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The goal of clinical trials that include suicidal people is not just prediction of risk

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Limited generalizability in the three clinical trials of adults with MDD

CO-MED: Combining Medications to Enhance Depression Outcomes (in MDD, n=665, RCT of escitalopram monotherapy vs. bupropion-plus-escitalopram or venlafaxine-plus-mirtazapine). *Patient with and without current suicidal ideation may be included in the study as long as outpatient treatment is clinically appropriate.*

EMBARC: Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (in MDD, n=296, RCT of sertraline vs. placebo). *Currently actively suicidal or considered a high suicide risk.*

SAMS: Suicide Assessment Methodology Study (in MDD, n=266, open label trial of SSRI). *Patients with and without current suicidal ideation may be included in the study. Patients whose clinical status requires inpatient treatment at the time of baseline interview.*

Irritability and DSM-5 criterion symptoms of major depressive episode

1. **Sad/depressed mood**
2. **Anhedonia**
3. Sleep (insomnia or hypersomnia)
4. Appetite/Weight (increased or decreased)
5. Concentration
6. Guilt
7. Psychomotor agitation/retardation
8. Energy/fatigue
9. Thoughts of death/suicidality

Irritability

Criterion symptom in children & adolescents but not in adults

40-50% adults with MDD experience significant irritability during their depressive episode

Irritability and risk of suicidal ideation or behavior in developmental literature

Trajectories of irritability, depression and anxiety between 6-12 years of age predicting active SI or suicide attempt between 13-17 years of age (n=1430)

Profile	Unadjusted	Adjusted ^b
Low irritability and depressive/anxious mood	1 [Reference]	1 [Reference]
Moderate irritability and low depressive/anxious mood	1.22 (0.83-1.78)	1.55 (1.05-2.29)
High depressive/anxious mood only	0.97 (0.49-1.93)	1.15 (0.57-2.33)
High irritability and high depressive/anxious mood	1.60 (0.99-2.59)	2.43 (1.46-4.04)

Features during adolescence that predict suicidality (any suicidal plans or attempts) over next 30 years (n=2226)

Adverse family experiences	1.1	(0.8-1.6)	0.5
Sexual abuse	1.6	(0.5-4.7)	0.4
Hard/harsh parenting	1.5	(0.5-4.4)	0.4
Mothers mental health	1.7	(0.8-3.7)	0.2
Minor depression	1.3	(0.4-3.8)	0.6
Anxiety (clinical criteria)	1.3	(0.4-3.7)	0.7
Negative relationship with parent	1.0	(0.4-2.7)	0.9
Lonely	2.0	(0.9-4.4)	0.1
Worry	2.2	(1.1-4.4)	0.03
Irritability	1.8	(1.2-2.7)	0.003

How to measure irritability and suicidal ideation?

Concise Associated Symptom Tracking scale (CAST-IRR)

1. “I wish people would just leave me alone”
2. “I feel very uptight”
3. “I find myself saying or doing things without thinking ”
4. “Lately everything seems to be annoying me”
5. “I find people get on my nerves easily”

Concise Health Risk Tracking – Suicidal Thoughts Factor

- “I have been having thoughts of killing myself”,
- “I have thoughts about how I might kill myself”, and
- “I have a plan to kill myself”.

Five-point Likert scale

1=“strongly disagree”

2=“disagree”

3=“neither agree nor disagree”

4=“agree”

5=“strongly agree”

Prediction of suicidal ideation and behavior

Baseline to week-2
change (Δ)



Week-2 to week-8
levels of SI

	β^*	p value
CO-MED		
Δ irritability	-0.08	0.023
Δ overall depression	-0.13	0.0001
EMBARC		
Δ irritability	-0.50	<0.0001
Δ overall depression	-0.03	0.51
SAMS		
Δ irritability	-0.12	0.024
Δ overall depression	-0.07	0.21



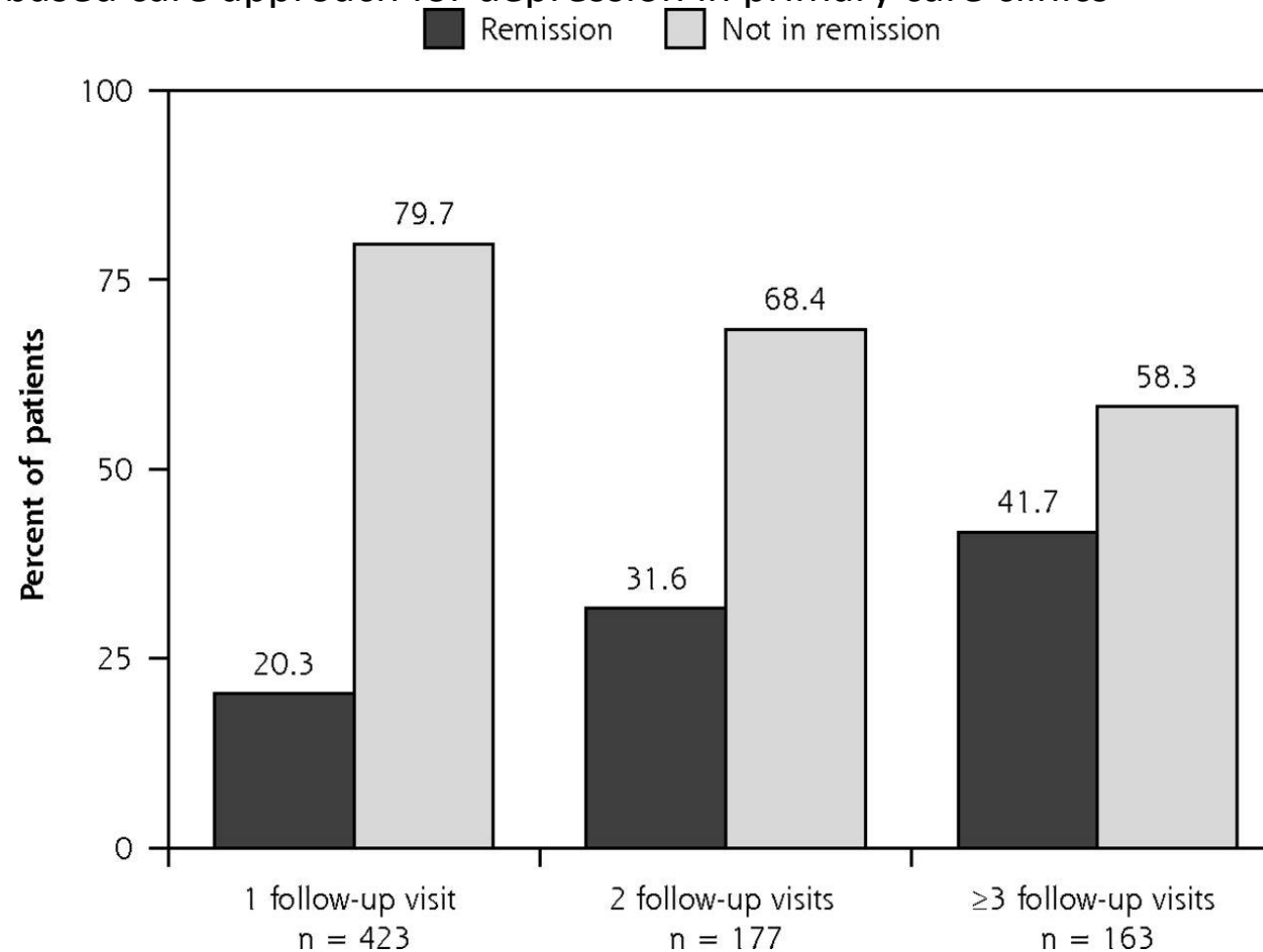
Component	Clinical Tasks	Methods	Challenges	Potential Solutions
Screening	Detect depression	Administer PHQ-2	Documented on paper	Document directly in electronic health record (EHR)
			Results not readily available to providers	Results routed directly to providers in EHR
			Positive PHQ-2 should be followed by PHQ-9	Screen automatically expands to PHQ-9
			Repeat screens as depression is episodic	Negative screens are re-screened annually
Diagnosis	Confirm or rule out depressive disorder	DSM-5 criteria-driven diagnostic interview	Lack of comfort with diagnostic interview	Online and in-person training
			Diagnose based on overall clinical impression	Use DSM-5 checklist embedded in EHR
			Specialist input needed for complicated cases	Access to consulting clinicians and referral sources
Treatment Selection	Shared decision-making options: <input type="checkbox"/> Active surveillance <input type="checkbox"/> Medication <input type="checkbox"/> Psychotherapy <input type="checkbox"/> Exercise Combination	Provider training and patient education	Frequent in-person visits for active surveillance	Remote assessments and provider review in EHR
			Lack of comfort with prescribing antidepressants	Online and in-person training
			Limited access to evidence-based psychotherapy	Tele-health programs for psychotherapy
			Limited knowledge of exercise prescription	Consultation with exercise specialists
			Optimize pharmacotherapy and psychotherapy	PCPs closely collaborate with tele-health therapist
Treatment Implementation	Deliver treatment Measure outcomes Assess response	Measurement-Based Care (MBC)	Assess improvement with treatment	Validated measures of symptom and functioning
			Limited time for clinician assessments	Use of self-report assessments
			Poor adherence to prescribed treatment	Systematically assess adherence at each visit
			Side-effects results in treatment discontinuation	Systematic assessment of side effects at each visit
			Inability to find previous paper forms	Easily searchable results in an electronic format
			Unable to visualize changes over time	Custom reports for outcomes over time
			Patient barriers prevent consistent follow-up	Implement patient navigation programs
Treatment Revision	Based on response	Clinical Decision Support System	How to handle treatment-resistant depression?	In-person or phone consultation; refer to specialist

Need for real-world evidence

- Measurement-based care approach for depression in primary care clinics
- Universal screening for depression
- Item-level data to predict clinical outcomes

Need for real-world evidence

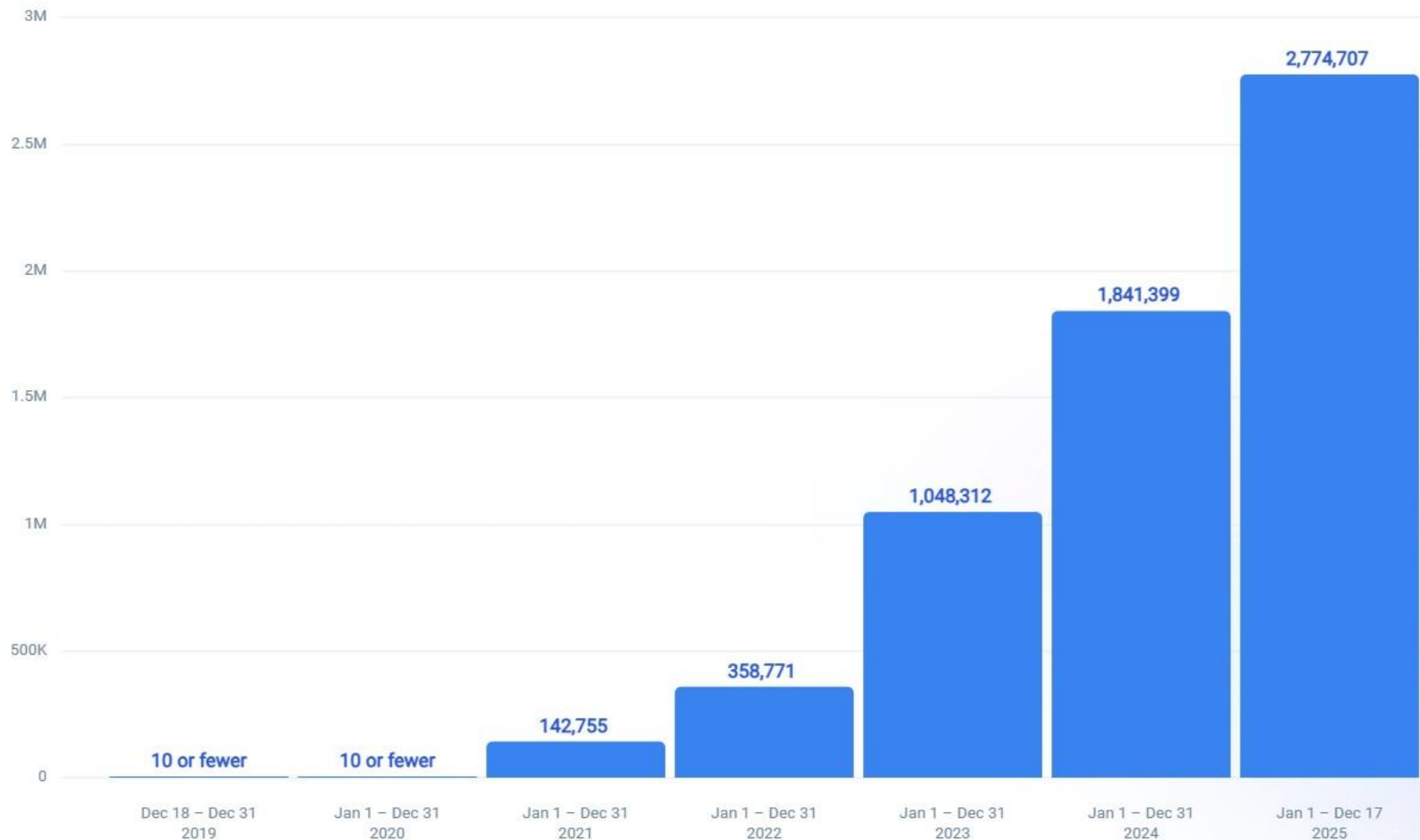
Measurement-based care approach for depression in primary care clinics



EHR as a tool

Number of Patient-Entered Questionnaire Responses

Between 12/18/2019 and 12/17/2025 by year





Eligibility criteria across clinical trials

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Examples of exclusion criteria in various clinical trials

Tirzepatide for methamphetamine use disorder (NCT06745128)

Require immediate hospitalization for psychiatric disorder or suicidal risk as assessed by a licensed study clinician.

Naltrexone-bupropion combination for methamphetamine use disorder (NCT06233799)

Has suicidal or homicidal ideation that requires immediate attention;

Ketamine for methamphetamine use disorder (NCT06496750)

Have active suicidal ideation with intent or plan in the past week based on the Concise Health Risk Tracking – Behavioral Module (CHRT-Beh), or have any current homicidal ideation based on Study Clinician evaluation.



Perspective from Investigator in Academic Setting

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Training requirements

- What measurement tool to use
- Clinical Training, standardization of assessment and follow-up approaches
- Safety planning/local institutional SOP
- Informed consent – reporting requirements per local/institutional requirements



Perspective from Investigator in Academic Setting

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Staffing requirements

- Who is going to do the assessment?
- Who to follow-up in case of positive responses/safety concerns?
- Partnering with other specialities, advanced practice providers and other licensed clinicians
- Who is acceptable to the sponsor, regulatory agencies including IRB



Perspective from Investigator in Academic Setting

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Logistics

- Planning for it in budget to account for this
- In-person versus virtual/telehealth visit
- Locator form for multiple contacts
- Measure at each visit
- Working with IRB

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