Population-based outreach to prevent suicidal behavior among outpatients reporting frequent suicidal ideation

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Start with the ending:

- We studied whether either of two low-intensity outreach interventions could reduce risk of self-harm or suicide attempt among people who report frequent suicidal ideation.
- We did not find that either intervention reduced risk.
- One of the interventions may have actually INCREASED risk.
- How do we understand that, and where do we go from here?

Where we started

- Routine questionnaires can identify outpatients at increased risk
- We have interventions that work - under specific circumstances.
  - Dialectical Behavior Therapy (DBT) – Structured individual and group therapy significantly reduces repeat self-harm among consenting research volunteers.
  - Cognitive Behavioral Therapy (CBT) – 10-session individual therapy reduced repeat self-harm among consenting research volunteers
  - Care Management interventions improve effectiveness of specific pharmacotherapy or psychotherapy for mood and anxiety disorders.
- Two candidate interventions:
  - DBT skills training (online program supported by coaching)
  - Risk-based care management to facilitate effective outpatient care
- Study question: Should health systems implement either of these programs to reduce risk of suicidal behavior among outpatients reporting frequent suicidal ideation on routinely administered questionnaires?

Design overview

- Four MHRN health systems (HealthPartners, KPWA, KPCO, KPNW)
- Automatically identify adult outpatients completing PHQ9 and reporting suicidal ideation “more than half the days” or “nearly every day”
  - Limit to those currently enrolled and using EHR portal online messaging
  - Exclude for: diagnosis of cognitive impairment, EHR indicator for needing interpreter
- Immediately randomized (concealed tables, permuted blocks of 6 or 9) to:
  - Continued usual care (never contacted)
  - Offer of Care Management program
  - Offer of Skills Training program
- Interventions offered and delivered for up to 12 mos
- Outcome: fatal or non-fatal self-harm over 18 mos following randomization
- Target sample size of 19,500 based on expected event rate of 3.75%

Invitation process (similar for two interventions)

- Initial invitation via EHR online messaging:
  - Expression of caring and concern
  - Description of specific intervention services
  - Abbreviated informed consent info (interventions are part of research, participation is voluntary, free to decline or withdraw)
- Reminder (phone or messaging) if no response in 3 days
- Repeat invitation process 4 and 8 weeks later if no response
- If no response after 3 “cycles” of invitation – not contacted again but could accept intervention services throughout 12-month period.

Care Management intervention

- Intended to supplement (not replace) existing outpatient care
- Aimed to incorporate key elements of effective CC/CM interventions
- Systematic outreach on measurement-based (adjustable) schedule
- Structured suicide risk assessments (CSSRS) at each contact
- Risk-based recommendations for outpatient mental health follow-up
- Motivational enhancement and care navigation as indicated
- Communication of recommendations to treating providers
- Outreach primarily via EHR messaging (with telephone as “backup”)
- Higher intensity follow-up in cases of high risk scores (CSSRS >=4)
- Outreach continued up to 12 months after randomization

Skills Training intervention

- Intended to supplement (not replace) existing outpatient care
- Aimed to provide brief/introductory training in specific DBT skills
- Online skills training program:
  - Introduce four skills: mindfulness, mindfulness of current emotion, opposite action, and paced breathing
  - Brief video description, video instruction from clinicians, examples from people with lived experience
  - Encouragement to commit to specific practice (with “homework” pages)
- Coaching support:
  - Tailored reinforcement messages after each visit
  - Reminder messages to those “overdue” for a visit – initially every month and spacing out to every 2 months.
- Reinforcing/reminding continued up to 12 months after randomization

Trial outcomes

- Primary outcome – time to first self-harm event, including:
  - Death attributed to self-harm or undetermined intent (from state mortality data)
  - Encounter diagnosis of intentional self-harm (usually from ED or inpatient)
  - "Potential" events not diagnosed as self-harm, but confirmed by full-text records

  (includes some self-harm without intent to die, as that can't be distinguished in records)
- Censored at time of health system disenrollment or death from cause other than self-harm
- Secondary analyses (planned and declared in advance):
  - Narrower: Limited to self-harm resulting in death or hospitalization
  - Broader: Include "potential" events even if not confirmed by clinical text

Blinding

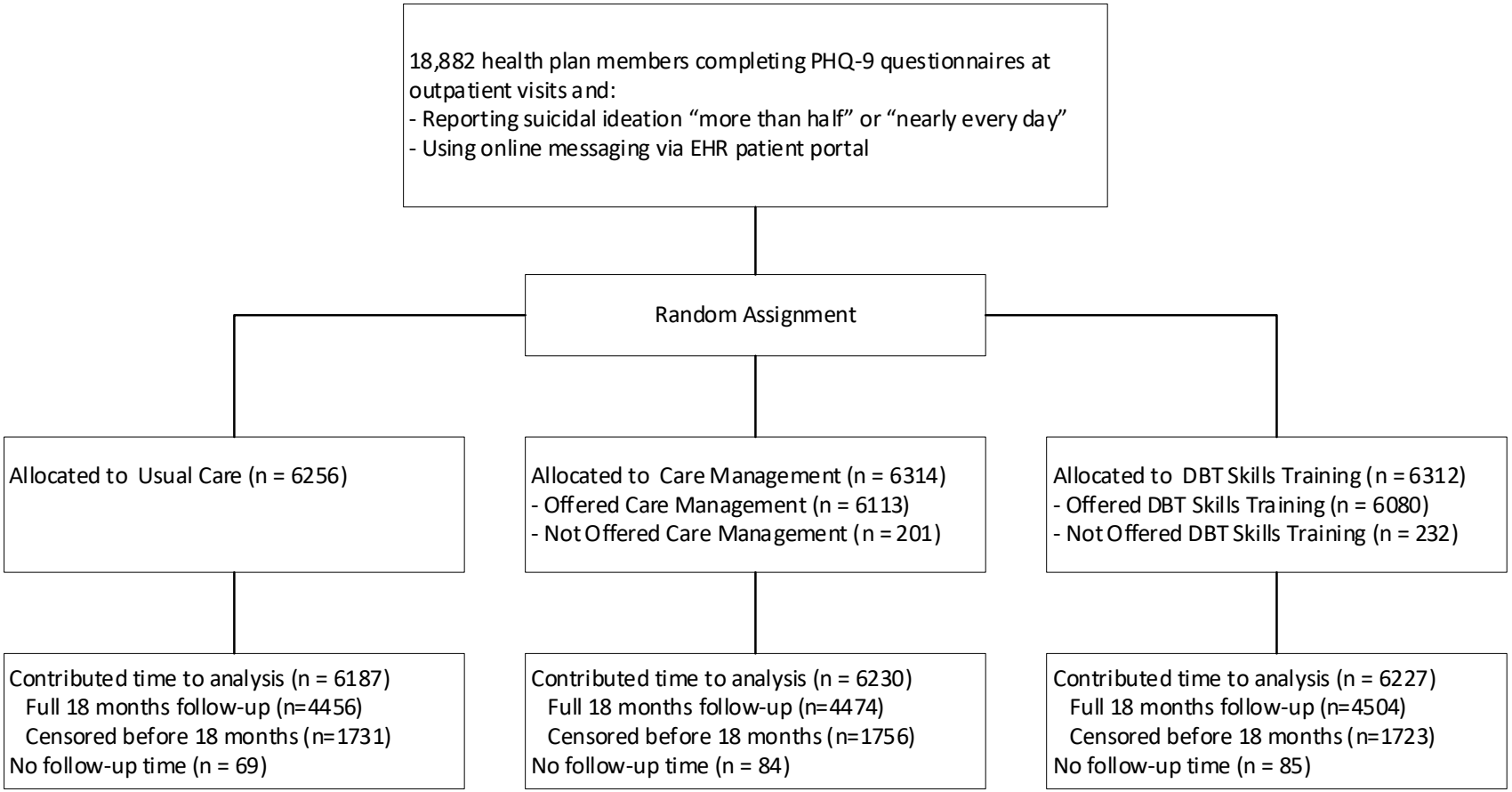
- Usual Care participants never contacted – unaware of study
- Participants assigned to each intervention aware of assignment, but not aware of other intervention or usual care group
- Health outpatient system clinicians aware of intervention assignments, but not assignments to usual care
- Emergency and inpatient clinicians not notified of study or individual assignments, but might have access to outpatient records

Pragmatic Design Features

- Participants identified automatically from existing clinical records
- Broad and simple eligibility criteria, with no “baseline” assessment
- Randomly assign all eligible, regardless of motivation or engagement
- Comparison to usual care, since that is the policy question.
- Participants free to decline or withdraw from any intervention services.
- Outcomes assessed from clinical and vital statistics records.
- Analysis by intent to treat, regardless of intervention uptake or participation

(Not so pragmatic: Intervention was delivered by centralized team with regular monitoring and supervision)

CONSORT diagram



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Analytic sample

	Usual Care n=6187	Care Management n=6230	Skills Training n=6227
Female	4,188 (67.7%)	4,195 (67.3%)	4,160 (66.8%)
Age Group			
18-29	1,457 (23.6%)	1,438 (23.1%)	1,440 (23.1%)
30-44	1,756 (28.4%)	1,747 (28.0%)	1,797 (28.9%)
45-64	2,067 (33.4%)	2,069 (33.2%)	2,056 (33.0%)
65+	907 (14.7%)	976 (15.7%)	934 (15.0%)
Race/Ethnicity			
Non-Hispanic White	4,561 (73.7%)	4,723 (75.8%)	4,651 (74.7%)
Hispanic	595 (8.6%)	495 (7.9%)	486 (7.8%)
Asian, Non-Hispanic	194 (3.1%)	179 (2.9%)	183 (2.9%)
Black, Non-Hispanic	237 (3.8%)	241 (3.9%)	272 (4.4%)
American Indian, Non-Hispanic	35 (0.6%)	56 (0.9%)	42 (0.7%)
Native Hawaiian or Pacific Islander	23 (0.4%)	24 (0.4%)	29 (0.5%)
More than one	203 (3.3%)	170 (2.7%)	188 (3.0%)
Other or not recorded	399 (6.5%)	342 (5.5%)	376 (6.0%)
Location of Index Visit			
Mental Health Specialty Clinic	3,040 (49.1%)	3,071 (49.3%)	3,111 (50.0)
General Medical Clinic	3,147 (50.9%)	3,159 (50.7%)	3,116 (50.0)
Baseline PHQ9 Item 9 Score			
More than half the days	4141 (66.9%)	4180 (67.1%)	4177 (67.1%)
Neary every day	2046 (33.1%)	2050 (32.9%)	2050 (32.9%)
Diagnoses recorded in past year			
Depressive disorder	4058 (65.6%)	4077 (65.4%)	4020 (64.6%)
Anxiety disorder	3653 (59.0%)	3692 (59.3%)	3700 (59.4%)
Bipolar disorder	621 (10.0%)	689 (11.1%)	686 (11.0%)
Drug use disorder	451 (7.3%)	462 (7.4%)	469 (7.5%)
Alcohol use disorder	349 (5.6%)	395 (6.3%)	364 (5.8%)
Personality disorder	510 (8.2%)	528 (8.5%)	561 (9.0%)
Self-harm injury or poisoning	141 (2.3%)	126 (2.0%)	148 (2.4%)
Service use in past year			
Mental health hospitalization	614 (9.9%)	656 (10.5%)	652 (10.5%)
Mental health emergency dept. visit	983 (15.9%)	1000 (16.1%)	1059 (17.0%)

Intervention participation

	Care Management n=6230	Skills Training n=6227
Not offered intervention[1] (n, %)	201 (3.2%)	232 (3.7%)
Actively declined invitation (n, %)	1345(21.6%)	799 (12.8%)
No response after 3 invitations (n, %)	2757 (44.3%)	2780 (44.6%)
Ever engaged in intervention[2] (n, %)	1927 (30.9%)	2416 (38.8%)
Engaged beyond 3 months[3] (n, %)	1612 (25.9%)	767 (12.3%)
Engaged beyond 6 months[3] (n, %)	1392 (22.3%)	268 (4.3%)
Engaged beyond 9 months[3] (n, %)	1049 (16.8%)	117 (1.9%)

Notes:

1 – Determined by treating clinicians or study staff to be unable to participate in intervention due advanced illness, significant cognitive impairment, or other reasons (see Appendix 5 for details)

2 – Ever actively engaged in intervention, regardless of subsequent participation or withdrawal

3 – Definitions of engagement specific to each intervention:

- Engaged in Care Management if ANY of below during interval:
  - Completed study risk assessment
  - Sent online message to care manager
  - Had telephone encounter with care manager
- Engaged in Skills Training if ANY of below:
  - Visited online skills training intervention
  - Sent online message to skills coach
  - Had telephone encounter with skills coach

Data and Safety Monitoring

- Data and safety monitory board (DSMB) met 3 times a year to monitor for patient safety and trial progress
  - Recruitment process and intervention uptake
  - High-risk outreach procedures adherence
  - Complaints or other adverse events
  - Interim analyses to identify a signal of increased risk
    - Safety outcome same as primary trial outcome: suicide attempt
    - Data limitations for monitoring: delay in suicide death data, chart review was conducted at trial completion
  - Bonus of data monitoring - many quality assurance (QA) test of data
    - Very valuable
  - Very limited information for both QA and safety comparisons early on
    - Rare outcome

Complexities of monitoring in SPOT study

- National Institute of Mental Health sponsored DSMB
  - No study team members had direct interaction with DSMB
    - NIMH representative for our trial was there to answer questions
  - Pragmatic trial, relying on “live” EHR data different from many other trials
- KPWA IRB ruled: for individuals who actively refused an intervention their outcome information could not be included in interim monitoring
  - A priori it was known some people would refuse intervention
    - About 20-25% of participants in intervention arms actively refused intervention
  - Biased comparison, two step procedure of signal
  - During monitoring if a signal was detected programmers has IRB permission to gather outcome data on all participants

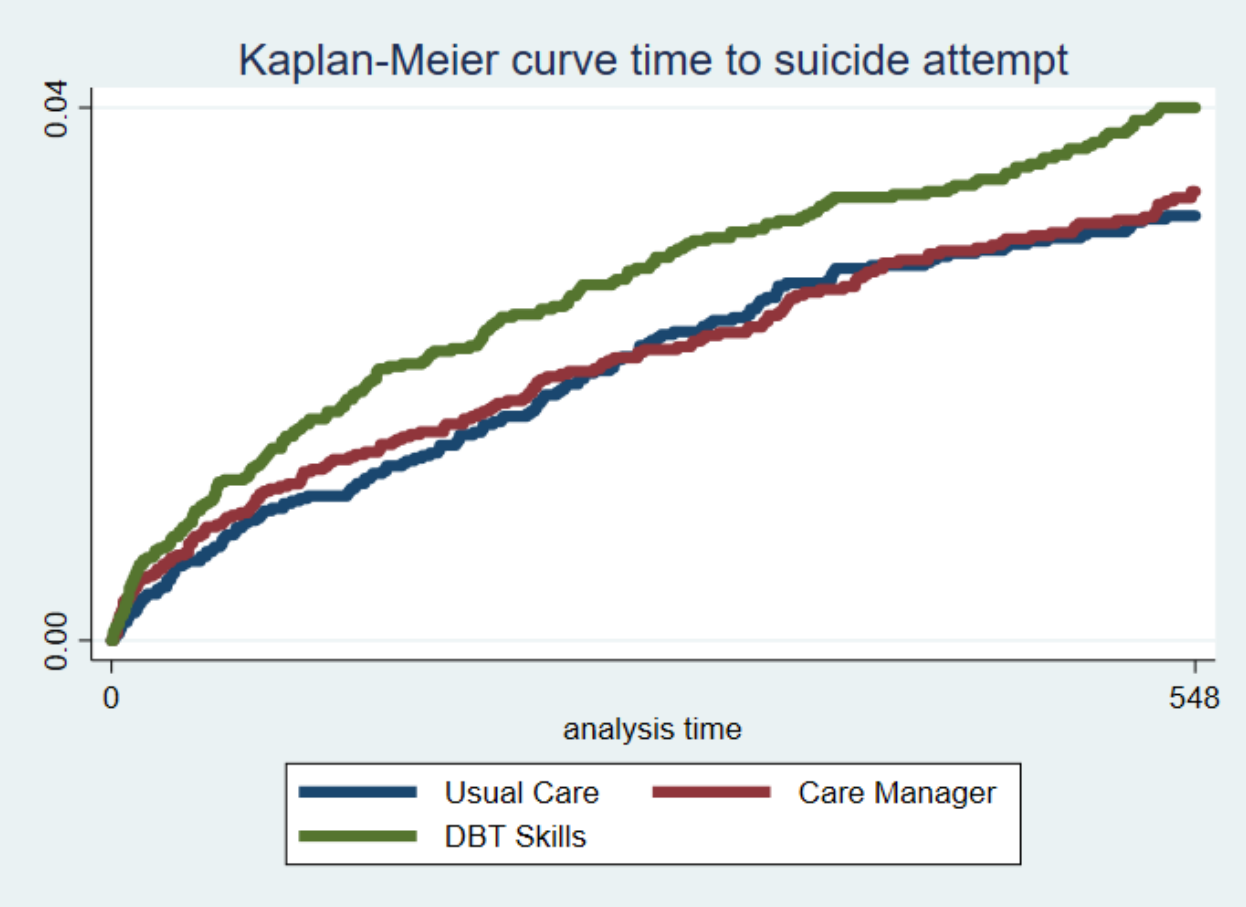
The unexpected happened – on the last look

- A signal was detected in analyst for the last DSMB report
  - Prepared April/May 2019, DSMB reviewed report in June 2019
  - Last patient planned to be randomized Sept 2019
- Programmers repulled data including all participants including those who active refused study interventions
- Analyses rerun and signal dropped below the signal threshold
  - DSMB recommended continuing trial to compete planned enrollment

Lessons I have taken away

- For trials with interim monitoring of serious outcome: at least two biostatisticians should be funded on the project
  - Thank you, Andrea Cook!
- All participants randomized should be included in interim monitoring
  - At the time, excluding “active refusers” from interim analyses seemed like a reasonable compromise between beneficence and autonomy
  - Now we know better!
- Interaction with DSMB is essential

Primary outcome: First fatal or non-fatal self-harm



n=216
n=175
n=167

- Care Management vs. Usual Care: X^2=0.26, p=0.561
- Skills Training vs. Usual Care: X^2=5.36, p=.02

Hazard Ratios from Cox Model

- Care Management vs. Usual Care: 1.07 (0.86 – 1.353
- Skills Training vs. Usual Care: 1.29 (1.05 – 1.659

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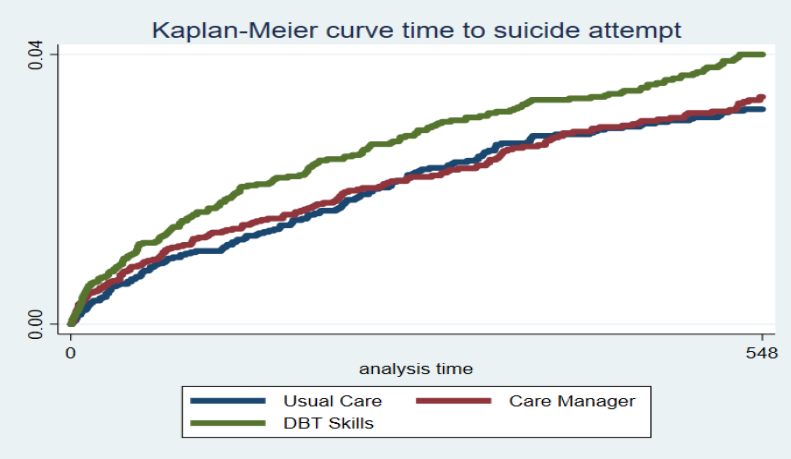
Lots of questions:

- Did we make a simple mistake (like mixing up group labels)?
- Could ascertainment of self-harm have been biased?
- Where and how did increased risk in skills training group occur?

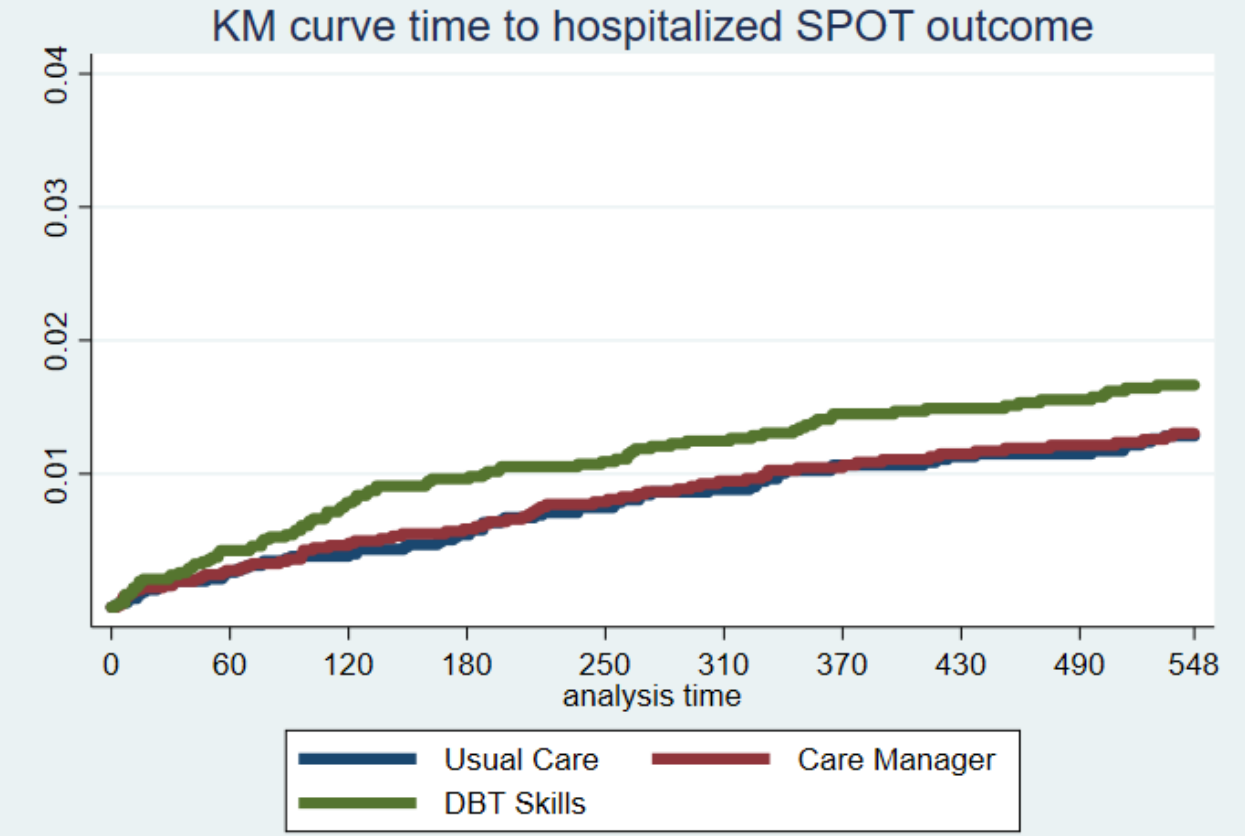


Threat to validity: Biased ascertainment of self-harm

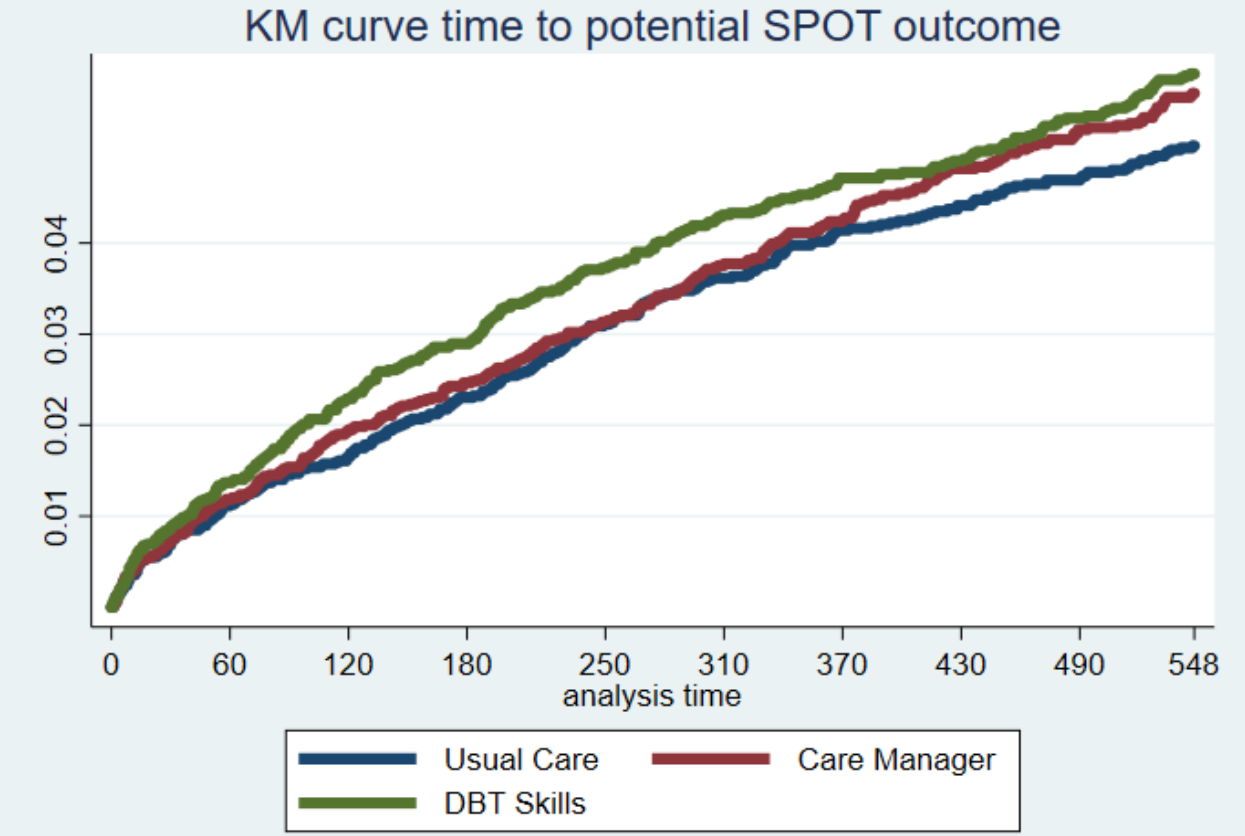
- Exposure to intervention could affect:
  - Likelihood of seeking health care after self-harm
  - Likelihood that self-harm intent would be revealed/detected/recorded
- Secondary analyses intended to address this:
  - Limitation to more severe events – assumes that care-seeking would be less “discretionary”
  - Including “potential events” even if not confirmed – attempts to remove any difference in revealing/detecting self-harm intent

Note: Surveys regarding self-harm are definitely NOT the solution to this potential problem.

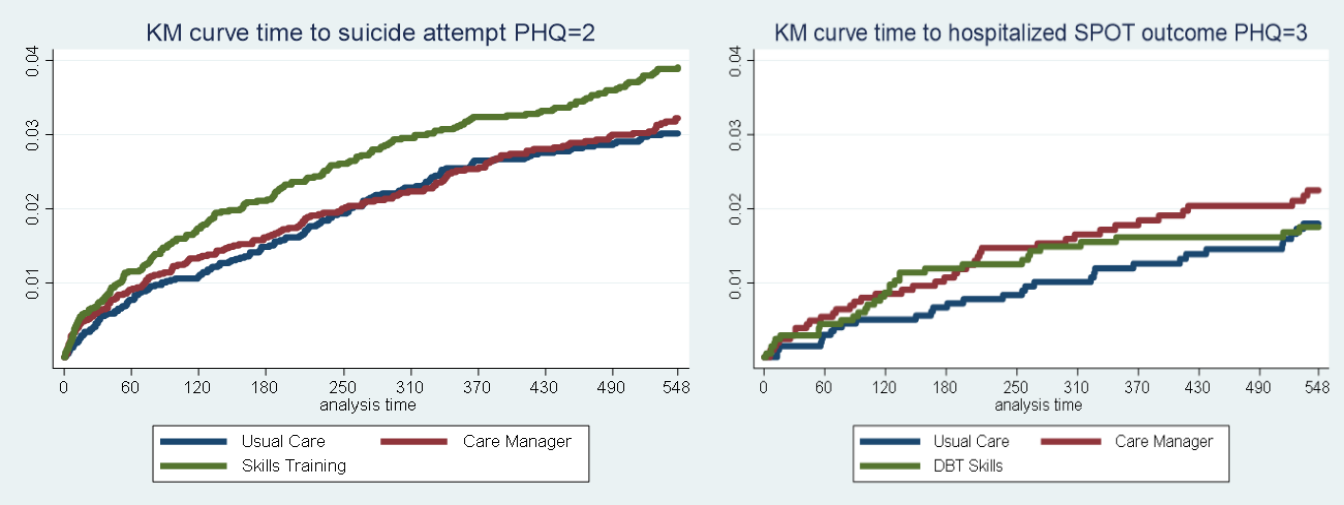
Secondary analyses (planned and declared)
Narrower: Self-harm leading to death or hospitalization



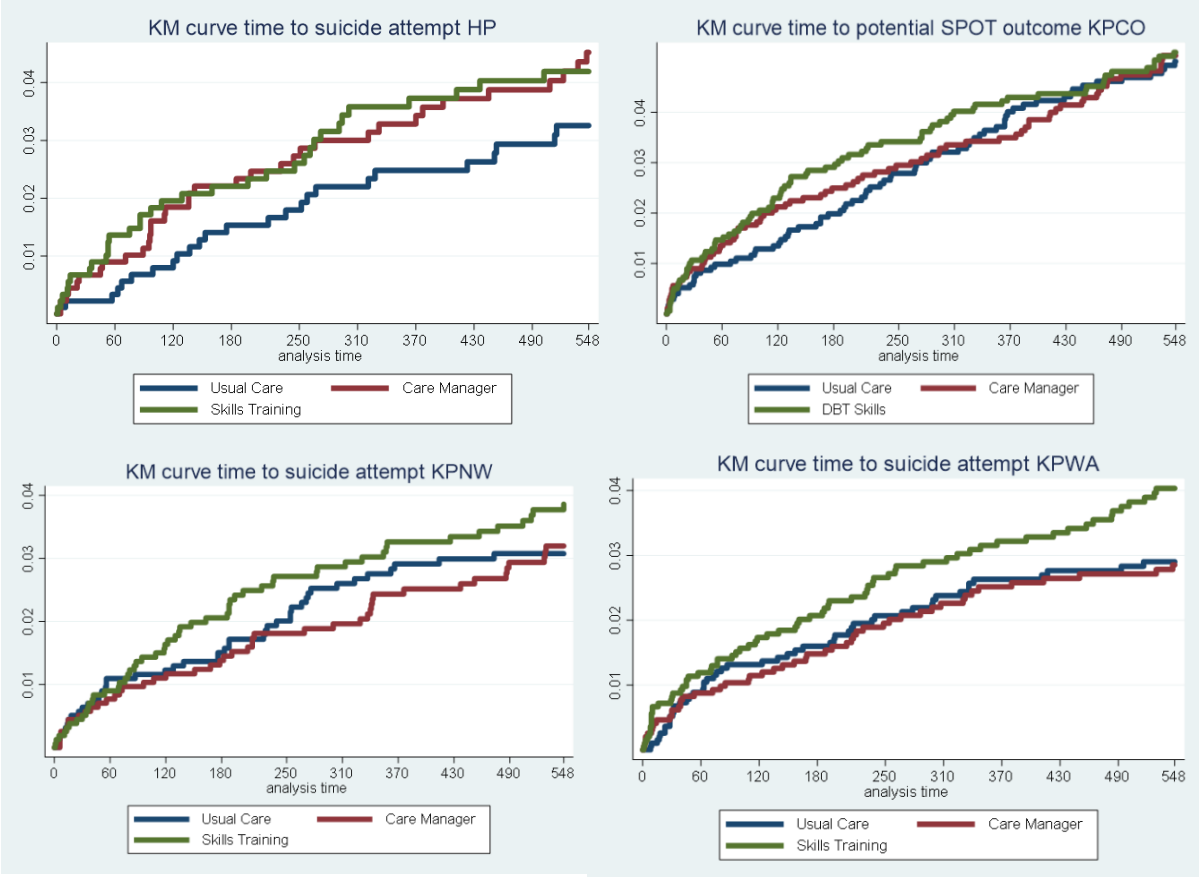
Secondary analyses (planned in advance)
Broader: Add “potential” self-harm not confirmed by chart review



Subgroup analyses: PHQ9 item 9 score at randomization



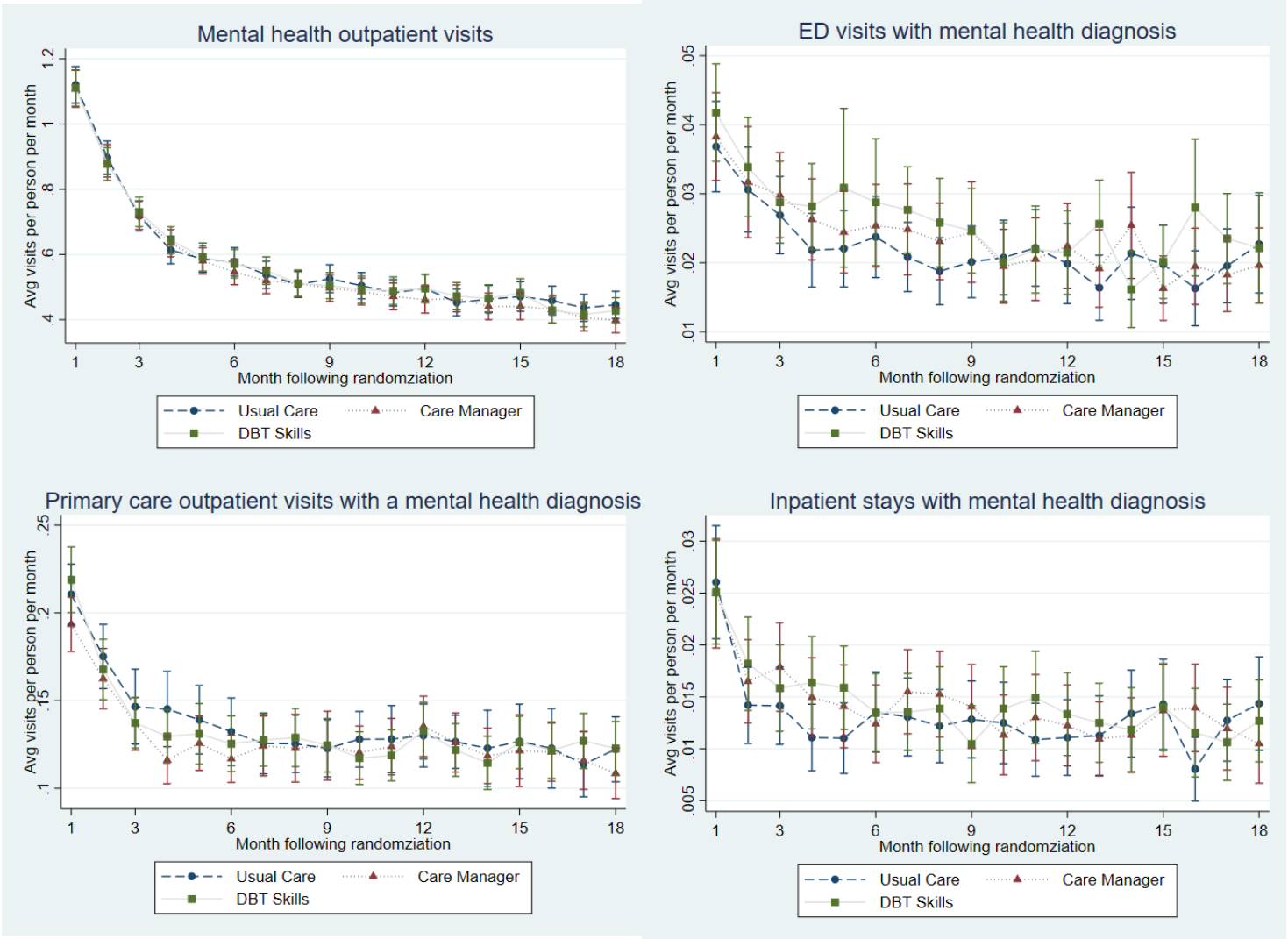
Subgroup analyses: Study site



Other subgroup analyses

	Care Management vs. Usual Care		Skills Training vs. Usual Care	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
PHQ 9 Item 9 Nearly every day (ref: More than half the days)	0.88 (0.57 – 1.35)	0.555	0.76 (0.50 – 1.16)	0.204
Site (ref: Site 1)		0.796		0.974
Site 2	0.74 (0.38 – 1.44)		0.95 (0.49 – 1.83)	
Site 3	0.74 (0.38 – 1.44)		0.99 (0.51 – 1.92)	
Site 4	0.76 (0.40 – 1.46)		1.08 (0.57 – 2.05)	
Randomization Year (ref: 2019)		0.553		0.856
2016	1.29 (0.61 – 2.74)		0.86 (0.43 – 1.72)	
2017	1.24 (0.62 – 2.49)		1.06 (0.57 – 1.97)	
2018	1.68 (0.79 – 3.57)		0.88 (0.43 – 1.79)	
Diagnoses recorded in the past 5 years (ref: No diagnoses in the past 5 years)				
Depressive disorder	0.75 (0.34 – 1.66)	0.485	1.01 (0.45 – 2.26)	0.989
Anxiety disorder	0.89 (0.48 – 1.67)	0.718	1.20 (0.64 – 2.26)	0.565
Bipolar disorder	0.97 (0.59 – 1.58)	0.898	1.07 (0.67 – 1.70)	0.789
Drug use disorder	1.31 (0.79 – 2.16)	0.297	1.34 (0.83 – 2.17)	0.229
Alcohol use disorder	0.86 (0.51 – 1.42)	0.548	0.99 (0.61 – 1.61)	0.969
Personality disorder	0.60 (0.37 – 0.95)	0.030	0.78 (0.51 – 1.21)	0.271
Self-harm injury or poisoning	1.01 (0.60 – 1.69)	0.976	1.29 (0.80 – 2.10)	0.293
Any injury or poisoning	0.57 (0.35 – 0.93)	0.024*	0.73 (0.45 – 1.17)	0.193
Service use in past year (ref: No utilization in the past 5 years)				
Mental health hospitalization	0.69 (0.45 – 1.08)	0.103	0.93 (0.62 – 1.42)	0.750
Mental health emergency dept. visit	0.81 (0.53 – 1.25)	0.346	1.15 (0.76 – 1.74)	0.514
Suicide Risk Prediction at Index Visit (ref: 0% to 0.5% predicted risk)		0.354		0.961
0.5% to 1% predicted risk	0.72 (0.37 – 1.40)		0.97 (0.50 – 1.85)	
1% through 100% predicted risk	0.66 (0.38 – 1.16)		0.93 (0.53 – 1.62)	

Use of non-study mental health services



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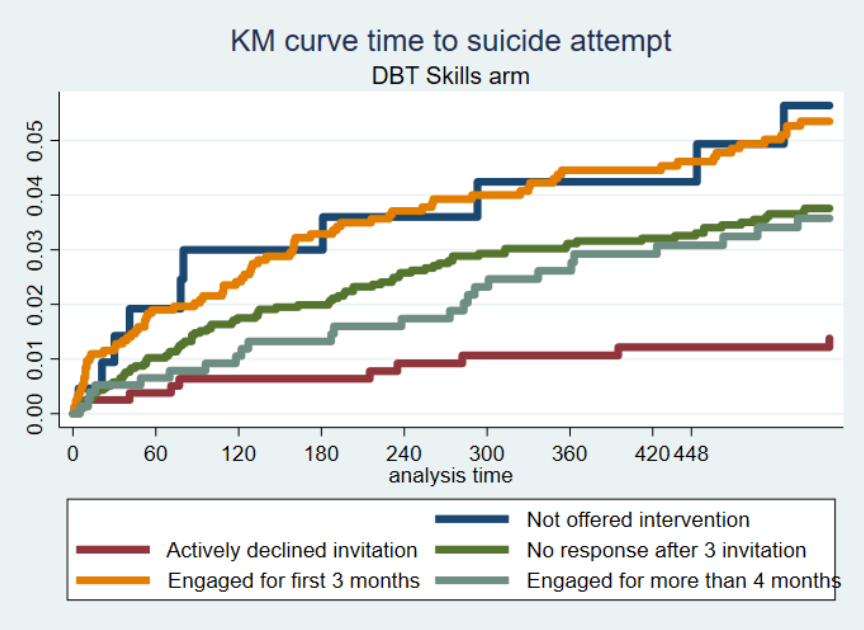
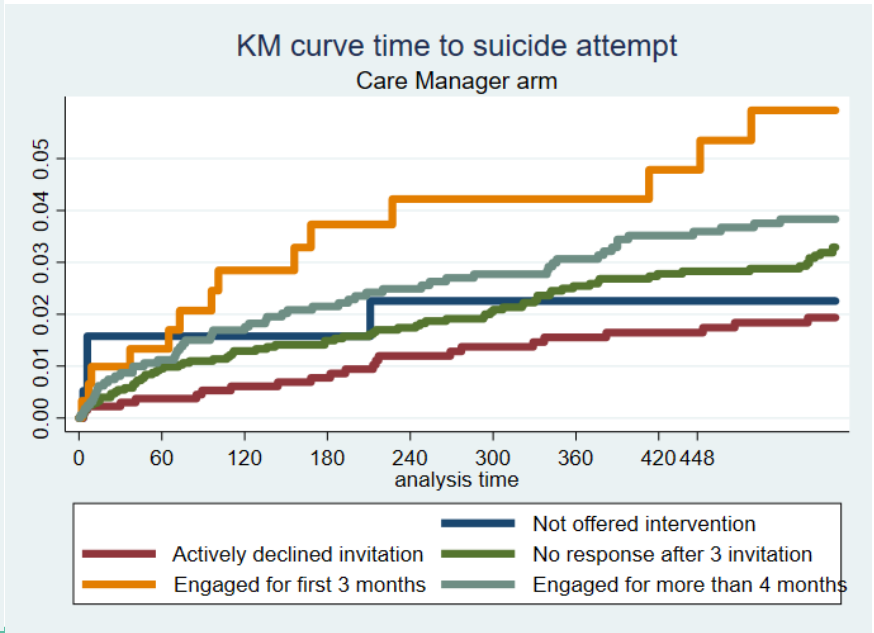
“As treated” comparison: Where is the increased risk?





	Care Management n=6188	Skills Training n=6228
Not offered intervention[1] (n, %)	193 (3.1%)	217 (3.5%)
Actively declined invitation (n, %)	1345(21.6%)	799 (12.8%)
No response after 3 invitations (n, %)	2777 (44.6%)	2796 (44.9%)
Ever engaged in intervention[2] (n, %)	1951 (31.7%)	2416 (38.8%)
Engaged beyond 3 months[3] (n, %)	1622 (26.0%)	777 (12.5%)
Engaged beyond 6 months[3] (n, %)	1400 (22.5%)	274 (4.4%)
Engaged beyond 9 months[3] (n, %)	1055 (16.9%)	119 (1.9%)

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In context

- This sample vs. previous clinical trials (DBT, CBT, ketamine)
  - Much wider range of baseline risk
  - No requirement to accept (or even consider) participating
- This care management vs. effective programs
  - Generally lower intensity, delivered by online messaging
  - Not focused on any specific psychotherapy or pharmacotherapy
- This Skills Training vs. effective DBT
  - Much lower intensity
  - Narrower range of skills
  - No group component

Did we skip a step?

- Samples of a few hundred
- Motivated/engaged participants
- More intensive and standardized interventions

What belongs in this gap?

- Samples of tens of thousands
- “All comers” regardless of engagement or motivation
- Low intensity and more variable interventions