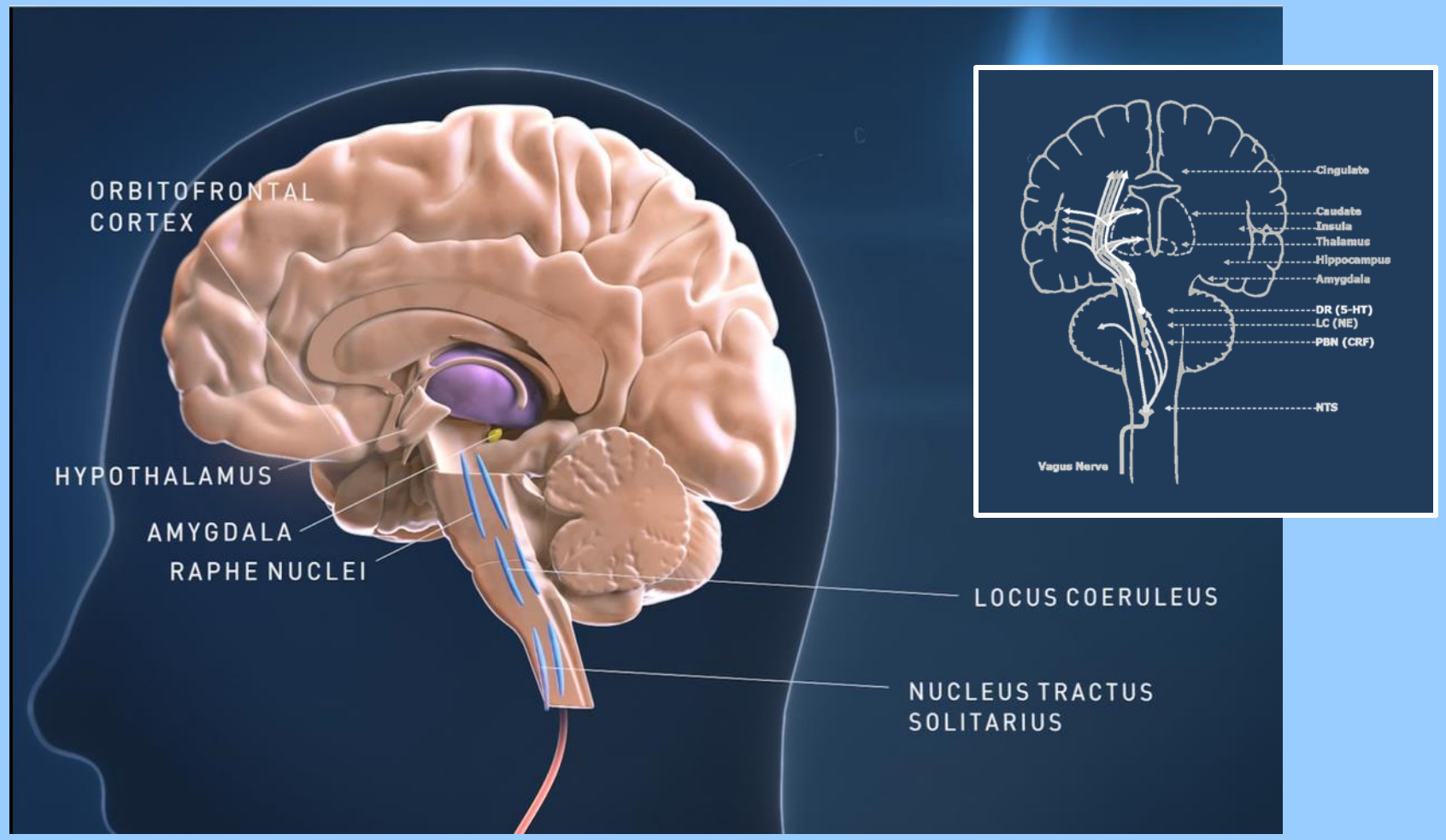
- **FDA-cleared for treatment-resistant MDE, but limited insurance coverage at present[a]**
- **Large Medicare-supported RCT recently reported on[a]**
  - **Results will impact Medicare coverage and other insurance policies**
- **Currently, research is underway to develop *external* VNS devices*[b]**



- *investigational
- MDE, major depressive episode.

a. CDC. Accessed May 15, 2023. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=292; b. Badran BW, et al. Bioelectron Med. 2022;8:13.

Anatomical connections of the vagus nerve[1]



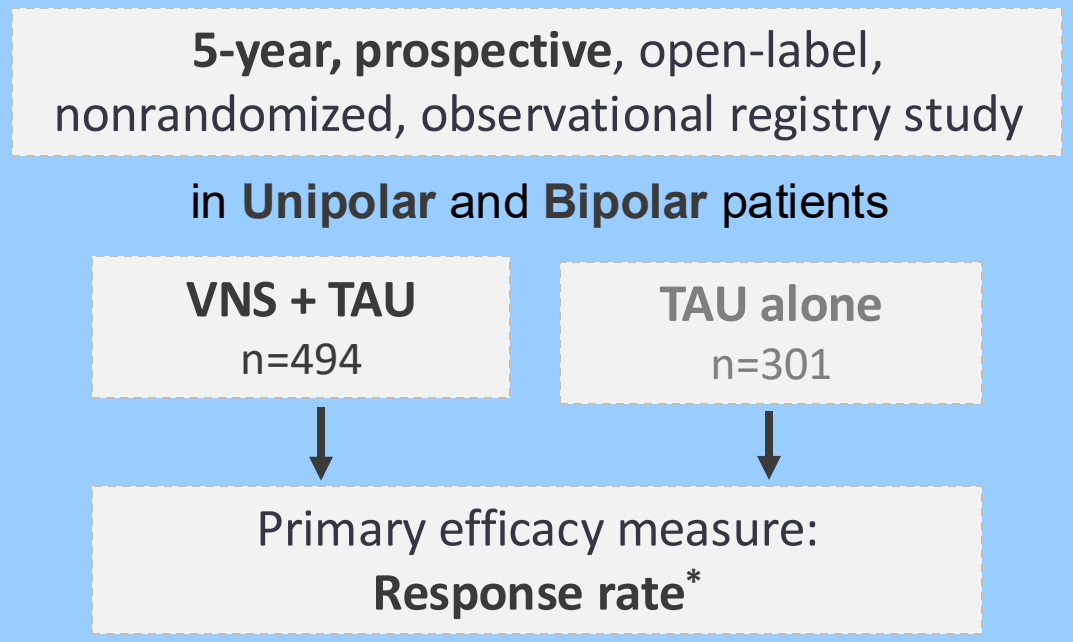
1. Pardo JV et al. *Neuroimage* 2008;42(2):879-889.

5-year long-term safety and efficacy data for VNS in TRD was published in the American Journal of Psychiatry[1]

ARTICLES

(TAU): Comparison of Response, Remission, and SuicidalityA 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual

Scott T. Aaronson, M.D., Peter Sears, C.C.R.P., Francis Ruvuna, Ph.D., et al.

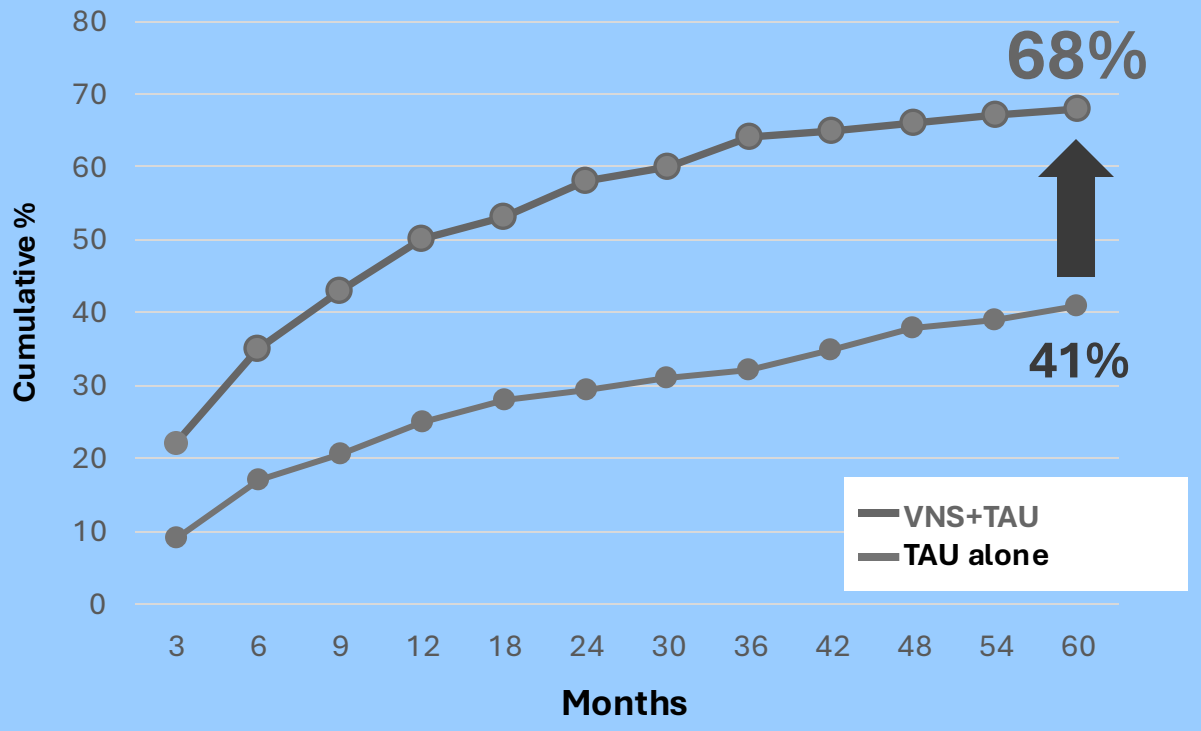


Treatment-as-usual (TAU) includes standard-of-care psychotropic medications and non-pharmacologic treatments, such as psychotherapy, cognitive behavioral therapy and ECT[1,2]

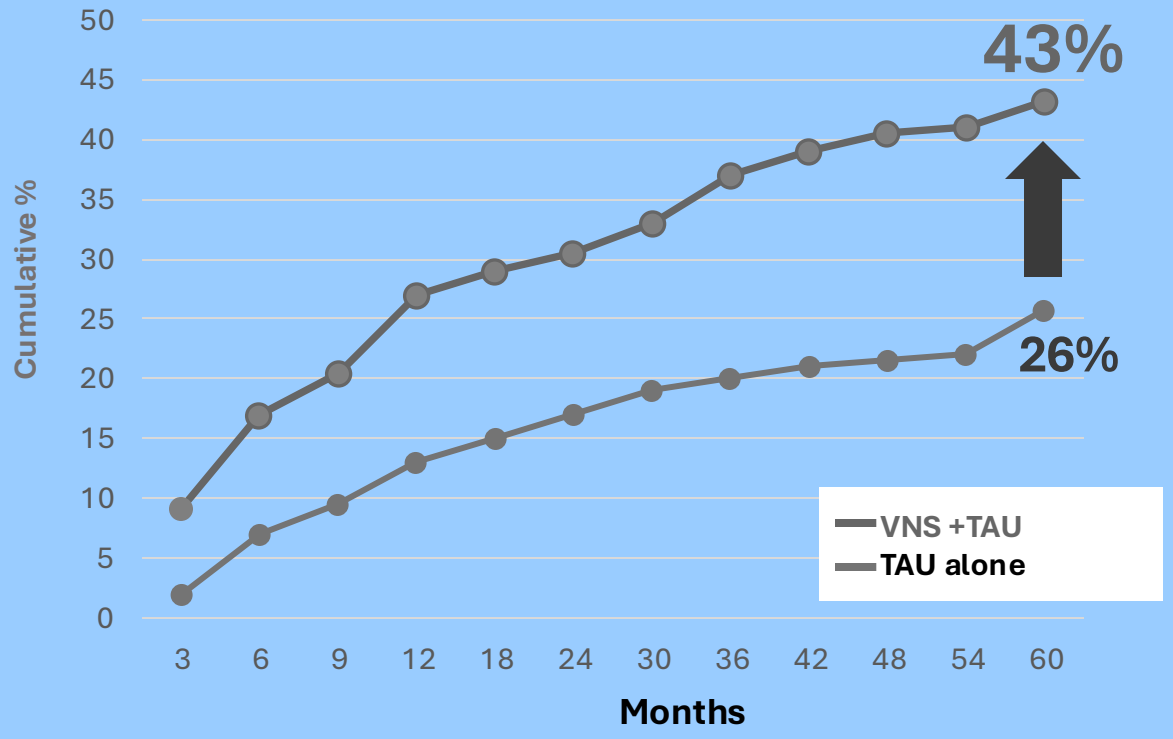
*Response rate defined as decrease of ≥50% from baseline in MADRS score at any post-baseline visit during the study. MADRS: Montgomery-Åsberg Depression Rating Scale.
1. Aaronson ST, Sears P, Ruvana F, et al. Am J Psychiatry. 2017;174:640-48. 2. LivaNova VNS Therapy® System Depression Physician's Manual, September 2019.

Cumulative Response Rates for Entire Sample of VNS (n=494) vs. Treatment as Usual (n=300) alone over 5 years[1]

Significantly higher 5-year cumulative **response rate*** (p<0.001)[1]



Significantly higher 5-year cumulative **remission rate**** (p<0.001)[1]

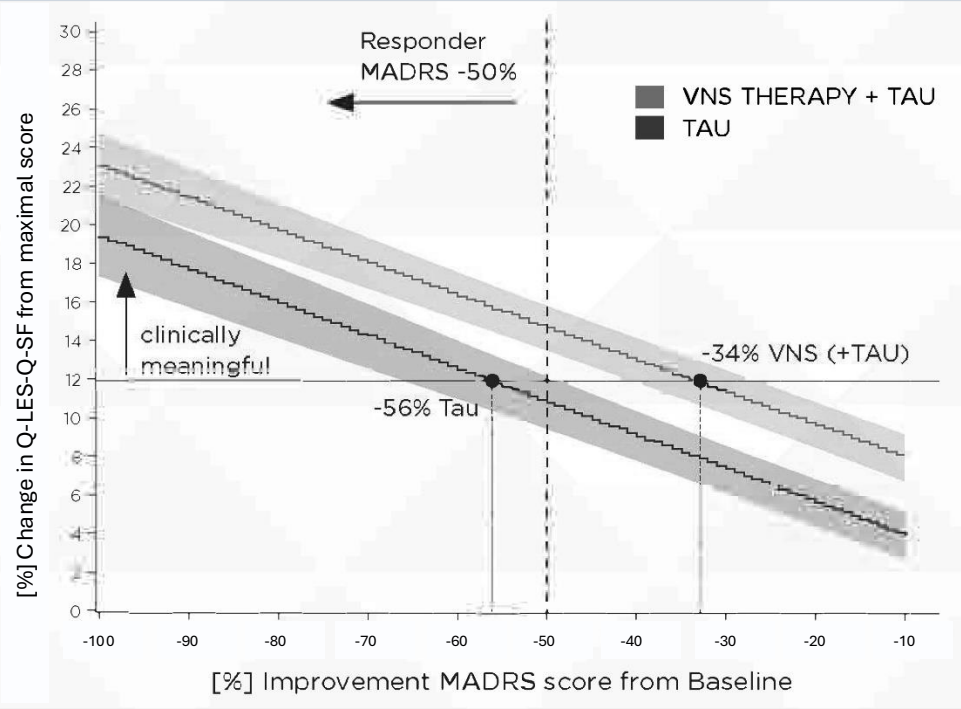


Efficacy analysis conducted on intent-to-treat population. *Response rate defined as decrease of ≥50% from baseline in MADRS score at any post-baseline visit during the study. **Remission based on MADRS score ≤9 at a post-baseline visit, a QIDS-SR score ≤5 at a post-baseline visit, and a CGI-I score of 1 at a postbaseline visit. ITT population was used for efficacy analysis.

1. Aaronson ST, Sears P, Ruvana F, et al. Am J Psychiatry. 2017;174:640-48.

QoL improvement relative to Clinical Depression Improvement

VNS Therapy (+ TAU) demonstrated a statistically significant greater improvement in quality of life than TAU alone.



- VNS Therapy(+ TAU) patients could achieve a clinically meaningful increase in QOL when the MADRS drop from baseline is at least 34%.*
- The TAU patients achieved the same clinically meaningful increase in Q-LES-Q-F percent max score when the MADRS drop from baseline is much higher (at least 56%).

Conway, CR et al., J Clin Psych; 2018; 79(5).

Tripartite Analysis of Symptoms, Quality of Life and Function

Journal of Mood & Anxiety Disorders
Volume 10, June 2025, 100121

An examination of symptoms, function and quality of life as conjoint clinical outcome domains for treatment-resistant depression

Charles R. Conway [a 1], A. John Rush [b c 1], Charles Gordon [d], Sheldon H. Preskorn [e], Harold A. Sackeim [f], Scott T. Aaronson [g], Roger S. McIntyre [h], Ying-Chieh (Lisa) Lee [d], Olivia Shy [d], Quyen Tran [d], Jeffrey Way [d], Mark T. Bunker [d]

A tripartite composite metric with depressive symptoms, daily function, and quality of life (QoL) to more accurately gauge treatment benefit in treatment-resistant depression (TRD)

The aim of depression treatment is to mitigate symptoms and optimize function and QoL

Standard depression symptom scales miss QoL and function

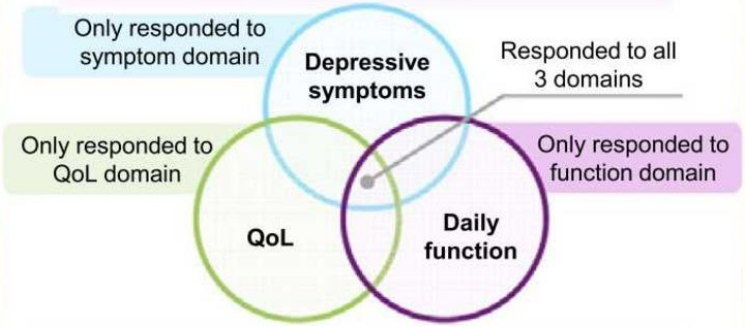
Partial response (30% improvement in depression measures) is the most reliable measure of benefit in marked TRD

Patients rate QoL and improvement in function as more critical than depressive symptoms

TRD significantly impacts function and QoL such that symptoms alone are insufficient outcomes

1 Create a tripartite metric that encompasses depressive symptoms, QoL, and function

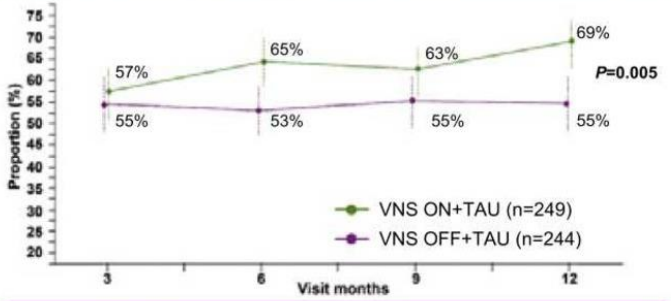
These 3 domains measure distinct and different areas of benefit



2 Compare the tripartite metric with a standard global clinical outcome (concurrent validity)

The tripartite metric using QIDS-C partial response and CGI-I partial response were significantly associated (χ^2=122, df=1, P<0.001) and were highly correlated (tetrachoric correlation=0.72), establishing concurrent validity as an outcome measure

3 Determine whether the tripartite metric is sensitive to detecting therapeutic benefits in marked TRD



Summary

- Standard depression measures miss many patients whose function or QoL meaningfully improve
- The tripartite metric is a valid, patient-centric, sensitive outcome measure
- The tripartite metric may be especially well suited for treatment outcome assessments in TRD; its use in less resistant depressions deserves study

CGI-I, Clinical Global Impression–Improvement; QIDS-C, Quick Inventory of Depressive Symptomatology–Clinician; TAU, treatment as usual; VNS, vagus nerve stimulation.

RECOVER: A National (USA), a multisite, prospective, randomized, double-blind, pivotal trial of VNS antidepressant efficacy in Medicare Patients

Charles R. Conway, MD
Professor of Psychiatry
Washington University School of Medicine

Lead Investigator, RECOVER trial

Irresistible Force (VNS) meets immovable object (markedly resistant TRD)!

RECOVER Overview

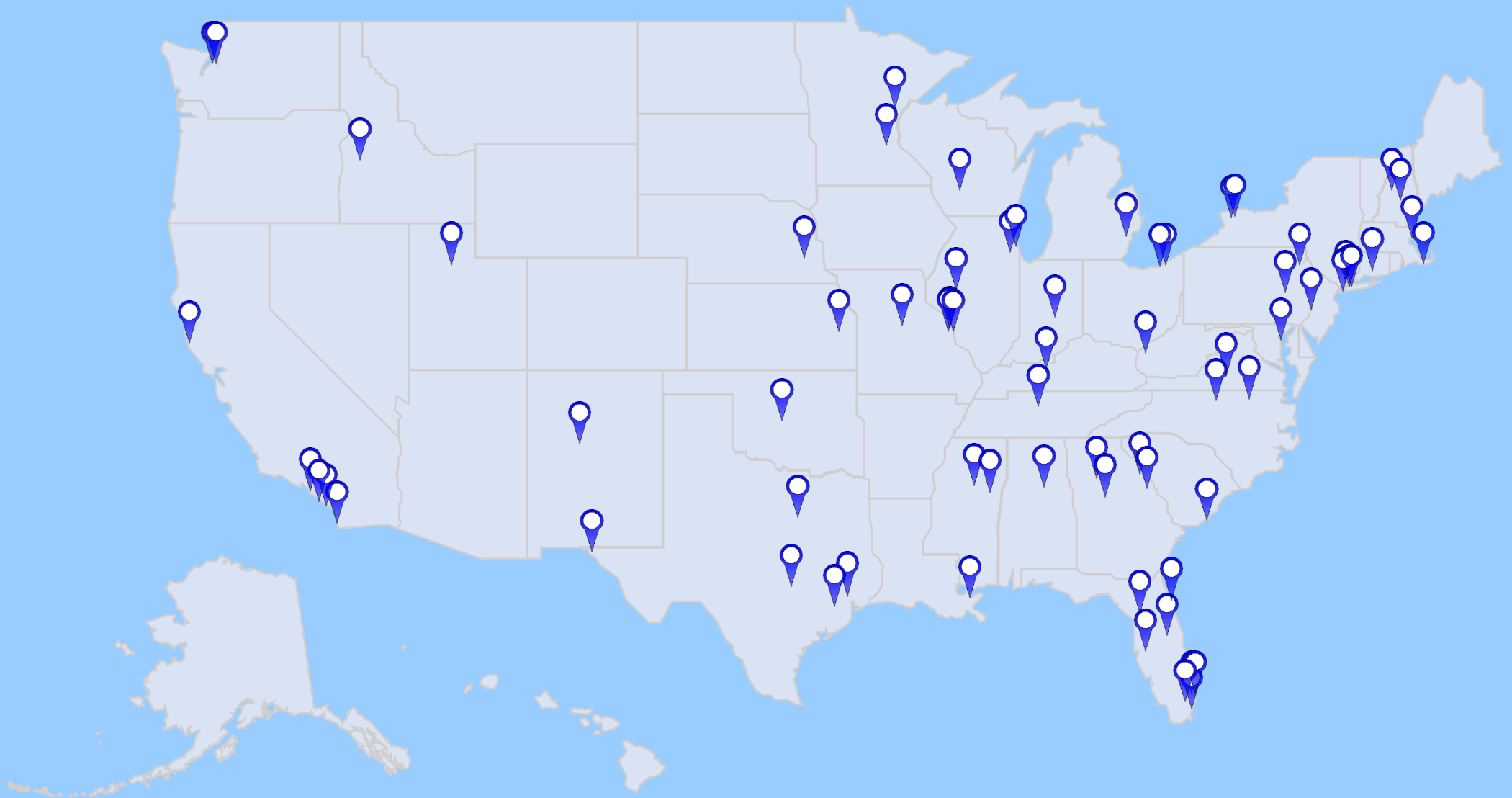
- **Largest** (N=84 sites, 493 patients in mITT group) and **longest** (1 year RCT; 4 years extension); double-blind, device-based TRMD study ever conducted.

- **Sickest/most-resistant patients** to ever enroll in a prospective, therapeutic clinical trial: mean of **13 failed lifetime treatments**, average of **29 years of depression**, constituting **53% of their lifetimes**. Minimum of 4 failed trials in the current treatment.

- First study to employ a **screening eligibility committee** to review each participant (required the last 2 years of psychiatric medical records).

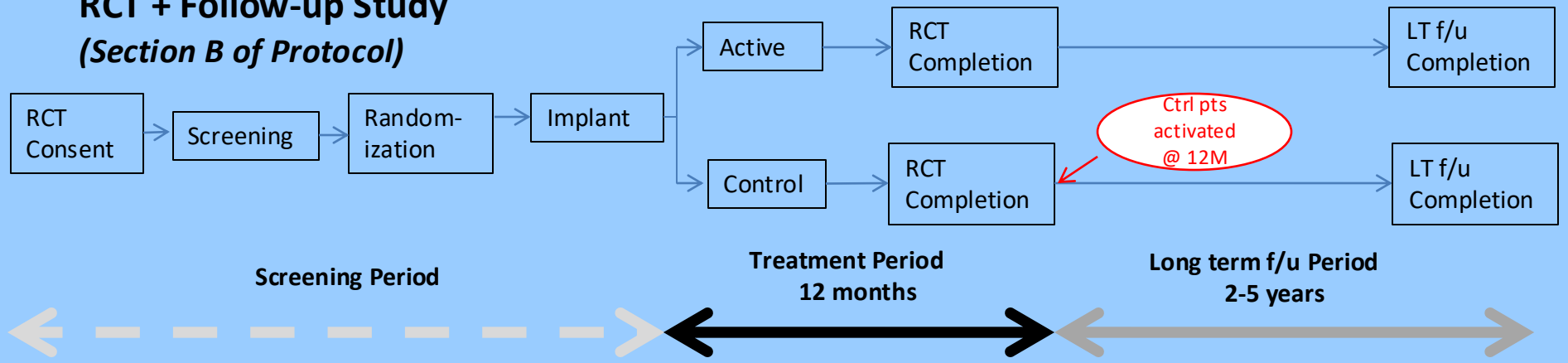
- Is a combined effort of academia, industry, and Medicare (CMS).

RECOVER Sites



RECOVER Overview

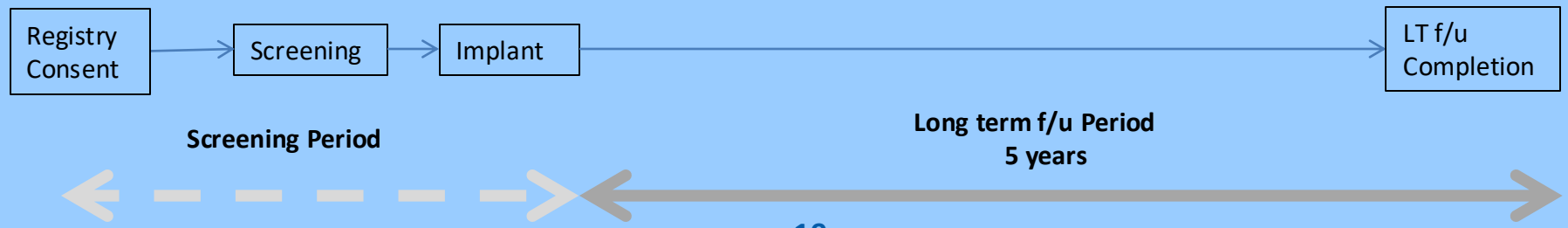
RCT + Follow-up Study
(Section B of Protocol)



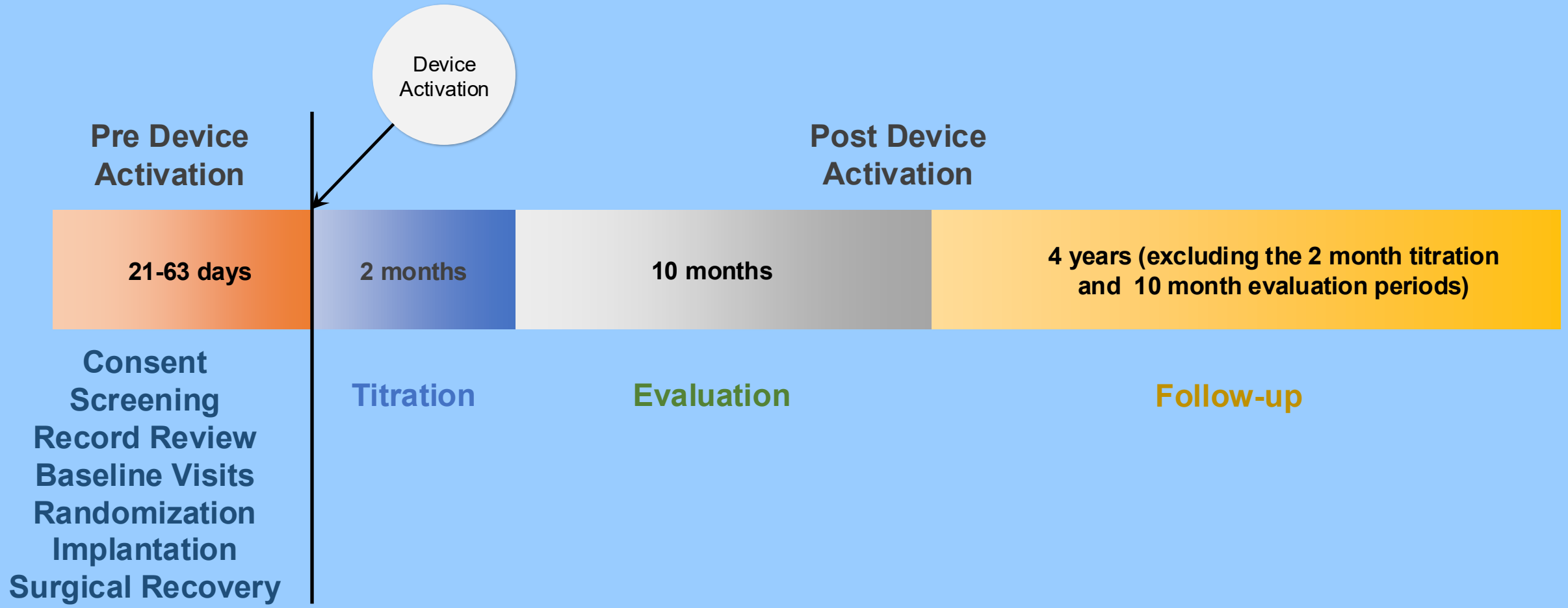
Longitudinal Registry
(Section C of Protocol)

Longitudinal registry starts **only** when RCT reaches 95% predictive probability of success

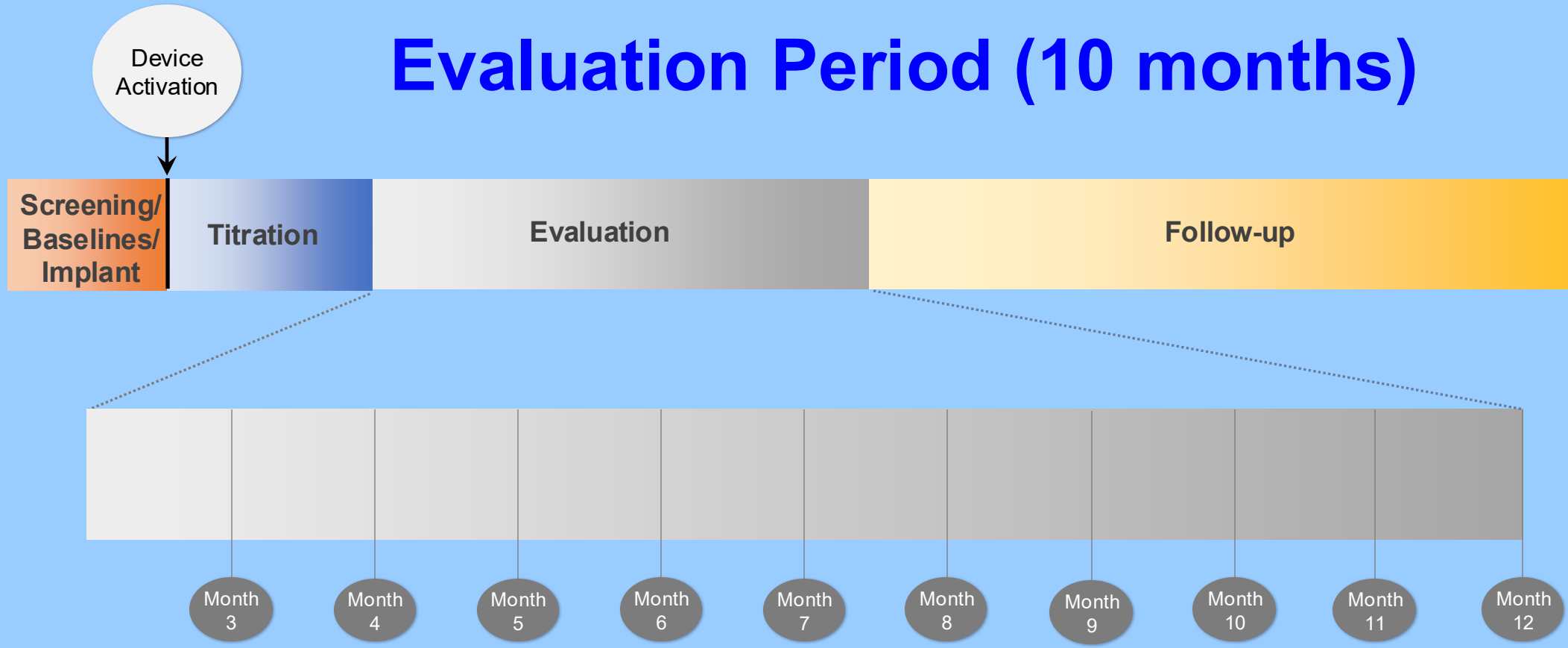
Separate Longitudinal Registry Triggers for Unipolar & Bipolar Subgroups



Sequence of Study Events



Evaluation Period (10 months)



The following information will be collected at each month time point:

Self Administered
- WHODAS*
- WPAI*
- QIDS-SR*
- Q-LES-Q-SF*
- EQ-5D-FL*

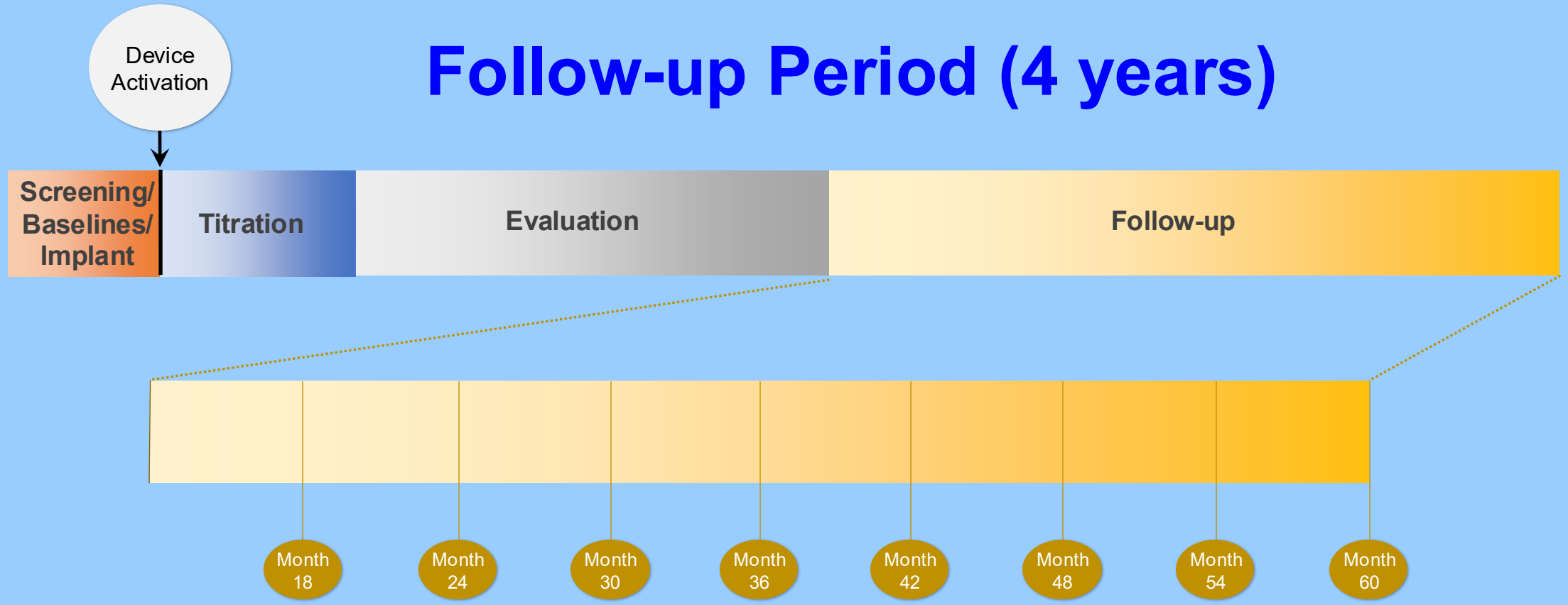
Site Collected
- Psychiatric Assessment Checklist
- Concomitant Treatments
- CGI-I
- S-STS
- YMRS

Central Rater
- **MADRS**
- QIDS-C

If Needed
- Adverse Events
- Protocol Deviations
- VNS Therapy Diagnostics/Sham
- Device Deficiencies

*months 3, 6, 9 & 12 only

Follow-up Period (4 years)



The following information will be collected at each month time point:

Self Administered Data
- WHODAS
- WPAI
- QIDS-SR
- Q-LES-Q-SF
- EQ-5D-FL

Site Collected Data
- Psychiatric Assessment Checklist
- Concomitant Treatments
- CGI-I
- S-STS
- YMRS

Central Rater
- **MADRS**
- QIDS-C

If Needed
- Adverse Events
- Protocol Deviations
- VNS Therapy Diagnostics/Sham
- Device Deficiencies

Key Mood, QoL, Function scales employed in RECOVER

Mood Symptoms	Clinical Impression	Quality of Life	Function/Disability	Additional Assessments
MADRS*,†	CGI-I	Q-LES-Q-SF	WHODAS	S-STS
QIDS-C†	CGI-S	**MINI-Q-LES-Q**	WPAI	YMRS
QIDS-SR		EQ-5D-5L		

* primary outcome,
†Offsite blinded raters using telephone ratings

The Screening Eligibility Committee: 1100 patients screened and counting…

Chris Kriedt, RN, SEC Manager,
RECOVER VNS Trial

RECOVER

Inclusion & Exclusion Criteria

Inclusion Criteria Summary

1. At least 18 years of age or older.
2. Have a current diagnosis of **major depressive episode and currently treated with an antidepressant treatment.**
3. Documented diagnosis of **chronic** (≥ 2 years) or **recurrent** (4 or more prior episodes, separated by two months without meeting criteria for MDD) major depressive disorder, according to DSM 5, that has not adequately responded to at least **four adequate trials of antidepressant treatment in the current episode**. Antidepressant treatments: medications (must include two antidepressant medications from different classes), psychotherapy, ECT, rTMS, or pharmacological interventions. This diagnosis must be documented using the Mini-International Neuropsychiatric Interview (MINI) and include a psychiatric medical record review.
4. Have a **score of at least 22 on both baseline administrations of the Montgomery-Åsberg Depression Rating Scale (MADRS)**, with a difference between the two scores that does not exceed 25%.
5. Medication regimen must be **stable for a minimum of 4 weeks before the baseline visit.**

Conway CR, Olin B, Aaronson ST, et al. (2020); *Contemporary clinical trials*, *95*, 106066

Exclusion Criteria Summary

1. Currently uses, or is expected to use during the study, short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy.
2. **An acute suicidal risk that requires inpatient treatment based on clinical judgment and history; suicide attempt within the last 6 months.**
3. Subject has had a prior VNS Therapy or deep brain stimulation (DBS) implant.
4. Subject has **a diagnosis of Substance Use Disorder as defined by DSM-V without sustained remission (12 months or longer).**
5. A **history of borderline or severe personality disorder** as determined by clinical judgment, which would significantly interfere with subject's participation in the study.
6. Any **history of one or more schizophrenia-spectrum or other psychotic disorders** including: schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, major depressive disorder with psychosis (unipolar or bipolar), and/or psychotic depression (unipolar or bipolar) based on the MINI (does not include psychosis occurring in the context of a manic episode).
7. Presence of any type of **dementia / Major Neurocognitive Disorder**.
8. Cognitive or psychiatric deficit (e.g. amnesia, delirium) that in the investigator's judgment would interfere with the subject's ability to accurately complete study assessments
9. **Current or lifetime history of psychotic features in any MDE**

Conway CR, Olin B, Aaronson ST, et al. (2020); *Contemporary clinical trials*, *95*, 106066.

Results

RECOVER Results summary

- Sample collected, to our knowledge, is the sickest TRMD group ever collected: **mean # failed treatments = 13; mean failed antidepressants = 11; mean years depressed = 29**; 53% of lifetime in **depression.**
- **Primary outcome measure** (# of months spent in response using the Montgomery Asberg Depression Rating Scale; MADRS) **did not achieve separation.**
- **MADRS offsite ratings had very high sham (placebo) response rate**.
- **Numerous other mood, clinical improvement, quality of life (QoL) and functional scales did demonstrate clinically meaningful and statistically significant improvements in response, partial response, and remission.**
- **Positive findings were observed regardless who was doing the rating**, i.e., blinded offsite raters, patients themselves (self-eval), and onsite clinicians.
- **Treatment very well-tolerated, excellent safety profile** with very limited difference between active VNS and sham VNS (except in those AE's associated with device being on, e.g., dyspnea).
- General conclusion: **the results demonstrated that in sample of severe, markedly TRMD patients active VNS demonstrated clinically meaningful therapeutic benefit over sham VNS on a large number of mood, quality of life, and function measures.**

RECOVER

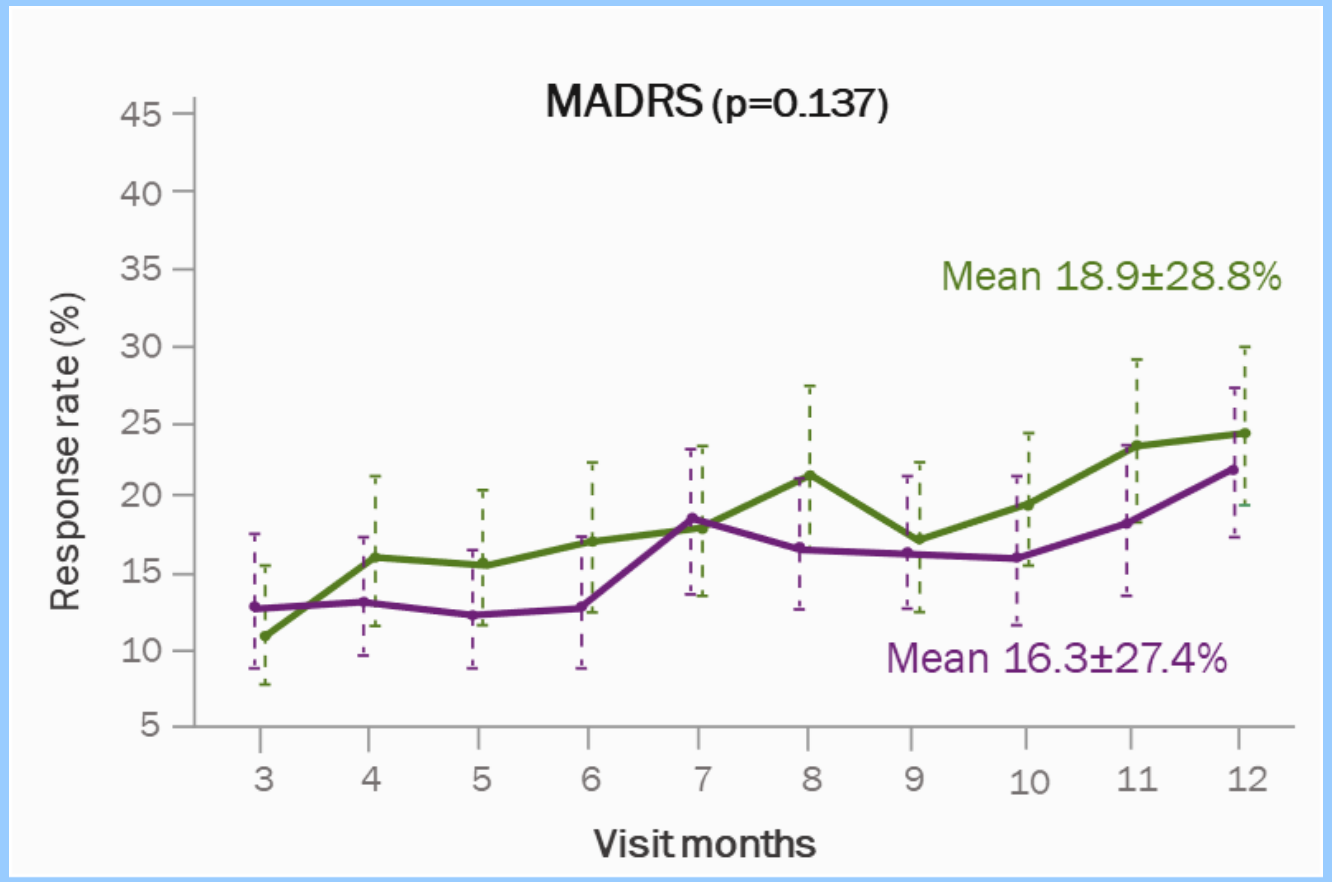
Results: Select Demographics, Disease Course and Treatment History

Age (mean)	55.5
18 to < 65	66.3%
≥ 65	33.7%
Female	65.6%
MADRS (mean)	34.3
CGI-S	
Mildly ill (3)	0.2%
Moderately ill (4)	19.1%
Markedly, extremely, severely ill (5-7)	80.7%
Duration of current MDE (mean years [SD])	17.8 [15.7]
Duration of lifetime years in MDE	29.4 [16.4]
% lifetime in MDE	53%
% with suicide attempts	40%
Failed lifetime AD treatments (mean)	13
Lifetime history of ECT	46%
Lifetime failed ECT	75%
rTMS current episode (failed)	50%
Lifetime Hospitalizations (mean)	2.1

Conway, C. R., Aaronson, S. T., Sackeim, H. A., et al. (2024). *Brain Stimulation*.

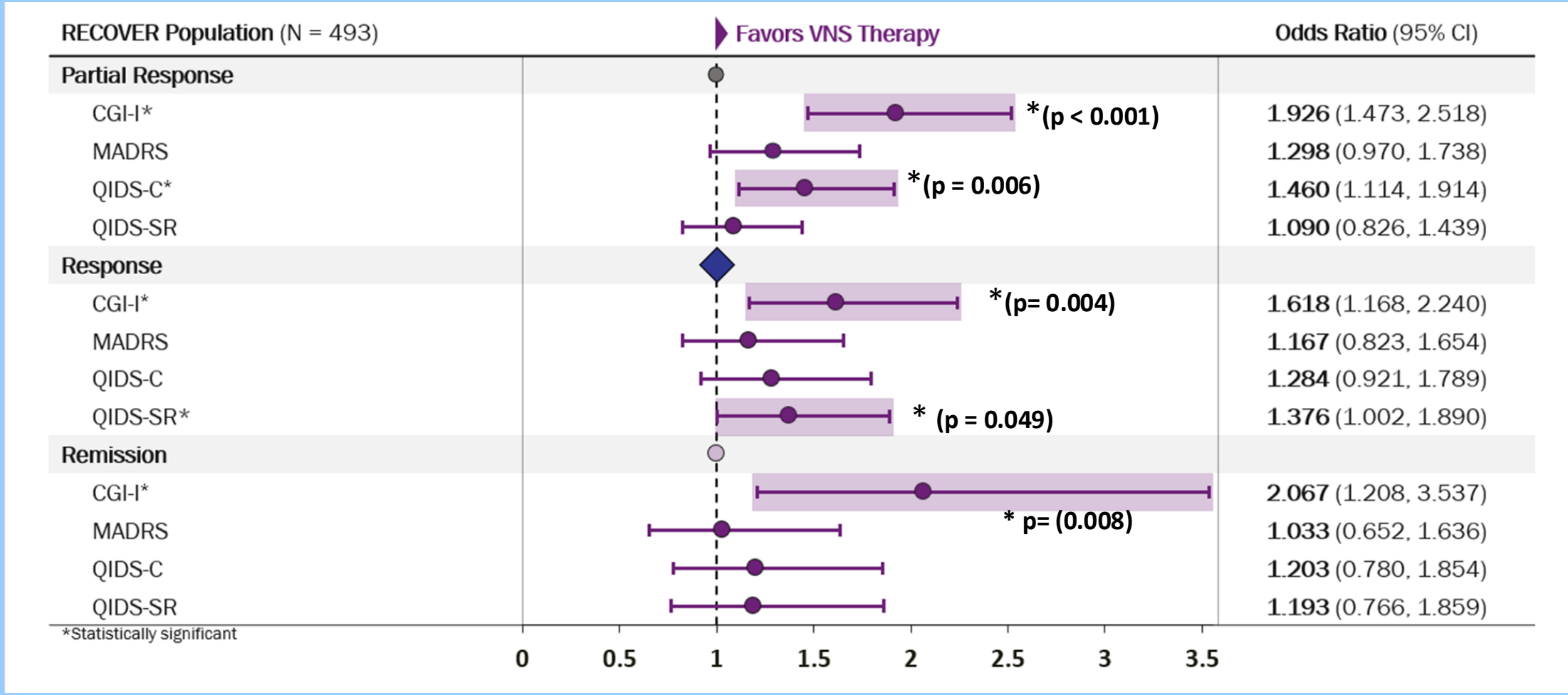
Mood Results

Time Spent in MADRS Response



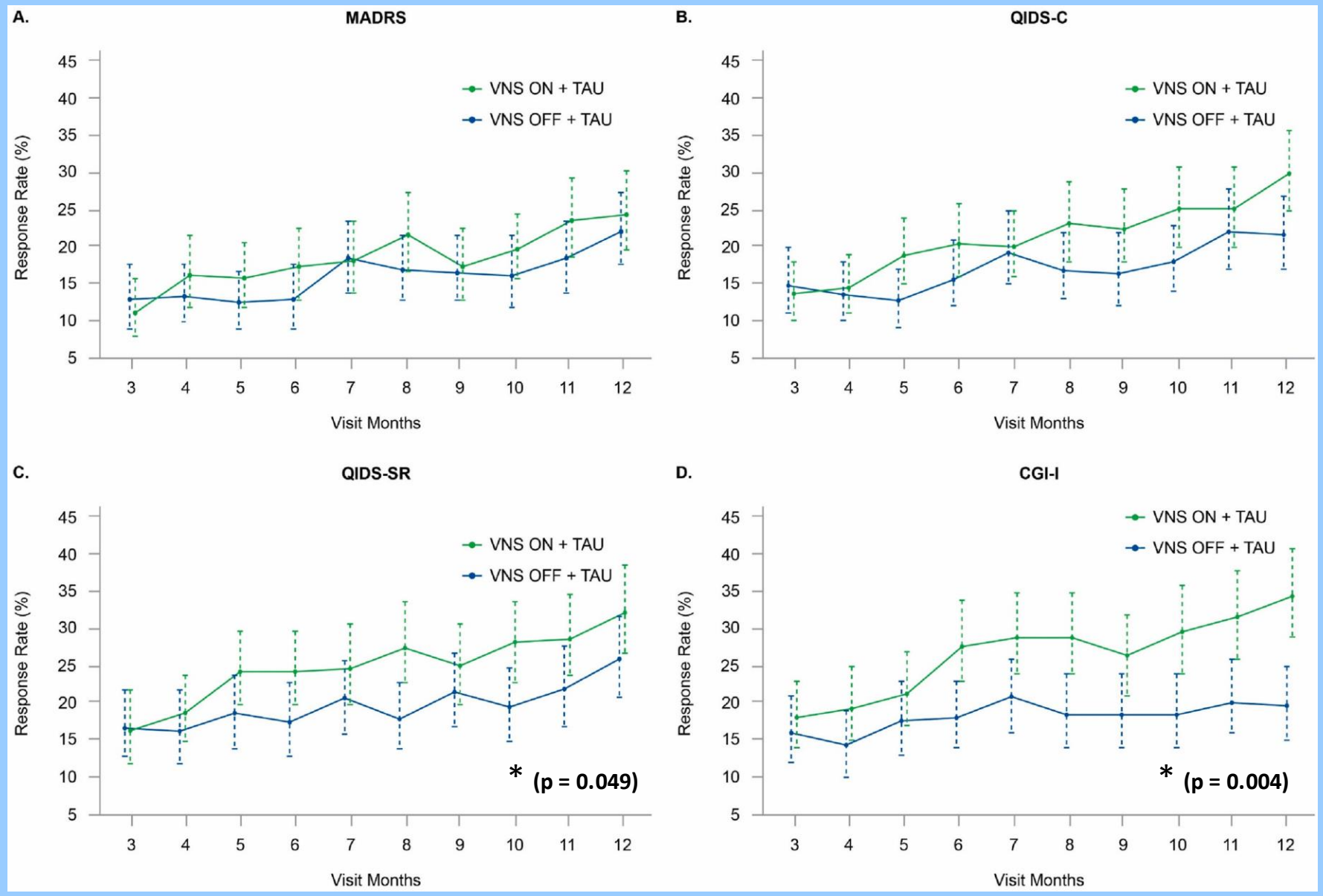
Conway, C. R., Aaronson, S. T., Sackeim, H. A., et al. (2024). *Brain Stimulation*.

RECOVER Mood results



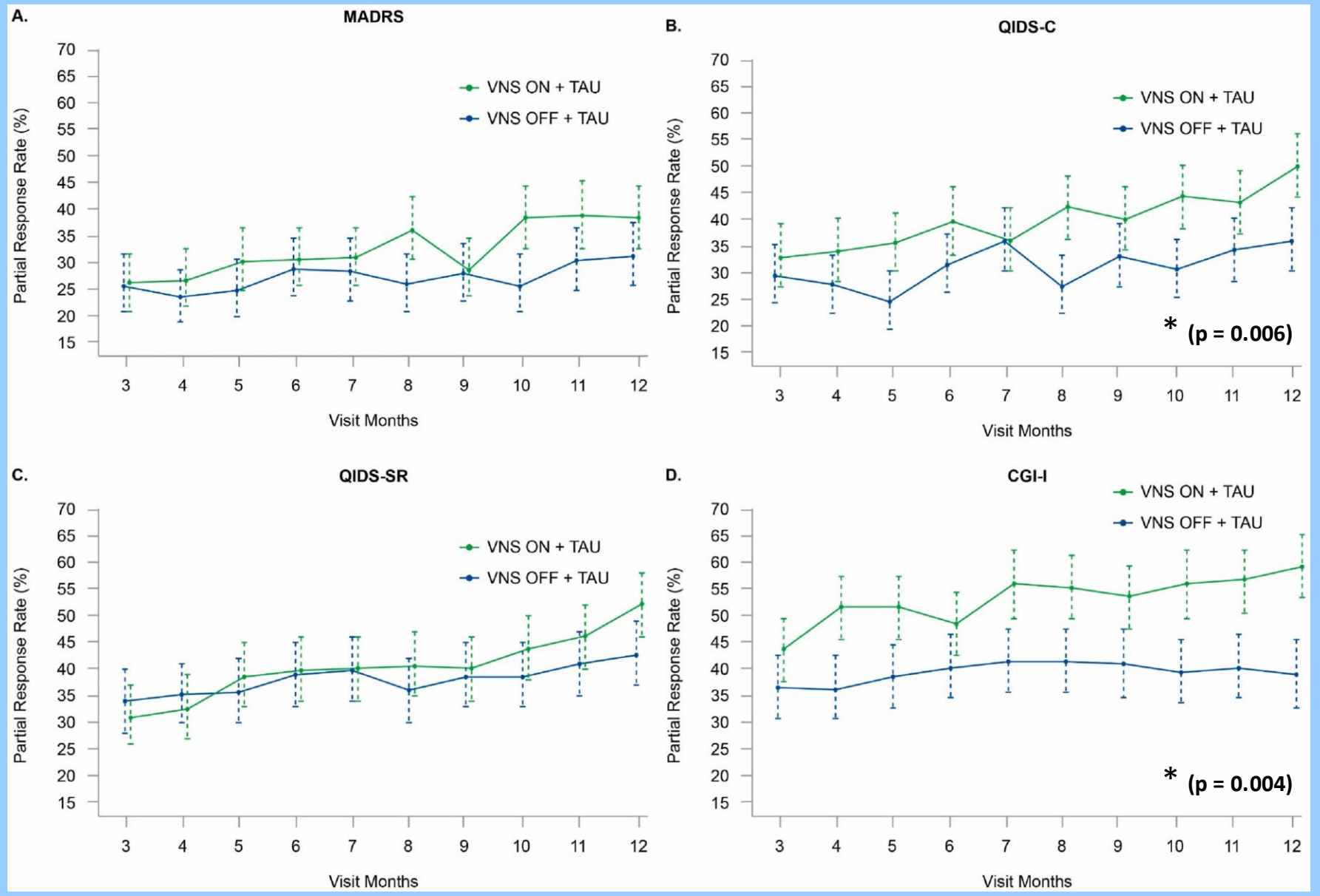
Conway, C. R., Aaronson, S. T., Sackeim, H. A., et al. (2024). *Brain Stimulation*.

RECOVER Mood and Clinical Improvement Results: response



Conway, C. R., Aaronson, S. T., Sackeim, H. A., et al. (2024). *Brain Stimulation*.

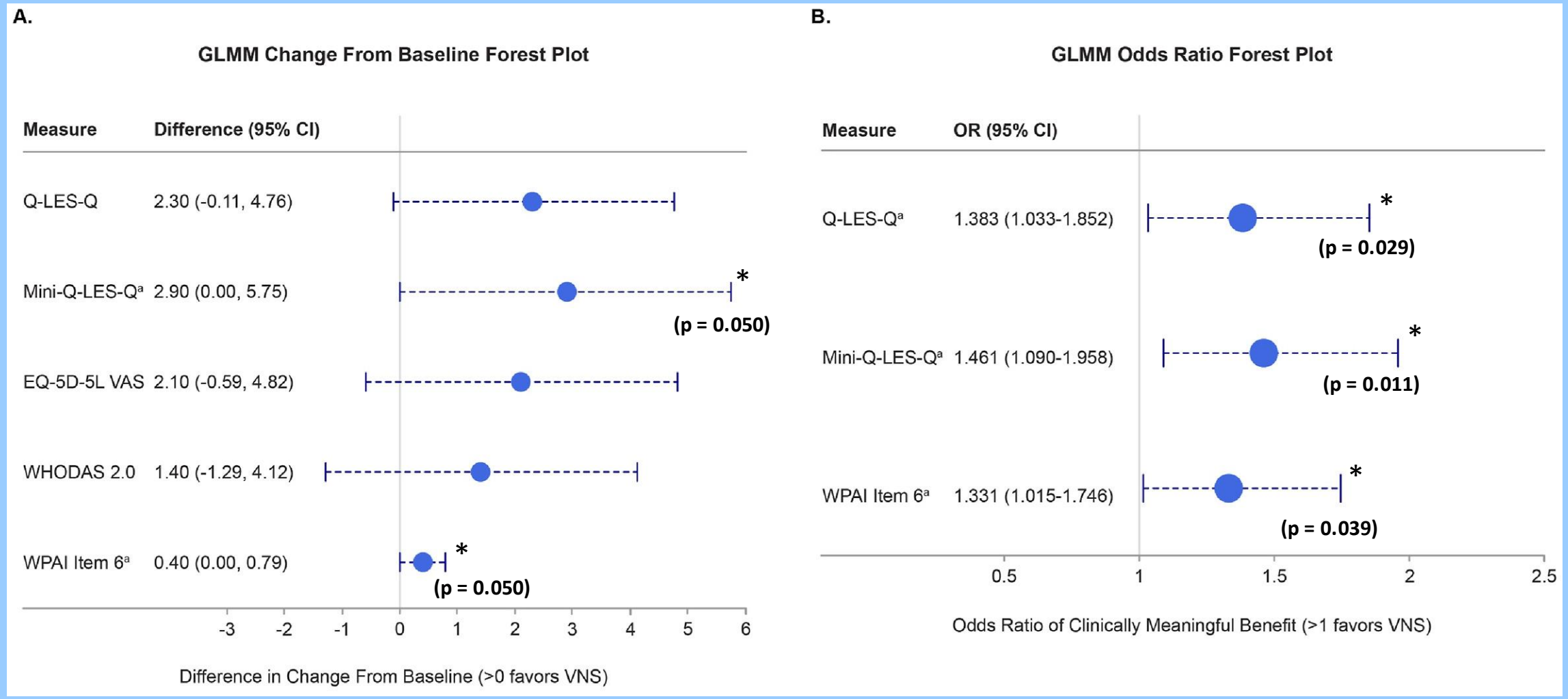
RECOVER Mood and Clinical Improvement Results: partial response



Conway, C. R., Aaronson, S. T., Sackeim, H. A., et al. (2024). *Brain Stimulation*.

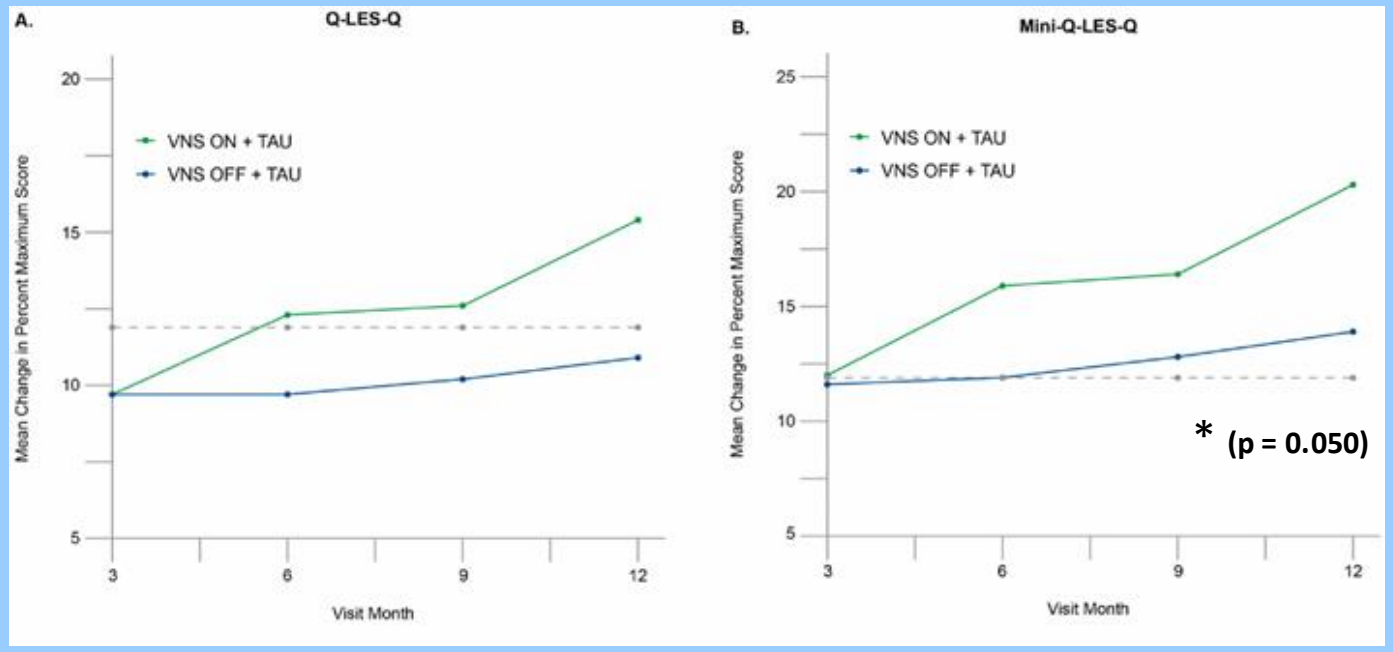
Quality of Life and Function Results

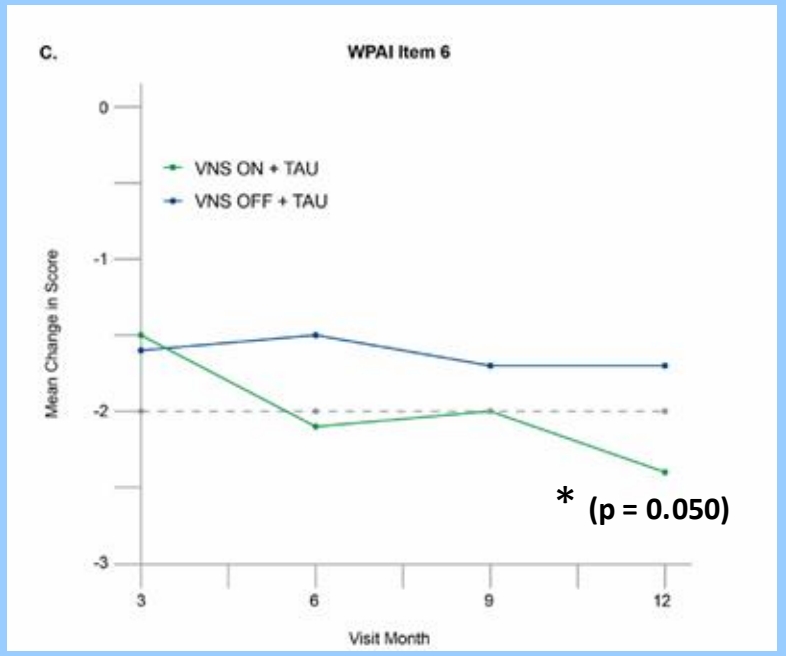
RECOVER Quality of Life and Function Results



Rush, A. J., Conway, C. R., Aaronson, S. T., et al., (2024). *Brain Stimulation*.

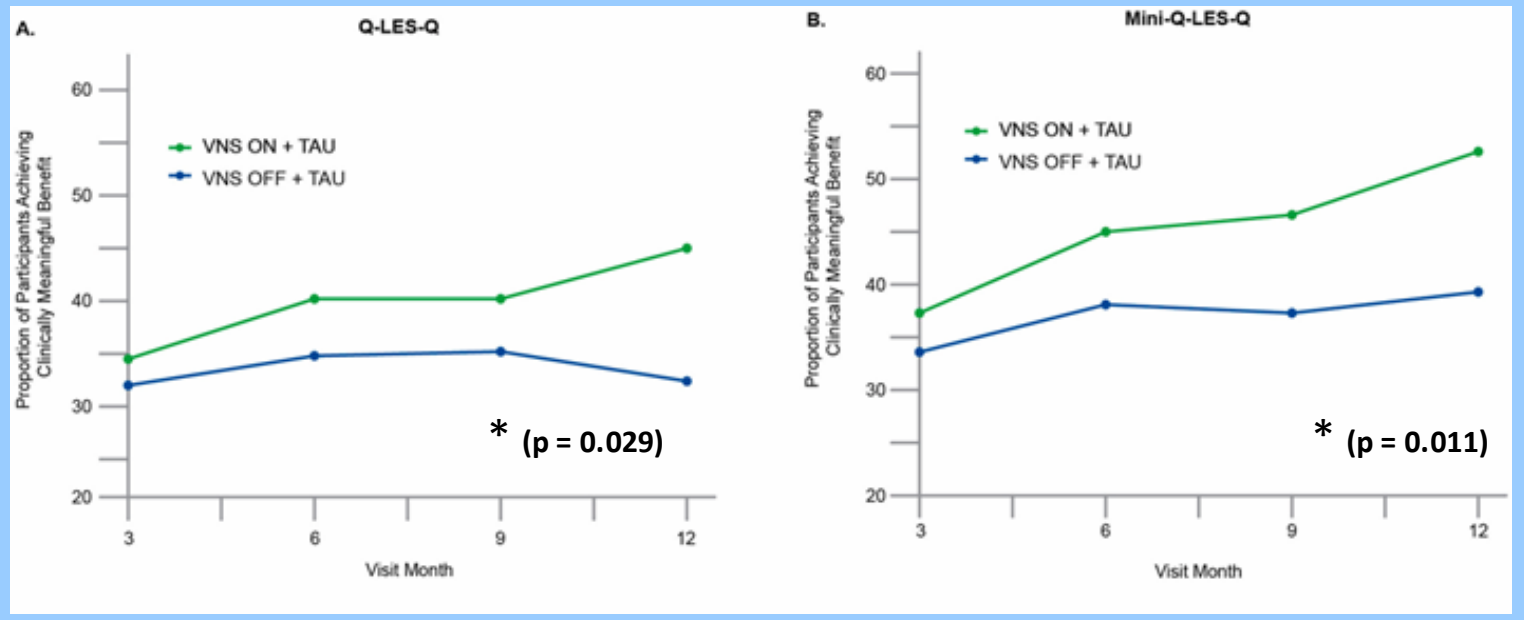
RECOVER Quality of Life and Function Results

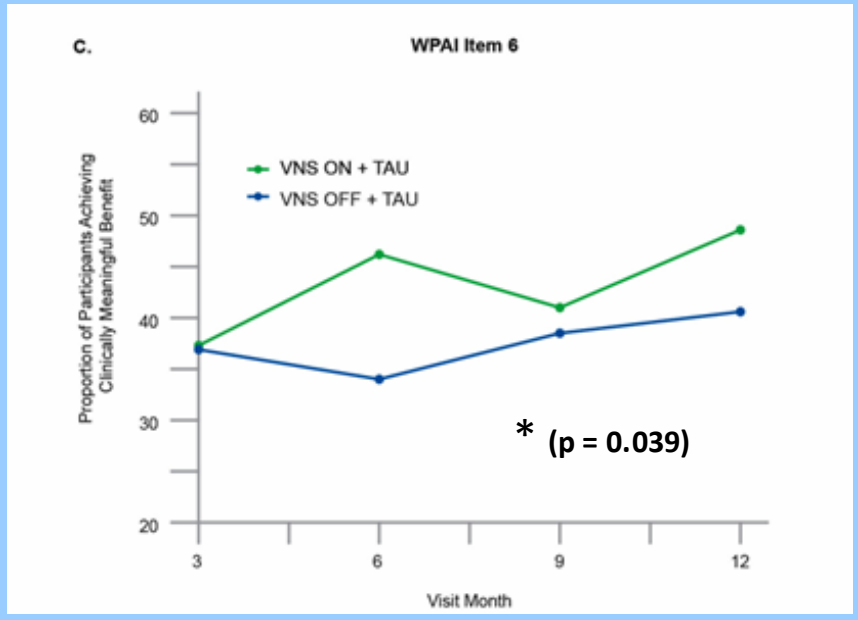




Rush, A. J., Conway, C. R., Aaronson, S. T., et al., (2024). *Brain Stimulation*.

RECOVER Quality of Life and Function Results: clinically meaningful improvements





The clinically significant improvement based on the MCID (≥11.89%) for **Q-LES-Q** was achieved by 45.0% of participants receiving VNS ON+TAU vs 32.4% receiving VNS OFF+TAU

The clinically significant improvement based on the MCID (≥11.89%) for **Mini Q-LES-Q** was achieved by 52.6% of participants receiving VNS ON+TAU vs 39.3% receiving VNS OFF+TAU

- For the **WPAI item 6** score, 48.6% of participants receiving VNS ON+TAU achieved a clinically meaningful improvement based on the MCID (≥2 points above baseline) in the ability to perform daily activities at the end of the 12-month study period vs 40.6% receiving VNS OFF+TAU

Rush, A. J., Conway, C. R., Aaronson, S. T., et al., (2024). *Brain Stimulation*.

RECOVER : a deeper dive into the results

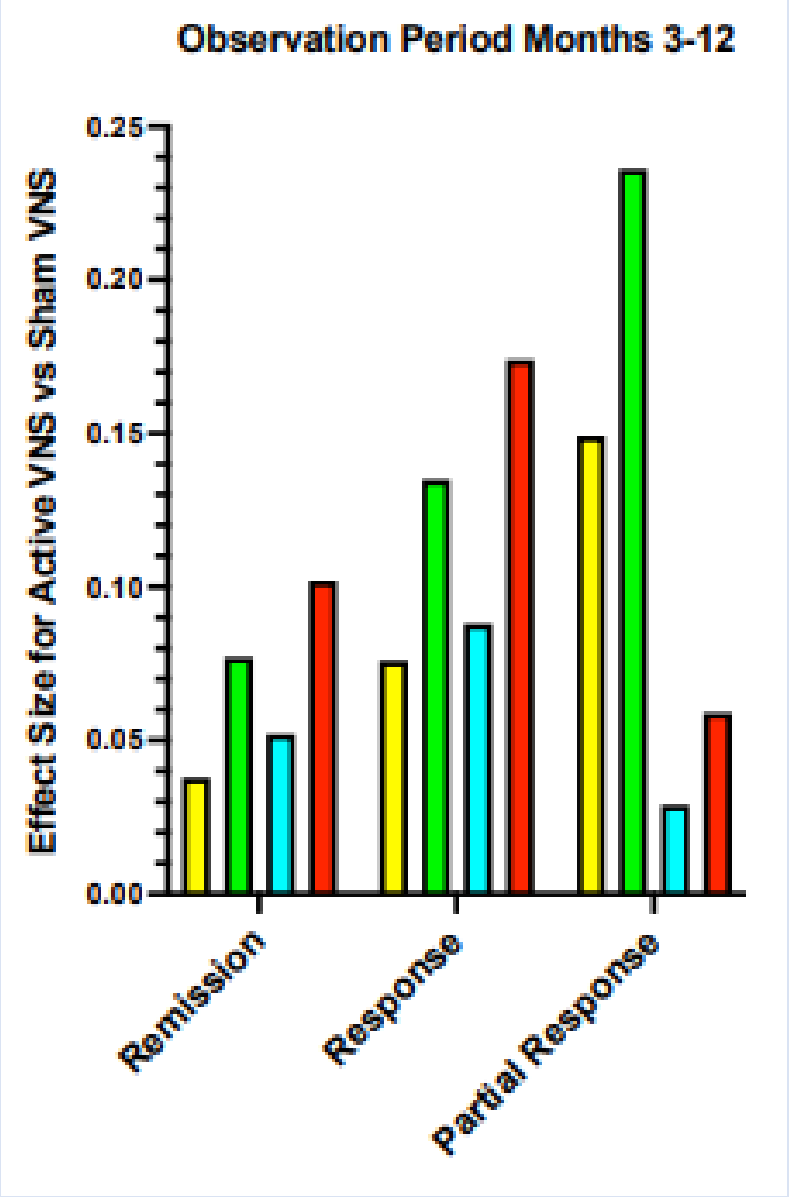
- **Partial response threshold** yielded **considerably large effects sizes** for the treatment group difference compared to either response or remission.

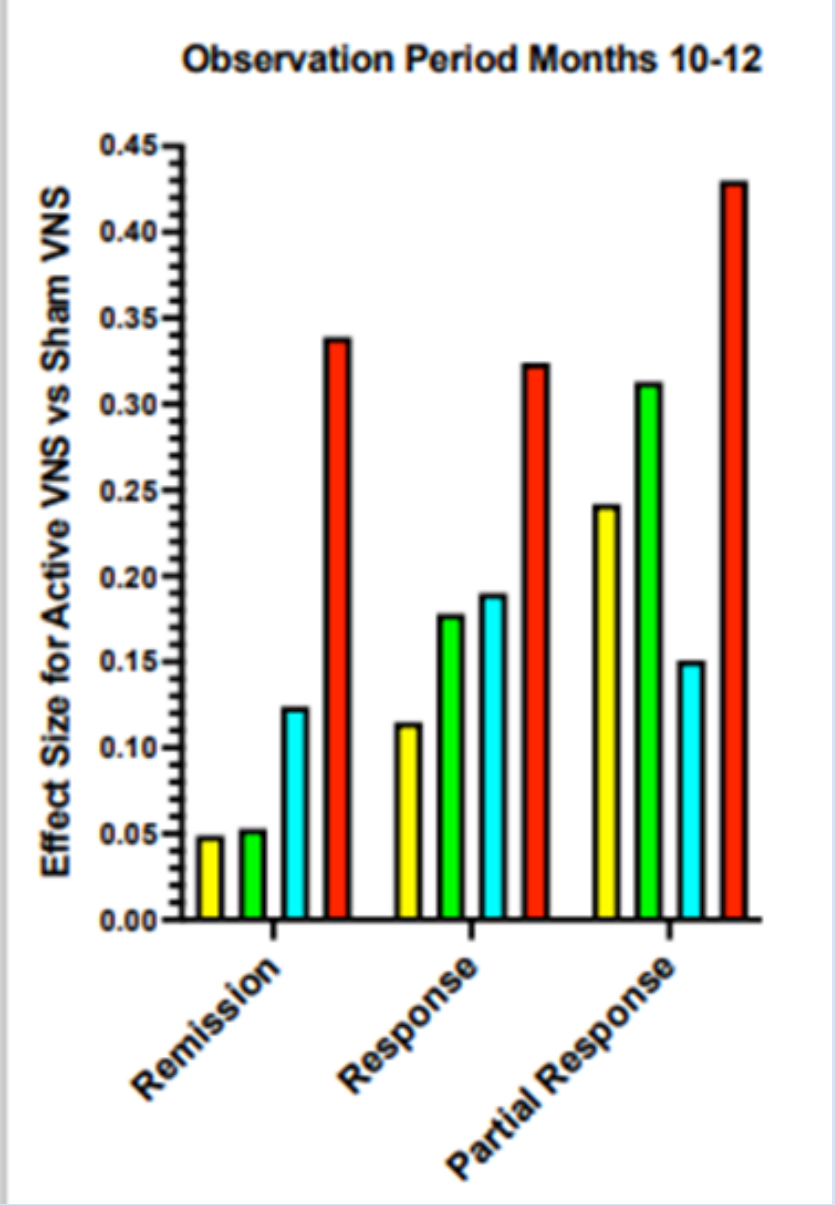
- Amongst the 4 scales measuring depression severity, **the MADRS yielded the lowest effect sizes.**

- **The optimal interval for distinguishing the treatment arms was, by far, the last 3 months of the trial (months 10-12),** with longer intervals resulting in considerably smaller effect sizes.

Sackeim et al., 2025, J Affective Disorders, 2025.

RECOVER : A deeper dive into the results





Sackeim et al., 2025, in submission

RECOVER Most Common Adverse Events: active VNS vs. sham VNS

	VNS ON+TAU (N=250)	VNS OFF+TAU (N=235)	P value	Total (N=485)
Depression[a], n (%)	75 (30.0)	62 (26.4)	0.377	137 (28.2)
Dysphonia, n (%)	64 (25.6)	51 (21.7)	0.313	115 (23.7)
Suicidal ideation, n (%)	27 (10.8)	36 (15.3)	0.139	63 (13.0)
Implant site pain, n (%)	27 (10.8)	28 (11.9)	0.699	55 (11.3)
COVID-19, n (%)	25 (10.0)	27 (11.5)	0.596	52 (10.7)
Cough, n (%)	24 (9.6)	21 (8.9)	0.801	45 (9.3)
Headache, n (%)	17 (6.8)	24 (10.2)	0.177	41 (8.5)
Dyspnea, n (%)	27 (10.8)	13 (5.5)	0.035 *	40 (8.2)
Neck pain, n (%)	19 (7.6)	16 (6.8)	0.736	35 (7.2)
Insomnia, n (%)	14 (5.6)	16 (6.8)	0.581	30 (6.2)
Anxiety, n (%)	11 (4.4)	16 (6.8)	0.248	27 (5.6)
Dysphagia, n (%)	16 (6.4)	11 (4.7)	0.409	27 (5.6)

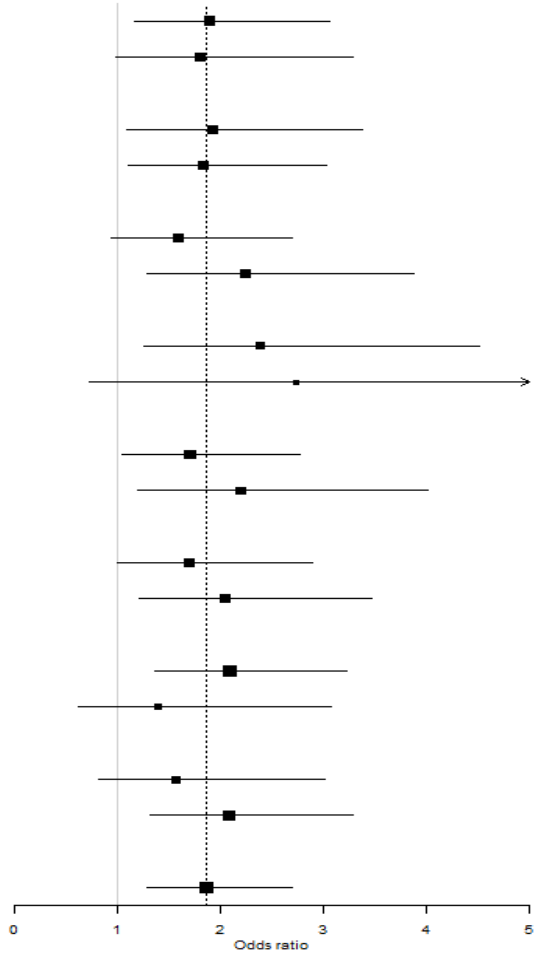
Conway, C. R., Aaronson, S. T., Sackeim, H. A., et al. (2024). *Brain Stimulation*.

Which Markedly TRD Patients are Best Suited for VNS?

[KM1]

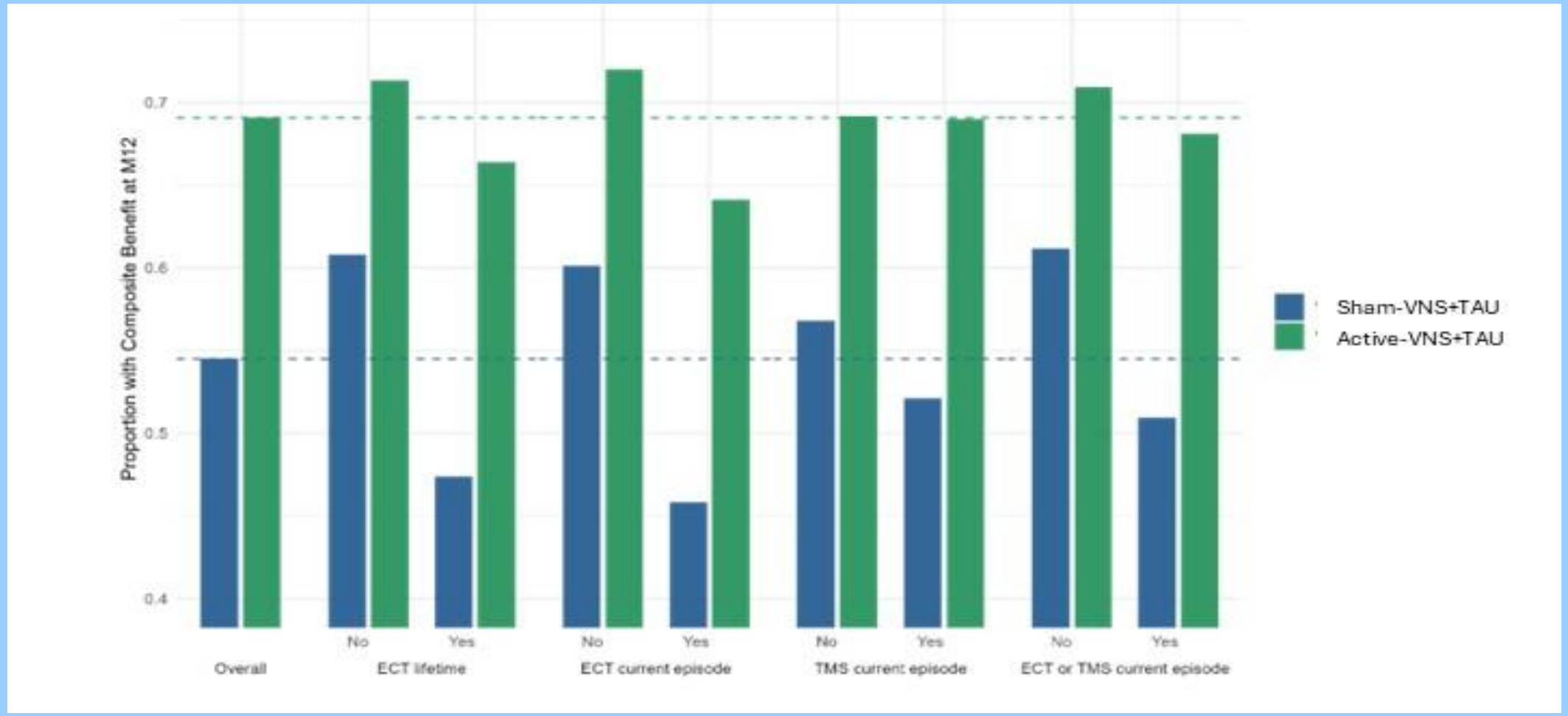
Odds Ratios of Positive Outcomes in VNS On vs VNS Off (JCP in press)

	N	OR (Lower - Upper)	NNT
Number of failed pharmacotherapies in lifetime			
<=10	300	1.90 (1.17-3.06)	6.7
>10	193	1.81 (0.99-3.28)	7.2
Number of failed treatments in lifetime			
<=10	226	1.92 (1.09-3.38)	6.8
>10	267	1.83 (1.10-3.03)	7.2
ECT exposure in lifetime			
No	266	1.60 (0.95-2.69)	9.5
Yes	227	2.24 (1.29-3.87)	5.3
ECT exposure in lifetime Yes			
Non-Responded	171	2.38 (1.26-4.52)	5.2
Responded	56	2.73 (0.73-10.19)	5.2
ECT exposure in current episode			
No	305	1.70 (1.05-2.77)	8.4
Yes	188	2.20 (1.20-4.02)	5.5
TMS exposure in current episode			
No	245	1.70 (1.00-2.90)	8.1
Yes	248	2.05 (1.21-3.46)	5.9
Esketamine exposure in current episode			
No	372	2.09 (1.36-3.23)	5.8
Yes	121	1.39 (0.63-3.07)	16.5
ECT or TMS exposure in current episode			
No	171	1.57 (0.82-3.01)	10.3
Yes	322	2.08 (1.31-3.29)	5.8
Overall			
	493	1.87 (1.29-2.70)	6.9



Aaronson et al., J Clin Psych, 2025, in press

12 Month Data for Benefit in Subjects with Hx of Interventional Treatment (sham vs active VNS)



Aaronson et al., J Clin Psych, 2025, in press

The End/The Beginning

"Surpass your imagination"