Section 1 - Basic Information (Study 326600)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Buprenorphine effect on suicidal behavior

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	❍ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 326600)

2.1. Conditions or Focus of Study

- Opioid use disorder, Suicidal Behavior

2.2. Eligibility Criteria

Enrolled in participating health system, Outpatient visit with diagnosis of opioid use disorder

2.3. Age Limits	Min Age: 16 Years	Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	Wom_Min_218019.040_Final.pdf	
2.5. Recruitment and Retention Plan	Recruit_Plan_218019.040_Final.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	Timeline_218019.040_Final.pdf	

INCLUSION OF WOMEN, CHILDREN, AND MINORITIES

Women will be included in proportion to representation in the population of people with OUD treated with buprenorphine – predicted to be approximately 45%.

Buprenorphine is not approved for treatment of OUD in children under age 16. Children aged 16 and older will be included in proportion to representation in the population of people with OUD treated with buprenorphine – predicted to be less than 5%.

Members of racial and ethnic minority groups will be included in proportion to representation in the population of people treated for OUD. Anticipated representation of specific racial and ethnic groups is described in the planned enrollment report below.

RECRUITMENT AND RETENTION PLAN

Participants will be identified from existing health system records; no participants will be recruited. Data will be extracted from health system records; retention is not applicable.

TIMELINE

Programming work for specification of all study variables, extraction of data from health system databases, and creation of analytic datasets is expected to be completed by approximately month 10 (the end of the first budget period).

Analyses to address specific aims will be completed by the end of the second budget period.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 326846	Domestic	Kaiser Permanente Washington, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Henry Ford Health System

Inclusion Enrollment Report 326846

Using an Existing Dataset or Resource* : ● Yes ❍ No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Kaiser Permanente Washington, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Henry Ford Health System

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	145	178	8	9	340
Asian	727	888	38	47	1700
Native Hawaiian or Other Pacific Islander	218	266	11	14	509
Black or African American	490	598	122	150	1360
White	4406	5386	1102	1346	12240
More than One Race	287	351	96	117	851
Total	6273	7667	1377	1683	17000

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 326600)

3.1. Protection of Human Subjects	Hum_Subj_218019.040_Final.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ❍ No ❍ N/A
If yes, describe the single IRB plan	SIRB_218019.040_Final.pdf
3.3. Data and Safety Monitoring Plan	DSMP_218019.040_Final.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	Team_218019.040_Final.pdf

PROTECTION OF HUMAN SUBJECTS

Note: Under the Revised Common Rule, research limited to existing records may be considered exempt from IRB review. Washington State law, however, still requires IRB review of records-based research. Consequently, we anticipate requesting and being granted a waiver of informed consent (rather than an exemption) to conduct this records-based research.

Human Subjects Involvement, Characteristics, and Design

Analyses will use existing health system records to examine effect of initiating buprenorphine treatment on risk of subsequent suicidal behavior. These analyses will use data regarding mental health and substance use disorder diagnoses and treatments to identify the study sample, identify the exposure of interest, assess covariates or confounders, and assess study outcomes.

Study Procedures, Materials, and Potential Risks

Whenever possible, analyses will rely on de-identified research warehouses at study sites. This research would generally be considered exempt. Some analyses involving non-standard data types (e.g. prescription drug monitoring program data may require use of identified primary data sources.

Any data shared between study sites will be completely de-identified – including rigorous assessment of re-identification risk using methods developed by MHRN.

The only risk to health system members would be breach of confidentiality by accidental disclosure of health information.

Adequacy of Protection Against Risks

Informed Consent

- We propose a waiver of consent to use records data for this purpose. Such a waiver is justified because:
  - Use of existing records for this purpose does not involve more than minimal risk
  - It would not be practicable (or even possible) to contact every health plan member to request consent for use of records. Requiring positive consent might also lead to significant bias, as patterns of diagnosis and treatment in those who respond to a research invitation might differ from patterns in the general population.
  - Use of records for this purpose will not affect patients' rights, privileges, or access to any effective treatments.

  In each of the participating health systems, the Notice of Privacy Practices includes explicit notification regarding use of records for research and the right to opt out of research use.

Protection Against Risk

All identified or identifiable data will remain at participating health systems, stored in password-protected files behind HITECH-compliant health system firewalls. At all sites, access to identified or identifiable data files will be monitored and tracked. All study staff will complete required training regarding HIPAA compliance, privacy protection, and protection of human research participants.

Potential Benefits of the Proposed Research to Research Participants and Others

Participation will not have any direct benefit to health system members who contribute data to these analyses.

Importance of the Knowledge to be Gained

As described in the associated Research Plan, these descriptive analyses have already made substantial contributions in several areas (racial/ethnic disparities in care, epidemiology of suicidal behavior, appropriate psychotropic prescribing). We anticipate that this ongoing work will make additional contributions, support future research, and address questions of interest to a range of stakeholders.

SINGLE IRB PLAN

Under the Revised Common Rule, research limited to existing records may be considered exempt from IRB review. Washington State law, however, still requires IRB review of records-based research. Consequently, the Kaiser Permanente Washington IRB will serve as the single IRB for these descriptive analyses and observational studies. If any other sites besides Kaiser Permanent Washington do not consider this work to be exempt (i.e. IRB review is required) then those sites will cede review to the Kaiser Permanente Washington IRB.

DATA AND SAFETY MONITORING

We do not believe that a data and safety monitoring plan is necessary for descriptive analyses using existing health system data.

Regarding monitoring of participant safety – Patients will not be contacted for this research. Analyses will use existing records data regarding diagnoses and treatments occurring months or years in the past. Even when analyses include data regarding risk or potential harm (e.g. suicidal ideation), no timely or clinically appropriate intervention would be possible. Any information available to study staff months or years later would already have been available to treating providers.

Regarding data quality or integrity – MHRN conducts detailed quarterly analyses to assess and (if necessary) improve quality of data in each participating health system's research data warehouse. No additional monitoring is necessary.

STRUCTURE OF STUDY TEAM

Dr. Simon will serve as overall principal investigator and lead investigator for the KP Washington site. Dr. Shortreed will design, lead, and supervise data analyses.

At each site, staff will include a programmer/analyst responsible for timely execution of distributed programs, a project manager responsible for regulatory compliance, and a lead investigator responsible for liaison with health system clinical and informatics leadership.

Section 4 - Protocol Synopsis (Study 326600)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Section 6 - Clinical Trial Milestone Plan (Study 326600)

6.1. Study Primary Completion Date
6.2. Study Final Completion Date
6.3. Enrollment and randomization

Enrollment of the first subject	07/01/2021	Anticipated
25% of planned enrollment recruited by		
50% of planned enrollment recruited by		
75% of planned enrollment recruited by		
100% of planned enrollment recruited by		

6.4. Completion of primary endpoint data analyses
6.5. Reporting of results in ClinicalTrials.gov
6.6. Is this an applicable clinical trial under FDAAA? ❍ Yes ❍ No

Section 1 - Basic Information (Study 278298)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Mental Health Research Network Methods Core

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	❍ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 278298)

2.1. Conditions or Focus of Study

- Mental Health

2.2. Eligibility Criteria

Descriptive analyses will include all enrolled members or affiliate patients in participating health systems.

2.3. Age Limits	Min Age: N/A (No limit)	Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	MethodsCore_Wom_Min_218019_Final.pdf	
2.5. Recruitment and Retention Plan	MethodsCore_Recruit_Plan_218019_Final.pdf	
2.6. Recruitment Status	Enrolling by invitation	
2.7. Study Timeline	MethodsCore_Timeline_218019_Final.pdf	

Descriptive analyses will include all enrolled members and/or affiliated patients in participating health systems – estimated to be over 25 million combined across all sites. Both men and women will be included. All ages, including children and the elderly will be included. All racial and ethnic groups will be included. Some targeted analyses may be limited to men or women, to specific age groups, or to specific racial or ethnic groups. These restrictions will be determined according to the scientific question being addressed by each specific analysis.

All analyses will use existing records data. Members or patients will not be contacted, and therefore will not be recruited.

As shown in the timeline in the associated Administrative Core Research Plan, descriptive analyses will be conducted approximately quarterly, beginning in month 3 and continuing through month 57.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 275666	Domestic	Baylor/Scott & White Health, Essentia Health, Harvard-Pilgrim Healthcare, HealthPartners, Henry Ford Health System, INSIGHT Network (NYC-CDRN), KP CO, KP GA, KP HI, KP NC, KP NW, KP SC, KP WA, Palo Alto Medical Foundation

Inclusion Enrollment Report 275666

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Baylor/Scott & White Health, Essentia Health, Harvard-Pilgrim Healthcare, HealthPartners, Henry Ford Health System, INSIGHT Network (NYC-CDRN), KP CO, KP GA, KP HI, KP NC, KP NW, KP SC, KP WA, Palo Alto Medical Foundation

Comments: Descriptive analyses will include all enrolled members and/or affiliated patients of participating health systems. Approximate numbers of members/patients in 2017 are shown in the planned table below. Reported enrollment reflects data from sites already completing analyses for the first quarter of 2020. We anticipate final results for the first quarter to include approximately 20 million members/patients & results for the full 5-year grant period to include over 25 million.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	100000	100000	0	0	200000
Asian	900000	900000	0	0	1800000
Native Hawaiian or Other Pacific Islander	100000	100000	0	0	200000
Black or African American	1050000	1050000	50000	50000	2200000
White	9400000	9400000	1500000	1500000	21800000
More than One Race	350000	350000	50000	50000	800000
Total	11900000	11900000	1600000	1600000	27000000

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	20440	17749	0	11765	10741	0	14999	13949	0	89643
Asian	394212	346483	0	27523	25195	0	456897	426519	0	1676829
Native Hawaiian or Other Pacific Islander	52091	48999	0	7578	7080	0	24894	23273	0	163915
Black or African American	252662	224538	0	20509	18790	0	249924	227459	0	993882
White	1685167	1456074	0	663543	612041	0	1307437	1215173	0	6939435
More than One Race	288	265	0	11957	11150	0	250	221	0	24131
Unknown or Not Reported	304753	273537	0	28087	25870	0	274818	250732	2400	1160197

Section 3 - Protection and Monitoring Plans (Study 278298)

3.1. Protection of Human Subjects	MethodsCore_Hum_Subj_218019_Final.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ❍ No ❍ N/A
If yes, describe the single IRB plan	MethodsCore_SIRB_218019_Final.pdf
3.3. Data and Safety Monitoring Plan	MethodsCore_DSMP_218019_Final.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	MethodsCore_Team_218019_Final.pdf

Note: Under the Revised Common Rule, research limited to existing records may be considered exempt from IRB review. Washington State law, however, still requires IRB review of records-based research. Consequently, we anticipate requesting and being granted a waiver of informed consent (rather than an exemption) to conduct this records-based research.

Human Subjects Involvement, Characteristics, and Design

Routine descriptive analyses will use existing health system records to examine counts and rates of mental health diagnoses and treatment in MHRN health systems. Analyses will examine cross-classification of diagnoses with treatments (e.g. proportion of people with diagnosis of bipolar disorder filling prescriptions for antidepressants) and cross-classification of diagnoses and/or treatments with demographic characteristics (e.g. proportion of youth with diagnoses of bipolar disorder prescribed lithium. These routine analyses are intended to monitor quality of MHRN data resources at each site and to identify important trends or patterns in mental health diagnoses and treatments. Additional more detailed analyses (to be determined as described in the associated Research Plan) will assess feasibility of specific research projects, develop pilot data for future research, or examine specific questions ide by internal or external stakeholders.

Study Procedures, Materials, and Potential Risks

Whenever possible, analyses will rely on de-identified research warehouses at study sites. This research would generally be considered exempt. Some analyses involving non-standard data types (e.g. clinical text, uncommon patient-reported outcome questionnaires) my require use of identified primary data sources.

Whenever possible, analyses will be conducted using privacy-preserving distributed analytic methods – sharing only aggregated results rather than individual-level data. It is possible, however, that some analyses may require sharing of individual-level data. In those cases, data will be completely de-identified – including rigorous assessment of re-identification risk as described in the associated Research Plan.

The only risk to health system members would be breach of confidentiality by accidental disclosure of health information.

Adequacy of Protection Against Risks

Informed Consent

- We propose a waiver of consent to use records data for this purpose. Such a waiver is justified because:
  - Use of existing records for this purpose does not involve more than minimal risk
  - It would not be practicable (or even possible) to contact every health plan member to request consent for use of records. Requiring positive consent might also lead to significant bias, as patterns of diagnosis and treatment in those who respond to a research invitation might differ from patterns in the general population.
  - Use of records for this purpose will not affect patients' rights, privileges, or access to any effective treatments.

  In each of the participating health systems, the Notice of Privacy Practices includes explicit notification regarding use of records for research and the right to opt out of research use.

Protection Against Risk

All identified or identifiable data will remain at participating health systems, stored in password-protected files behind HITECH-compliant health system firewalls. At all sites, access to identified or identifiable data files will be monitored and tracked. All study staff will complete required training regarding HIPAA compliance, privacy protection, and protection of human research participants.

Potential Benefits of the Proposed Research to Research Participants and Others

Participation will not have any direct benefit to health system members who contribute data to these analyses.

Importance of the Knowledge to be Gained

As described in the associated Research Plan, these descriptive analyses have already made substantial contributions in several areas (racial/ethnic disparities in care, epidemiology of suicidal behavior, appropriate psychotropic prescribing). We anticipate that this ongoing work will make additional contributions, support future research, and address questions of interest to a range of stakeholders.

Under the Revised Common Rule, research limited to existing records may be considered exempt from IRB review. Washington State law, however, still requires IRB review of records-based research. Consequently, the Kaiser Permanente Washington IRB will serve as the single IRB for these descriptive analyses and observational studies. If any other sites besides Kaiser Permanent Washington do not consider this work to be exempt (i.e. IRB review is required) then those sites will be expected to cede review to the Kaiser Permanente Washington IRB. The MHRN has long used IRB reliance agreements developed by the broader Health Care Systems Research Network, and all MHRN sites are accustomed to ceding for studies limited to analyses of records data.

We do not believe that a data and safety monitoring plan is necessary for descriptive analyses using existing health system data.

Regarding monitoring of participant safety – Patients will not be contacted for this research. Analyses will use existing records data regarding diagnoses and treatments occurring months or years in the past. Even when analyses include data regarding risk or potential harm (e.g. suicidal ideation), no timely or clinically appropriate intervention would be possible. Any information available to study staff months or years later would already have been available to treating providers.

Regarding data quality or integrity – These analyses will be conducted as part of MHRN's ongoing assessment of data quality and integrity. The associated Research Plan describes process to address data quality concerns. No additional monitoring is necessary.

Descriptive analyses, feasibility/pilot analyses, and analyses to address stakeholder queries will be led by Dr. Christine Stewart as described in the associated Research Plan. Programs developed by Dr. Stewart and colleagues (with consultation from Dr. Simon and other MHRN investigators) will be executed against distributed data resources at each site.

At each site, staff (supported by the Administrative Core budget) will include a programmer/analyst responsible for timely execution of distributed programs, a project manager responsible for regulatory compliance, and a lead investigator responsible for liaison with health sysem clinical and informatics leadership.

Section 4 - Protocol Synopsis (Study 278298)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Section 6 - Clinical Trial Milestone Plan (Study 278298)

6.1. Study Primary Completion Date
6.2. Study Final Completion Date
6.3. Enrollment and randomization

Enrollment of the first subject	03/04/2020	Actual
25% of planned enrollment recruited by		
50% of planned enrollment recruited by		
75% of planned enrollment recruited by		
100% of planned enrollment recruited by		

6.4. Completion of primary endpoint data analyses
6.5. Reporting of results in ClinicalTrials.gov
6.6. Is this an applicable clinical trial under FDAAA? ❍ Yes ❍ No

Section 1 - Basic Information (Study 278296)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Mental Health Research Network Administrative Core

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	❍ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 278296)

2.1. Conditions or Focus of Study

- Mental Health

2.2. Eligibility Criteria

Descriptive analyses will include all enrolled members or affiliate patients in participating health systems.

2.3. Age Limits	Min Age: N/A (No limit) Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	AdminCore_Wom_Min_218019_Final.pdf
2.5. Recruitment and Retention Plan	AdminCore_Recruit_Plan_218019_Final.pdf
2.6. Recruitment Status	Enrolling by invitation
2.7. Study Timeline	AdminCore_Timeline_218019_Final.pdf

Descriptive analyses will include all enrolled members and/or affiliate patients in participating health systems – estimated to be over 30 million combined across all sites. Both men and women will be included. All ages, including children and the elderly will be included. All racial and ethnic groups will be included. Some targeted analyses may be limited to men or women, to specific age groups, or to specific racial or ethnic groups. These restrictions will be determined according to the scientific question being addressed by any specific analysis.

All analyses will use existing records data. Members or patients will not be contacted, and therefore will not be recruited.

As shown in the timeline in the associated Research Plan, descriptive analyses will be conducted approximately quarterly, beginning in month 3 and continuing through month 57.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 275664	Domestic	Baylor/Scott & White Health, Essentia Health, Harvard-Pilgrim Healthcare, HealthPartners, Henry Ford Health System, INSIGHT Network (NYC-CDRN), KP CO, KP GA, KP HI, KP NC, KP NW, KP SC, KP WA, Palo Alto Medical Foundation

Inclusion Enrollment Report 275664

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Baylor/Scott & White Health, Essentia Health, Harvard-Pilgrim Healthcare, HealthPartners, Henry Ford Health System, INSIGHT Network (NYC-CDRN), KP CO, KP GA, KP HI, KP NC, KP NW, KP SC, KP WA, Palo Alto Medical Foundation

Comments: Descriptive analyses will include all enrolled members and/or affiliated patients of participating health systems. Approximate numbers of members/patients in 2017 are shown in the planned table below. Reported enrollment reflects data from sites already completing analyses for the first quarter of 2020. We anticipate final results for the first quarter to include approximately 20 million members/patients and results for the full 5-year grant period to include over 25 million.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	100000	100000	0	0	200000
Asian	900000	900000	0	0	1800000
Native Hawaiian or Other Pacific Islander	100000	100000	0	0	200000
Black or African American	1050000	1050000	50000	50000	2200000
White	9400000	9400000	1500000	1500000	21800000
More than One Race	350000	350000	50000	50000	800000
Total	11900000	11900000	1600000	1600000	27000000

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	20440	17749	0	11765	10741	0	14999	13949	0	89643
Asian	394212	346483	0	27523	25195	0	456897	426519	0	1676829
Native Hawaiian or Other Pacific Islander	52091	48999	0	7578	7080	0	24894	23273	0	163915
Black or African American	252662	224538	0	20509	18790	0	249924	227459	0	993882
White	1685167	1456074	0	663543	612041	0	1307437	1215173	0	6939435
More than One Race	288	265	0	11957	11150	0	250	221	0	24131
Unknown or Not Reported	304753	273537	0	28087	25870	0	274818	250732	2400	1160197

Section 3 - Protection and Monitoring Plans (Study 278296)

3.1. Protection of Human Subjects	AdminCore_Hum_Subj_218019_Final.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ❍ No ❍ N/A
If yes, describe the single IRB plan	AdminCore_SIRB_218019_Final.pdf
3.3. Data and Safety Monitoring Plan	AdminCore_DSMP_218019_Final.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	AdminCore_Team_218019_Final.pdf

Note: Under the Revised Common Rule, research limited to existing records may be considered exempt from IRB review. Washington State law, however, still requires IRB review of records-based research. Consequently, we anticipate requesting and being granted a waiver of informed consent (rather than an exemption) to conduct this records-based research.

Human Subjects Involvement, Characteristics, and Design

Routine descriptive analyses will use existing health system records to examine counts and rates of mental health diagnoses and treatment in MHRN health systems. Analyses will examine cross-classification of diagnoses with treatments (e.g. proportion of people with diagnosis of bipolar disorder filling prescriptions for antidepressants) and cross-classification of diagnoses and/or treatments with demographic characteristics (e.g. proportion of youth with diagnoses of bipolar disorder prescribed lithium. These routine analyses are intended to monitor quality of MHRN data resources at each site and to identify important trends or patterns in mental health diagnoses and treatments. Additional more detailed analyses (to be determined as described in the associated Research Plan) will assess feasibility of specific research projects, develop pilot data for future research, or examine specific questions identified by internal or external stakeholders.

Study Procedures, Materials, and Potential Risks

Whenever possible, analyses will rely on de-identified research warehouses at study sites. This research would generally be considered exempt. Some analyses involving non-standard data types (e.g. clinical text, uncommon patient-reported outcome questionnaires) may require use of identified primary data sources.

Whenever possible, analyses will be conducted using privacy-preserving distributed analytic methods – sharing only aggregated results rather than individual-level data. It is possible, however, that some analyses may require sharing of individual-level data. In those cases, data will be completely de-identified – including rigorous assessment of re-identification risk as described in the associated Research Plan.

The only risk to health system members would be breach of confidentiality by accidental disclosure of health information.

Adequacy of Protection Against Risks

Informed Consent

- We propose a waiver of consent to use records data for this purpose. Such a waiver is justified because:
  - Use of existing records for this purpose does not involve more than minimal risk
  - It would not be practicable (or even possible) to contact every health plan member to request consent for use of records. Requiring positive consent might also lead to significant bias, as patterns of diagnosis and treatment in those who respond to a research invitation might differ from patterns in the general population.
  - Use of records for this purpose will not affect patients' rights, privileges, or access to any effective treatments.

  In each of the participating health systems, the Notice of Privacy Practices includes explicit notification regarding use of records for research and the right to opt out of research use.

Protection Against Risk

All identified or identifiable data will remain at participating health systems, stored in password-protected files behind HITECH-compliant health system firewalls. At all sites, access to identified or identifiable data files will be monitored and tracked. All study staff will complete required training regarding HIPAA compliance, privacy protection, and protection of human research participants.

Potential Benefits of the Proposed Research to Research Participants and Others

Participation will not have any direct benefit to health system members who contribute data to these analyses.

Importance of the Knowledge to be Gained

As described in the associated Research Plan, these descriptive analyses have already made substantial contributions in several areas (racial/ethnic disparities in care, epidemiology of suicidal behavior, appropriate psychotropic prescribing). We anticipate that this ongoing work will make additional contributions, support future research, and address questions of interest to a range of stakeholders.

Under the Revised Common Rule, research limited to existing records may be considered exempt from IRB review. Washington State law, however, still requires IRB review of records-based research. Consequently, the Kaiser Permanente Washington IRB will serve as the single IRB for these descriptive analyses and observational studies. If any other sites besides Kaiser Permanent Washington do not consider this work to be exempt (i.e. IRB review is required) then those sites will be expected to cede review to the Kaiser Permanente Washington IRB. The MHRN has long used IRB reliance agreements developed by the broader Health Care Systems Research Network, and all MHRN sites are accustomed to ceding for studies limited to analyses of records data.

We do not believe that a data and safety monitoring plan is necessary for descriptive analyses using existing health system data.

Regarding monitoring of participant safety – Patients will not be contacted for this research. Analyses will use existing records data regarding diagnoses and treatments occurring months or years in the past. Even when analyses include data regarding risk or potential harm (e.g. suicidal ideation), no timely or clinically appropriate intervention would be possible. Any information available to study staff months or years later would already have been available to treating providers.

Regarding data quality or integrity – These analyses will be conducted as part of MHRN's ongoing assessment of data quality and integrity. The associated Research Plan describes process to address data quality concerns. No additional monitoring is necessary.

Descriptive analyses, feasibility/pilot analyses, and analyses to address stakeholder queries will be led by Dr. Christine Stewart as described in the associated Research Plan. Programs developed by Dr. Stewart and colleagues (with consultation from Dr. Simon and other MHRN investigators) will be executed against distributed data resources at each site.

At each site, staff will include a programmer/analyst responsible for timely execution of distributed programs, a project manager responsible for regulatory compliance, and a lead investigator responsible for liaison with health sysem clinical and informatics leadership.

Section 4 - Protocol Synopsis (Study 278296)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Section 6 - Clinical Trial Milestone Plan (Study 278296)

6.1. Study Primary Completion Date
6.2. Study Final Completion Date
6.3. Enrollment and randomization

Enrollment of the first subject	03/04/2020	Actual
25% of planned enrollment recruited by		
50% of planned enrollment recruited by		
75% of planned enrollment recruited by		
100% of planned enrollment recruited by		

6.4. Completion of primary endpoint data analyses
6.5. Reporting of results in ClinicalTrials.gov
6.6. Is this an applicable clinical trial under FDAAA? ❍ Yes ❍ No

Section 1 - Basic Information (Study 278300)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Pragmatic Effectiveness/Implementation Trial of Digital Mindfulness-Based Cognitive Therapy for Prevention of Perinatal Depression.

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	❍ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	❍ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 278300)

2.1. Conditions or Focus of Study

- Pragmatic effectiveness trial of digitally-delivered Mindfulness Based Cognitive Therapy for the prevention of perinatal depression.

2.2. Eligibility Criteria

Participants will be women greater than or equal to18 years of age, receiving prenatal care, 12-28 weeks gestation, with at least one prior episode of MDD, and current PHQ-9 score <10. Women with a diagnosis of a psychotic, bipolar, or substance use disorder or at immediate risk of self-harm will be excluded. Since the intervention is in English only, patients who are unable to speak and read English will be excluded.

2.3. Age Limits	Min Age: 18 Years	Max Age: 45 Years
2.4. Inclusion of Women, Minorities, and Children	SP1_Wom_Min_218019_Final.pdf	
2.5. Recruitment and Retention Plan	SP1_Recruit_Plan_218019_Final.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	SP1_Timeline_218019_Final.pdf	

Inclusion of women – All participants will be women since this study focuses on perinatal depression.

Inclusion of minorities – We anticipate that the race/ethnicity of the target population of this trial will mirror the membership of the participating sites.

Inclusion of children – Children under 18 will not be included. Trial design is determined by treatment guidelines specific to adults, assessment tools specific to adults, and EHR functionalities only available to adult health system members.

Participant recruitment and retention procedures

The effectiveness trial will involve recruiting and randomizing 460 pregnant women at risk for recurrent depression to receive the digital intervention, Mindful Mood Balance for Moms (MMBFM) (N=230) or Usual Care (UC) (N=230). Recruitment will be done at Kaiser Permanente Colorado (KPCO) and Kaiser Permanente Southern California (KPSC). We will use electronic medical records to identify potentially eligible women receiving routine prenatal care. Study participants will be recruited using methods suitable for each site, including bulk email and/or secure message through the EMR patient portal, or by regular mail. The outreach message will contain a link to a recruiting survey containing a description of the study and brief questions to determine initial eligibility, followed by online consent. Women who pass the initial screen and consent will be called by the study staff at KPCO to review the online consent, complete the baseline clinical assessment and be randomized into MMBFM or UC.

Recruitment and referral sources

The primary recruitment source will be data on prenatal visits that we will extract from the virtual data warehouses at KPCO and KPSC using distributed programming code. There were approximately 6,000 births at KPCO and 39,000 births at KPSC in 2016. We will exclude women <18 years of age and non-English speakers. We will include women with a history of depression from clinical interview at baseline, and a baseline PHQ-9 score <10, yielding an estimated 1,040 eligible women at KPCO and 6,638 at KPSC. We conservatively estimate a 10% enrollment rate and 70% retention rate, which will provide a sample of 538 over a one-year enrollment period.

Procedures that will be used to monitor enrollment and track/retain participants for any proposed follow-up assessments

Participant enrollment, tracking, and outcome assessment will be centralized at KPCO using REDCap (Research Electronic Data Capture, a web-based survey technology). REDCap functionality includes participant outreach and follow-up messages, reminders to complete outcome assessments, and participant tracking that provides alerts to the research staff to contact participants who have not responded to outreach. Retention will be facilitated by a combination of multiple supportive email and phone messages reminding participants to complete outcome assessments. For the MMBFM intervention participants, additional telephonic and digital coaching will be provided to foster engagement in the program and completion of outcome assessments.

Outcome data for preterm birth and gestational age will be obtained from electronic medical records data. Based on prior MHRN research, we anticipate that these data will be unavailable for less than 5% of participants due to disenrollment from their respective health plans during the study.

The KPCO study team has extensive experience using REDCap for participant tracking and outcome assessment, including the recent pragmatic trial of digital MBCT for 460 participants (Strategies for Overcoming Residual Depression (Segal, MH102229), and the Suicide Prevention Outreach Trial (Simon, 5UH3MH007755) of nearly 5,000 participants.

Strategies that will be used to ensure a diverse, representative sample

The population of members at KPCO and KPSC is diverse. Racial and ethnic distribution for the two sites combined indicate approximately 62% are racial minorities and 44% are Hispanic. We will track race and ethnicity during recruitment and enrollment to determine if participants are representative of the larger population. If necessary, we will increase recruitment of racial and ethnic minority participants by focusing our outreach efforts on clinics with the highest proportion of racial and ethnic minority members.

Potential recruitment/enrollment challenges and strategies to address them

We estimate that accrual of the sample of 460 will take less than one year, which is the timeframe we propose for recruitment and enrollment. This is because we will be able to retrospectively recruit pregnant women who received prenatal care 3 months prior to the start date for the trial. In addition, we estimate a conservative enrollment rate of 10% which may be higher among pregnant women who are motivated to engage in a non-pharmacologic intervention that may help them avoid depression recurrence during pregnancy or postpartum. Finally, should recruitment and enrollment fall short of projections, we will work with OB providers to distribute recruitment flyers to patients at prenatal visits, and to refer interested women to the study

Evidence to support the feasibility of enrollment

Our study team and MHRN colleagues have successfully used automated outreach, recruitment, consent, and enrollment procedures for several large pragmatic trials. These include the recent pragmatic trial of digital MBCT for 460 participants (Strategies for Overcoming Residual Depression (Segal, MH102229), and the Suicide Prevention Outreach Trial (Simon, 5UH3MH007755) of nearly 5,000 participants. In addition, we have conducted several pragmatic trials and feasibility studies involving both practice-based and population-based recruitment of pregnant women over the last 10 years, including the evaluation of Mindfulness Based Cognitive Therapy (MBCT) for perinatal depression, both in person and online, and training both allied health professionals and peers with lived experience to deliver behavioral activation to depressed pregnant women. (1-3) These trials have involved KPCO, KPWA, KPGA, and HP, demonstrating our capacity to conduct pragmatic trials efficiently in populations of pregnant women receiving prenatal care in large health systems.

Our research team also has extensive experience conducting large-scale multi-site implementation studies of integrated care interventions for depression, and assessing patient outcomes, including Depression Improvement Across Minnesota–Offering a New Direction (DIAMOND, 5R01MH080692-04),(4) and Care Of Mental, Physical And Substance-use Syndromes (COMPASS, 1C1CMS331048).(5, 6).

Timeline	Y1				Y2				Y3				Y4				Y5			
Task	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
IRB, programming, outreach prep, stakeholder engagement																				
effectiveness trial recruitment, enrollment																				
implementation trial enrollment																				
8-week post intervention assessment																				
delivery																				
3-month postpartum assessment																				
6-month postpartum assessment																				
RE-AIM analysis																				
sustainment phase																				
final effectiveness analyses																				
sustainment analysis																				
cost effectiveness analysis																				
manuscript preparation																				

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 275668	Domestic	Kaiser Permanente Colorado, Kaiser Permanente Southern California

Inclusion Enrollment Report 275668

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Kaiser Permanente Colorado, Kaiser Permanente Southern California

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	28	0	26	0	54
Native Hawaiian or Other Pacific Islander	24	0	25	0	49
Black or African American	30	0	28	0	58
White	163	0	111	0	274
More than One Race	12	0	12	0	24
Total	258	0	202	0	460

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 278300)

3.1. Protection of Human Subjects	SP1_Hum_Subj_218019_Final.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ❍ No ❍ N/A
If yes, describe the single IRB plan	SP1_SIRB_218019_Final.pdf
3.3. Data and Safety Monitoring Plan	SP1_DSMP_218019_Final.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	● Yes ❍ No
3.5. Overall structure of the study team	SP1_Team_218019_Final.pdf

1. Risks to Human Subjects

1.a. Human Subjects Involvement, Characteristics and Design

The overall study is an Optimization, Effectiveness, and Implementation (OEI) hybrid effectiveness trial-implementation study. The effectiveness trial will be a two-arm randomized design comparing Mindful Mood Balance for Moms (MMBFM) to usual care (UC) on change in the primary outcomes of depression symptom severity and relapse rates from baseline through 6-months postpartum for women at risk for recurrent depression. The trial will be conducted at Kaiser Permanente Colorado and Kaiser Permanente Southern California. The implementation study will assess systematic implementation strategies at Kaiser Permanente Georgia and HealthPartners and is being submitted as a delayed onset study. A separate human subjects section will be submitted at a later date.

The trial will enroll pregnant women age 18 and older, receiving prenatal care, 12-28 weeks gestation, with at least one prior episode of MDD, and a current Patient Health Questionnaire (PHQ-9) or Edinburgh Postnatal Depression Scale Scores (EPDS) score <10. We will exclude women with a diagnosis of a bipolar or psychotic disorder, active mania or psychosis or substance abuse, or at immediate risk of self-harm. We will also exclude patients who are unable to speak and read English given that the intervention and materials are only available in English at this time.

1.b. Study Procedures, Materials, and Potential Risks

The study will utilize a population-based recruitment strategy using electronic medical records (EMR) for case finding. Through participation in building the data infrastructure for the MHRN, we have access to programming code to identify from the EMR potentially eligible women receiving routine prenatal care. Study participants will be recruited using methods suitable for each site, including bulk email and/or secure message through the EMR portal or by regular mail. The outreach message will include a link to a recruiting survey containing a description of the study and brief questions to determine initial eligibility. 460 women will be randomized into MMBFM (N=230) or UC (N=230). This sample size is specifically powered to detect group differences for the primary effectiveness outcomes of depression symptom severity and relapse rates.

The MMBFM program includes eight sessions that teach mindfulness practice and cognitive behavioral skills to help reduce automatic, depressogenic modes of thoughts, emotions, and sensations. Adaptations to the program for pregnant women include brief informal mindfulness, social support, and self-compassion practices as well as psychoeducation about mood and anxiety during the transition to parenthood. MMBFM is delivered in a mobile first digital format, accessible from desktop or mobile devices, and provided in an individually tailored manner that includes experiential practice, video-based vicarious learning, and didactic information. Accompanying materials are provided for each session via digital access to forms and audio or video guides identical to those used in standard MBCT, modified for digital format. Participants are asked to logon to the program to complete one session each week and to set a regular routine for sessions and homework practice. Telephonic outreach and coaching supplemented by email check-in and supportive messaging, will be delivered by the KPCO site for the duration of the 8-week intervention, as described in the MMBFM coaching manual (see other clinical trial attachment). The KPCO site will also moderate site activity, including coaching feedback and online community interactions.

Data collection will be done using a combination of REDCap (Research Electronic Data Capture) and programming to extract data from electronic medical records and Virtual Data Warehouses (VDWs) at each site. Baseline data will include demographic variables, contact information, current and previous mental health treatment history, and a screener for substance abuse. Depression symptom severity will be assessed with the PHQ-9. The mood module of the *MINI* will be administered at baseline to assess depression diagnoses, prior episodes, and comorbidity.

- *Intervention Adherence* – MMBFM participants will be asked to use a Home Practice Record to monitor mindfulness practices weekly during MMBFM, and monthly through 6-months postpartum.
- *Clinical and Functional Outcomes* – The following self-report measures will be administered at baseline, 8 weeks post-intervention, and at 3 and 6 months postpartum
    - PHQ-9 to assess depression relapse, defined as a score of >13, and depressive symptom burden

- anxiety severity, assessed using the Generalized Anxiety Disorder 7-item Questionnaire (GAD-7)
- functional status, assessed using the SF-12

o *Infant outcomes* – Preterm birth and gestational age will be measured from perinatal data recorded in the EMR and linked with maternal records.
o *Maternal outcomes* – The Parenting Stress Index-Short Form (PSI-4/SF) and Perceived Maternal Parenting Self-Efficacy Scale (PMP S-E) will be administered at 6 months postpartum.
o *Intervention Exposure and Satisfaction* – Backend website analytics will be used to assess MMBFM exposure. We will use the Client Satisfaction Questionnaire (CSQ-8) to assess perceptions satisfaction with MMBFM and UC at 6 months postpartum.
o *Putative Targets of MMBFM* – Putative targets will be measured at baseline, post-intervention, and at 3 and 6 months postpartum using the Five Facet Mindfulness Questionnaire (FFMQ), a 39-item self-report measure of domains of mindfulness (observing, describing, acting with awareness, accepting without judgment, non-reactivity), and the Ruminative Response Scale (RRS), a measure of ruminative responses to negative affect.

Potential risks include:
o *Breach of confidentiality* – While the study will take many precautions to maintain confidentiality, there is a potential risk to participants of breach of confidentiality. Breach of confidentiality could occur during electronic transfer of data between research staff and storage of identifiable information. There are risks to confidentiality and privacy associated with participation in all research studies. In the next section, we describe steps we have taken to protect against or minimize risks to confidentiality and privacy.
o *Inconvenience*: Participants may also feel inconvenienced by the time required to complete the study tasks. The expected time commitment will be explicitly stated in the consent form.
o *Psychological risks associated with assessment* – There is the possibility that participants could be upset or offended by survey questions. In order to minimize psychological risk of harm, information about potential risks is included in the consent form. Participants also will be instructed that they are free to not answer any questions they do not wish to answer on the surveys.
o *Psychological risks associated with intervention* - As in any study related to mental health concerns, participants may experience psychological discomfort related to the assessments or the MMBFM program. Participants may also experience worsening of depression symptoms. In the next section, we describe steps we have taken to protect against or minimize psychological risks.
o *Physical risks* – We do not anticipate any physical risks for participants or clinicians. Participants' physical care needs will remain in the hands of their OB and primary care physicians during the study.

2. Adequacy of Protection Against Risks

2.a. Informed Consent and Assent

Potential participants, identified by EMR, will receive a paper or electronic study brochure which will explain the study and include the study website internet address. The recruitment materials will include contact information for the study team in the event potential participants would like more information before deciding to enroll in the trial. The project website's home page will include a description of the study and a brief recruiting survey to determine initial eligibility. At this point, individuals can continue with the online consent process or opt out, requesting no further contact from the study team. To proceed, each person will be asked to enter a unique identifier printed in their outreach materials (email or mail). This number is not linked to any individual identifier but is used to verify that individuals receiving the outreach are KPCO or KPSC members. These recruited individuals will then proceed to the electronic consent and HIPAA Authorization forms.

Information provided in the informed consent will address the background and purpose of the study, the scope and length of participation, the nature of the research, the study procedures (including baseline and post-treatment assessments), legal and ethical limits to confidentiality, risks, benefits, alternatives, payments, procedures for addressing injuries, voluntary participation and termination, protections of confidentiality, and whom to contact with questions. In addition, the Kaiser Permanente Medical Care Program Research Participants' Bill of Rights and HIPAA Authorization forms will be provided. Participants will be encouraged to read each section and provide their consent by clicking "I Agree" at the bottom of each page. Individuals who click "I Do Not Agree" will be informed that it is not possible for them to participate in the study and we will provide them with a list of links to depression information websites, followed by online consent.

Women who pass the initial screen and consent will be called by the study staff at KPCO to review the online consent, complete the baseline clinical assessment and be randomized into MMBFM or UC. In addition, they will be asked to respond to questions that assess the degree to which they adequately understood important study information, and they will be provided with contact information and encouraged to contact study staff with questions via email or phone. Consenting participants will complete a baseline assessment with a suggestion that they print and retain personal copies of the study consent and HIPAA forms.

2.b. Protections Against Risk

Training of Staff

All research staff will be trained in the regulations governing the conduct of human subjects research, as well as HIPAA regulations. All investigators and consultants have passed the IRB examination, which requires knowledge of ethical principles and federal regulations concerning human subjects research. Investigators will assure that all research assistants complete the same training.

Protection against Physical Risk

As mentioned above, we do not anticipate any physical risks for participants. Participants' physical care needs will remain in the hands of their OB and primary care physicians during the study. We will ask KPSC participants to provide the contact information and a release of information to Kaiser Permanente Colorado staff to contact the OB provider in order to communicate about any physical health concerns during study involvement, should the need arise.

Patients will be informed that if they are harmed as a direct result of the study, medical treatment will be provided at no additional cost within the limits of their current existing health care coverage through Kaiser Permanente.

Protection against Psychological Risk

In order to minimize psychological risk of harm, we will include detailed information about possible risks in the informed consent form and process, which illustrates the most sensitive types of questions about which subjects will be asked on the assessment instruments. Participants will also be instructed that they are free to not answer any questions they do not wish to answer during the assessments, and that that they may discontinue participation in the MMBFM program and/or choose not to complete assessments at any time by informing the research team by phone or email.

All participants will be provided with the contact information for the behavioral health crisis team in their respective healthcare system (KPCO or KPSC) and the contact information for the KPCO study team if participants experience significant increases in depressive symptoms or suicidal ideation. In addition, members of the study team will contact the crisis team if a participant's PHQ-9 score is > 15 or he/she expresses suicidal ideation (score of 1 or greater on the Columbia Suicide Severity Risk Scale) during baseline or any follow-up assessments. Participants will be informed of these procedures for addressing risk during the enrollment and consenting process.

Participants will be informed about the expected duration of each assessment time point and MMBFM sessions for patients in that condition, and we have designed the assessment procedures to minimize burden on participants. Patients will receive a total of $50 for completing the 5 assessments (baseline, 16 weeks post-randomization, and at 3 and 6 months postpartum). These amounts are consistent with other studies conducted in KPCO. Participants assigned to MMBFM will also receive the intervention at no cost. Participants who terminate participation early will be paid a prorated amount of $10 per assessment completed. If the investigators end a participant's involvement in the study, the participant will receive the full payment for participation.

Management of Potential Clinical Deterioration

Participants who participate in this study may experience a relapse or worsening of depression symptoms. We have developed clear, detailed, and actionable protocols to guide staff to ensure that concerns about clinical

deterioration and suicide risk are carefully addressed. Our protocols are informed by our prior and current studies within KPCO.

We will use the PHQ-9 administered at scheduled assessment points to monitor depressive symptoms. In addition, participants in the MMBFM arm will be asked to complete a PHQ-9 following each of the 8 weekly program modules. If a patient scores >15 on PHQ-9, study staff and investigators will be notified immediately via an algorithm programmed into our online data collection and management system on REDCap. Study staff will reach out to participants who score >15 to provide assistance with linkages to behavioral health care services offered by KPCO or KPSC.

We will use the suicide ideation item (#9) on the PHQ-9 to monitor suicide risk. Any response of “More than half the days” or “Nearly every day” to item 9 of the PHQ-9 (regarding thoughts of death or self-harm) will activate a structured response used successfully in the MHRN Suicide Prevention Outreach Trial:

- Clinically-trained study staff will respond immediately by online messaging AND initiate telephone outreach to administer the Columbia Suicide Severity Rating Scale (CSSRS), and
  will then recommend and facilitate follow-up care with type and timing of care recommendation depending on CSSRS score:
  - CSSRS score 5 = Specialty mental health or emergency department visit within 2 days
  - CSSRS score 4 = Specialty mental health visit within 7 days
  - CSSRS score 3 = Specialty mental health visit within 2 weeks
  - CSSRS score 1 or 2 = Specialty mental health or primary care visit within 4 weeks

Assessment findings and disposition will be recorded in the electronic health record with a copy to the primary care physician recording the eligibility diagnosis.

Protection against Risks to Confidentiality

A number of steps have been taken to safeguard privacy and confidentiality across the study. All study staff will be required to take the KPCO compliance training - *HIPPA For Researchers*. Study personnel and materials will assure that participants understand the confidentiality measures taken in this study to protect them and their information. Participants will be invited at any time to share their concerns with the study coordinator, investigators or KPCO IRB representative.

Participating in this study will involve access to two websites: Brella which hosts the MMBFM program, and REDCap for participant tracking, outreach, and outcome assessment. The MMBFM program will be secured using a firewall and password access, with a 128-bit level of SSL encryption. User passwords will be distributed to the participants via email. Passwords and their associated web access will be deleted from the study registry by the research assistant at the close of this study or at the participant’s termination or completion of the study, whichever is earlier. The study team will have administrative access to the MMBFM website. Brella is experienced in managing confidential data using encryption and passwords.

Participants will be emailed secured links by the study team with assessment instruments hosted by KPCO’s REDCap system, which resides behind a firewall with user-limited access. All participants enter their responses to instruments using a study assigned ID, so that identifying data is never recorded in REDCap. Survey response data stored in REDCap are accessed only by the study team who must provide a user ID and password.

A number of other steps have been taken to safeguard privacy and confidentiality across the study. All study staff will be required to sign statements indicating that they understand confidentiality and agree to protect confidentiality. Direct identifiers such as name, phone number, address, and locator information will be collected for purposes of scheduling and conducting the assessments or intervention sessions. All information that directly identifies the subjects will be stored on a secured network that meets HIPPA data storage requirements at the KPCO Institute for Health Research, accessible only by research staff. The crosswalk that links study id to direct personal identifiers will be further secured on the network in a password protected file. Only de-identified data will be used in publications.

The MMBFM program makes available an online community, which will be moderated by the research team to

Limits to Confidentiality

Limits to confidentiality will be detailed on the electronic ICF. Participants will be informed that a statement about their participation will be included in a documentation note in the EMR. This is necessary to ensure adequate continuity of care and communication between providers in the KPCO and KPSC systems. Additionally, subjects will be informed that they will not be asked specifically about any illegal activities, but if they should discuss such activities, the information could be requested by authorities such as the police or court system. They will also be told that there are limits to confidentiality, including our requirement to report information about: child abuse or neglect, a crime that the subject plans to commit, or harm that may come to the subject or others. If there is risk of harming self or others, research staff will take necessary actions per the duty to report laws, including notifying significant others who may assist in the protection of the subject's safety or notifying others who might be affected, such as intended victims, or notifying the police or the medical and behavioral health providers in the KPCO or KPSC systems.

2.c. Vulnerable Subjects

Pregnant women who have experienced prior episodes of depression will be included in this study. We estimate this to be a greater than minimal risk study, based on the targeting of a vulnerable population; however, we note that the procedures employed are likely to be low risk. The risk to the fetus is not greater than minimal.

3. Potential Benefits of the Proposed Research to Research Subjects and Others

This study may provide participants with insight into their risk factors for depressive relapse and equip them with strategies to manage these risk factors. If this intervention proves to be effective, it may represent an important, non-pharmacological treatment option for perinatal depression. Preventing and decreasing the severity of perinatal depression offers significant benefits to society, given that depression is a leading cause of disability worldwide with serious consequences for the offspring; these benefits would be particularly marked if the MMBFM intervention demonstrates cost-effectiveness from the healthcare system perspective. Finally, if the MMBFM implementation study is successful, the potential for broader dissemination across healthcare systems is high, potentially reaching several hundred thousand pregnant women.

4. Importance of Knowledge to be Gained

Our work may contribute knowledge regarding the effectiveness of digitally-delivered MBCT to pregnant women at risk for depression, and the feasibility of implementing this program in healthcare systems. Currently available preventive treatments are not adequate to address the needs of these women during pregnancy and the postpartum. Although antidepressant medication is the most frequently provided intervention for depression during pregnancy, many pregnant women discontinue antidepressant treatment and experience depressive relapse. Pregnant women prefer non-pharmacological treatment, however, access to psychotherapy in OB settings is limited. The proposed project has the potential for contributing knowledge to address a major gap in current healthcare for pregnant women, thereby potentially impacting the health of pregnant women and their offspring.

Under the Revised Common Rule, non-exempt multi-site human subject research is required to use a single IRB to conduct the ethical review. For this study, each site will conduct the same protocol.

Kaiser Permanente Colorado will serve as the single IRB. Participating sites will cede review to the Kaiser Permanente Colorado IRB. Similar to the MHRN, reliance agreements developed by the broader Health Care Systems Research Network will be used. All sites are accustomed to ceding for studies in this manner. The study PI, Dr. Arne Beck, will be responsible for having a management and communication plan in place and designated people to manage it. This includes preparing and submitting the applications and amendments to the KPCO IRB and providing documentation of IRB determinations and IRB-approved materials.

Each participating research site will remain responsible for researcher training, conflict of interest disclosures, HIPPA, conducting ancillary reviewed for safety, compliant research conduct, and maintaining oversight with respect to state and local laws and other institutional policies.

Overview. Specific procedures regarding monitoring for adverse events, responding to urgent clinical needs, and monitoring data quality and integrity are described below. Lead investigators at each site will have primary responsibility for adherence to these procedures. This trial warrants the creation of a Data and Safety Monitoring Board (DSMB) which will consist of a psychiatrist with expertise in perinatal mental health, a psychologist with expertise in the design and implementation of pragmatic clinical trials, a Ph.D. biostatistician, and an expert in digital mental health interventions. None of these persons will be involved directly in the trial. The DSMB will have the following aims:

- To assure the safety, privacy, and confidentiality of human subjects.
- To assure the reliability, validity, completeness, and integrity of the data collection, entry, and management process.
- To review implementation of the human subjects protocol, including all proposed protocol amendments and modifications.
- To review all serious adverse events, less serious adverse events, rates of dropout or trial withdrawal, and rates of missing data.

The DSMB will have a minimum of one teleconference per year for the trial duration. Members will also meet via email or, if necessary, via conference call if serious adverse events attributable to trial procedures are reported. The DSMB will be provided with reports of trial enrollment and patient flow as well as blinded reports of treatment efficacy to inform judgments about possible over or underestimation of ES and the value of interim analyses.

Prior to its regular meetings, the study team will prepare reports to the DSMB about progress toward achieving the scientific aims, dropout and retention, data quality, confidentiality, and safety issues. The DSMB will issue independent reports to the IRB and the NIMH summarizing its review of these domains. If the DSMB believes that participants are being endangered, the Board will make recommendations to the NIMH and IRBs as to whether the trial should be stopped or procedures modified. The independent reports from the DSMB will suggest ways to reduce risk and improve the quality of care of participants, and ways to improve the reliability, validity, integrity, and confidentiality of the data collection procedures.

Response to Suicide Risk or Other Urgent Clinical Needs – Suicidal ideation or moderate to severe depression discovered during baseline or outcome assessments would not be considered an adverse effect of trial participation or the trial intervention. However, given recent data about self-harm as a common cause of pregnancy-associated mortality, study staff must be prepared to respond appropriately to urgent clinical need. Any response of “More than half the days” or “Nearly every day” to item 9 of the PHQ-9 (regarding thoughts of death or self-harm) will activate a structured response used successfully in the MHRN Suicide Prevention Outreach Trial:

- Clinically-trained study staff will respond immediately by online messaging AND initiate telephone outreach to administer the Columbia Suicide Severity Rating Scale (CSSRS), and
  will then recommend and facilitate follow-up care with type and timing of care recommendation depending on CSSRS score:
  - CSSRS score 5 = Specialty mental health or emergency department visit within 2 days
  - CSSRS score 4 = Specialty mental health visit within 7 days
  - CSSRS score 3 = Specialty mental health visit within 2 weeks
  - CSSRS score 1 or 2 = Specialty mental health or primary care visit within 4 weeks

Assessment findings and disposition will be recorded in the electronic health record with a copy to the primary care physician recording the eligibility diagnosis.

Any PHQ-9 total score of 15 or greater will also prompt immediate online messaging and telephone outreach by study staff to assess urgent need and to advise and facilitate specialty mental health follow-up care within 7 days.

Study staff will record outreach efforts, assessment findings, and disposition for each of these events. At each site, these records will be reviewed by the principal investigator to assure adequate outreach efforts and appropriate clinical recommendations.

Monitoring for Adverse Events – While trial participants could experience adverse events such as suicide attempts or psychiatric hospitalization, we do not propose to review these events to determine “relatedness” to

but with no clinically significant depression symptoms on enrollment in the trial, and we do not believe it would be possible to determine whether any event was related to the trial intervention or telephone contacts. We also do not propose to compare rates of such events in the intervention and control groups. Based on previous MHRN research, the expected number of psychiatric hospitalizations and the expected number of suicide attempts in this population (pregnant women receiving prenatal care who have histories of depression but no current clinically significant symptoms) over the study enrollment and follow-up period would be too low to support any meaningful conclusions regarding intervention effects with sufficient precision.

We do, however, identify some adverse events that might require evaluation and corrective action. Any of the following adverse events will be reported to the DSMB and the responsible Institutional Review Board:

- Breach of confidentiality (e.g., inadvertent disclosure of protected health information by the outreach clinician to someone other than the participant)
- Violation of study protocol (e.g., failure or significant delay in sending outreach messages)
- Participant complaint (e.g., participant complains that trial is a misuse of health data or that messages are bothersome)

The DSMB and IRB will review reports of each of these events and recommend any appropriate change in trial procedures or other corrective action.

Data Security. Participating in this trial will involve access to two websites: Brella and REDCap. The digital platform for MBCT will be hosted at Brella for the trial's duration. Direct access to the server is secured by a firewall with IP whitelisting and account verification. HTTPS, SSL access, and user passwords are secured with 256-bit level encryption. The KPCO site will program and host the survey for screening, baseline assessment and follow-up data collection using REDCap (Research Electronic Data Capture), which is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Participants will be emailed secured links by the KPCO study team with assessment instruments that reside behind the firewall with user limited access. The KPCO team has developed and used the surveys and tasks in prior studies and can maximize efficiencies by building on prior work. All participants enter their responses using a study assigned ID, and data stored in REDCap is accessed only by the study team who must provide a user ID and password.

Monitoring Data Quality and Integrity – Trial outcomes will be obtained from electronic surveys and from health system records. Accuracy and completeness of data elements contributing to the primary trial outcome (depression symptom burden and relapse/clinically-significant worsening) will be monitored quarterly by the KPCO study team.

Study staff at each site will include:

- A lead investigator responsible for all study operations, who will collaborate with local OB and BH clinical operations leaders, and health system leaders, and facilitate BH clinician/crisis team response to urgent clinical situations.
- A project manager responsible for communications within and across study sites, fiscal management, and regulatory compliance.
- A programmer/analyst responsible for extracting relevant data from health system records, developing/implementing study tools for identification and outreach of potential study participants, and linking maternal and infant records of study participants to assess outcomes.

Study staff at the lead site will also include:

- The principal investigator who will oversee the contribution and participation of several consultants with expertise in the following areas:
  - RE-AIM framework
  - Mindfulness-Based Cognitive Therapy and its digital adaptations
  - Technology-assisted behavioral and psychological interventions
  - Economic evaluation of depression programs
  - Effect of maternal depression on children
- A programmer who will rely on MHRN's standard data extraction programs to develop distributed code for data extraction, link maternal and infant records, and compile site data into an analytic dataset.
- A research specialist who will develop and manage the REDCap participant tracking database and electronic surveys for outcome assessment. In addition, the research specialists and a research assistant will provide centralized supportive telephonic coaching to participants in the MMBFM program from the KPCO and KPSC sites.
- Biostatisticians who will manage data quality for the analytic dataset for KPCO and KPSC, and conduct the effectiveness trial outcome analyses.

Section 4 - Protocol Synopsis (Study 278300)

4.1. Brief Summary

An increasing number of digital mental health technologies are being developed to expand access to mental health treatments and deliver them in a cost-effective manner. Although efficacy trials of these technologies demonstrate improved patient outcomes, especially when combined with coaching support, there is little evidence that such digital tools can be widely implemented and sustained in routine care settings.

Perinatal depression is one area of significant public health concern where the role of digital mental health technology is especially relevant. Approximately 30-40% of women with histories of depression experience relapse during the perinatal period, a majority show poor adherence to antidepressants (ADs), the most common prevention treatment, and a majority express a preference for non-pharmacologic treatments. However, effective and easily accessible non-pharmacologic treatments are not widely available. Inadequate treatment for perinatal depression poses unique risks, including potential obstetrical and neonatal complications associated with perinatal depression itself and with fetal exposure to ADs. It is therefore imperative to test the implementation of effective and scalable non-pharmacological treatments to reduce the risk of depression relapse in the perinatal period.

Mindfulness Based Cognitive Therapy (MBCT) is a promising preventive intervention for pregnant women with recurrent depression (as well as for adults in general), demonstrating significant reductions in rates of depressive relapse and residual depressive symptoms. MBCT is an eight-session in-person group intervention targeting risk factors for depressive relapse through a combination of mindfulness meditation and cognitive-behavioral strategies. Because of challenges in delivering in-person MBCT (difficulty for health systems to scale up the intervention, barriers to access for pregnant women), we developed a mobile-first digital adaptation of MBCT for pregnant women, Mindful Mood Balance for Moms (MMBFM).

The critical next phase of our work is to evaluate the potential of MMBFM as an effective intervention that can be more widely adopted, implemented and sustained across heterogeneous patient populations and health care systems. We propose a large pragmatic hybrid type II effectiveness--implementation trial comparing MMBFM to usual care (UC) among pregnant women at risk for recurrent depression at four MHRN sites: KP Colorado, KP Southern California, HealthPartners, and KP Georgia to address the following aims:

AIM 1: Test the effectiveness of MMBFM in reducing depression symptoms, reducing risk of relapse or significant worsening, and improving perinatal outcomes when implemented in real-world health systems.

AIM 2: Evaluate the incremental cost effectiveness of MMBFM compared to UC.

AIM 3: Evaluate healthcare system's implementation of MMBFM using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) model.

4.2. Study Design

4.2.a. Narrative Study Description

Study Design: This pragmatic trial will be guided by the Accelerated Creation-to-Sustainment (ACTS) model for technology-enabled service that is sustainable in a real-world healthcare setting. The model specifies three phases, with associated sets of activities and related evaluation metrics: 1) create; 2) conduct Optimization, Effectiveness, and Implementation (OEI) hybrid trial; and 3) sustainment. We propose to conduct an effectiveness trial as part of the OEI phase, using a two-arm randomized design comparing Mindful Mood Balance for Moms (MMBFM) to Usual Care (UC) on the primary outcome of changes in depression symptom severity and relapse / clinically worsening symptoms, from baseline through 6-months postpartum. Eligibility and Exclusion Criteria: Participants will be women greater than or equal to 18 years of age, receiving prenatal care, 12-28 weeks gestation, with at least one prior episode of MDD, and current PHQ-9 score <10. Women with a diagnosis of a psychotic, bipolar, or substance use disorder or at immediate risk of self-harm will be excluded. Since the intervention is in English only, patients who are unable to speak and read English will be excluded as well patients who previously requested to not be contacted for research. Intervention Assignment: Women who meet the inclusion criteria will be randomly assigned (1:1 ratio) to either continued usual care or MMBFM using a masked table of computer-generated random assignments. Assignment will be stratified by study site. Waiver/Modification of Consent: Participants will be emailed or mailed an outreach message that includes a link to the study description and brief eligibility survey, followed by online consent, which will be confirmed by study staff at baseline assessment. Outreach Intervention: MMBFM will be delivered in a mobile first digital format provided in an individually tailored manner that includes experiential practice, video-based vicarious learning, and didactive information. Accompanying materials will be provided for each of the 8 sessions. Participants will be asked to logon to the program daily until program completion and to set a regular routine for sessions and homework practice. Telephone and digital coaching will be provided by KPCO study staff using the MMBFM coaching manual (see attachment under other clinical-trial related attachments section). Clinical measures: Baseline clinical assessments - Information on demographics, contact information, and treatment history will be obtained at baseline, in addition to a substance abuse screen. The mood module of the MINI will also be administered to assess depression diagnoses, prior episodes, and comorbidity. In addition, the following self-report measures will be administered: PHQ-9, GAD-7, Five Facet Mindfulness Questionnaire (FFMQ), and Ruminative Response Scale. Intervention adherence - Participants will use a Weekly Home Practice Record to monitor mindfulness practice weekly during the MMBFM program and monthly through 6 months postpartum. Clinical and functional outcomes - Participants will complete the PHQ-9, GAD-7, and SF-12 self-report

instruments at 8 weeks post-randomization and at 3 and 6 months postpartum. Infant outcomes - Linked maternal and infant data will be obtained from the EMR to assess preterm birth and gestational age. Maternal outcomes - The Parenting Stress Index-Short Form and Perceived maternal parenting Self-Efficacy Scale will be administered at 6 months postpartum. Intervention exposure and satisfaction - The MMBFM platform will be used to record the number of sessions completed, frequency of use, and date and duration of logins. The Client Satisfaction Questionnaire will be used to assess perceptions of and satisfaction with MMBFM and UC at 6 months postpartum. Putative targets of MMBRM - Participants will complete the FFMQ, assessing domains of mindfulness, and the Ruminative Response Scale, assessing ruminative responses to negative affect, at baseline, 8 weeks post-randomization, and at 3 and 6 monsth postpartum. Effectiveness Trial Outcomes: The primary outcome will be reduction depressive symptom burden, defined as change from baseline through 6 months postpartum on PHQ-9 scores, and risk of relapse / clinically significant worsening, defined as time to PHQ-9 scores >13. Secondary outcomes include: Reduction in stress and anxiety through 6-months postpartum, higher infant gestational age and lower rates of preterm birth at delivey, and better maternal functioning at 6 months postpartum. Additionally, we will evaluate incremental cost effectiveness of MMBFM relative to the UC group, based on the health care system perspective.

4.2.b. Primary Purpose: Prevention

4.2.c. Interventions

Type	Name	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Digitally-delivered Mindfulness-Based Cognitive Therapy adapted for pregnant women	The 8-session protocol for MMBFM is based on the theory underlying Mindfulness-Based Cognitive Therapy (MBCT). The sessions teach mindfulness practice and cognitive behavioral skills to help reduce automatic, depressogenic modes of thoughts, emotions, and sensations. Additions to the standard MBCT curriculum for pregnant women include brief informal mindfulness, social support, and self-compassion practices as well as psychoeducation about mood and anxiety during the transition to parenthood. MMBFM is delivered in a mobile first digital format, accessible from desktop or mobile devices, and provided in an individually tailored manner that includes experiential practice, video-based vicarious learning, and didactic information. Accompanying materials are provided for each session via digital access to forms and audio or video guides. Telephonic and digital coaching will also be provided to foster engagement in the program and completion of outcome assessments.

4.2.d. Study Phase: Phase 4

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ● No

4.2.e. Intervention Model: Parallel

4.2.f. Masking ❍ Yes ● No

❏ Participant ❏ Care Provider ❏ Investigator ❏ Outcomes Assessor

4.2.g. Allocation: Randomized

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	PHQ-9	Baseline, 8-weeks, 3- and 6-months postpartum	PHQ-9 will be used to assess differences between MMBFM and UC on changes in depression symptom severity and time to relapse (defined as a PHQ-9 score >13) from baseline to 6-months postpartum.
Secondary	GAD-7	Baseline, 8-weeks, 3- and 6-months postpartum	GAD-7 will be used to assess differences between MMBFM and UC on changes in anxiety symptom severity from baseline to 6-months postpartum.

Secondary	Intervention adherence	Weekly during the 8-week MMBFM intervention, and monthly through 6-months postpartum	Participants will be asked to use a Home Practice Record to monitor mindfulness practices.
Secondary	Infant outcomes	Birth	We will examine differences between MMBFM and UC participants on outcomes of pre-term birth and gestational age.
Secondary	Maternal outcomes	6-months postpartum	We will examine differences between MMBFM and UC participants on the Parenting Stress Index-Short Form (PSI-4/SF), and Perceived Maternal Parenting Self-Efficacy Scale (PMP S-E).
Secondary	Intervention exposure and satisfaction	6-months postpartum	Backend website analytics will be used to assess MMBFM exposure. We will use the Client Satisfaction Questionnaire (CSQ-8) to assess perceptions satisfaction with MMBFM and UC.
Secondary	Putative targets of MMBFM	Baseline, post-intervention, and at 3 and 6 months postpartum	Putative targets will be measured using the Five Facet Mindfulness Questionnaire (FFMQ), a 39-item self-report measure of domains of mindfulness (observing, describing, acting with awareness, accepting without judgment, non-reactivity), and the Ruminative Response Scale (RRS), a measure of ruminative responses to negative affect.

4.4. Statistical Design and Power — SP1_Stat_Power_218019_Final.pdf

4.5. Subject Participation Duration — For the effectiveness trial is up to 12 months.

4.6. Will the study use an FDA-regulated intervention? — ❍ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan — SP1_Diss_Plan_218019_Final.pdf

Analysis plan. Demographic, clinical, and self-report data for the cohort will be reported with descriptive statistics. Baseline differences between MMBFM and UC will be assessed using chi-square tests for binary variables, Cochran-Mantel-Haenszel tests for categorical variables, and t-tests for continuous variables. Variables that show significant group differences and predict outcome will be used as covariates in subsequent multivariate analyses. All participants will be included in the analysis (intent-to-treat sample). Significance levels will be evaluated at $p<.05$, and effect sizes reported.

H1a: Reduction in depressive symptom burden and relapse at 6 months postpartum. Hierarchical Linear Models (HLM) will be used to compare change over time between groups on depressive symptom severity using the PHQ-9. Using power estimates for linear mixed models, an effect size of .25 (which is much smaller than the .70 effect size observed in our trial of MBCT for pregnant women), two-tailed alpha level of .05, and a within-subjects correlation of 0.5, a sample size of 228 per group will provide 86.5% to detect this difference, allowing for 30% attrition. We will examine time to relapse as measured by PHQ-9 scores >13 during pregnancy and across the 6-month postpartum follow-up using survival analysis. Survival rates will be compared using Cox proportional hazard regression and illustrated in Kaplan-Meier curves. However, time to attrition is a competing risk that can be related to time to relapse. We will adopt the sub-distribution hazard model (SHM) developed by Fine and Gray to account for the possible nonindependence of the censoring mechanism. In our efficacy study of MBCT, pregnant women who received MBCT evidenced an approximately 30% lower rate of relapse than UC. We will use a more conservative approach estimating 15% lower relapse rates among MMBFM participants. A sample of 217 participants per study arm is required to detect this difference with 80% power and a two-tailed alpha-level of .05, allowing for an estimated 30% attrition over the 6-month postpartum period.

H1b: (exploratory outcomes): Reduction in stress and anxiety through 6 months postpartum. Hierarchical Linear Models (HLM) will be used to compare change over time between groups on PSS and GAD-7 scores. Though these outcomes are exploratory, we estimate an effect size comparable to that for depression symptom reduction, and therefore expect to have sufficient power to assess these outcomes.

H1c (exploratory outcomes): Higher infant gestational age at delivery, and lower rates of preterm birth. For these exploratory outcomes, we will use HLM to compare differences in mean gestational age between groups and modified Poisson regression to assess differences in preterm birth rates. However, power to detect modest differences in preterm birth will be low (e.g., 10% vs. 15%, will provide 63% power for our sample of 460).

H1d (exploratory outcomes): Better maternal functioning at 6 months postpartum. Analyses of variance will be used to assess group differences in PSI-4/SF and PMP S-E scores 6 months postpartum. Effect size estimates for these measures are expected to be comparable to those for H1a and H1b, and we anticipate sufficient power to detect group differences in these outcomes.

H2: MMBFM will demonstrate incremental cost effectiveness relative to the UC group, based on the health care system perspective. We will estimate the cost of delivering MMBFM, the total costs associated with MMBFM relative to UC, costs per participant, and the incremental cost per depression-free days (DFDs) and quality-adjusted life year (QALYs) over the 6 months postpartum period. The incremental cost-effectiveness ratio (ICER) will be calculated as the difference in mean cost divided by the difference in the mean clinical outcome (e.g., DFD, QALY). In order to represent uncertainty around the ICER estimate, we will create 1000 bootstrap replications of the data and use these to a create a 95% confidence interval. In addition, we will use the bootstrapped data to create a cost-effectiveness acceptability curve to represent the uncertainty regarding the maximum cost-effectiveness ratio that a decision-maker would likely consider reasonable. We have used these methods successfully in multiple previous studies.

This pragmatic randomized effectiveness trial will be combined with an implementation study at two sites, HealthPartners in Minnesota (HP) and Kaiser Permanente Georgia (KPGA), as part of a larger hybrid type II effectiveness-implementation trial to test strategies for broader dissemination of MMBFM. Implementation site investigators will identify key stakeholders from obstetrics, behavioral health, and health system administration, as well as women with lived experience of perinatal depression, to collaboratively develop site-specific implementation and sustainment plans for the MMBFM program in their respective systems. Key stakeholder interviews will be conducted to provide qualitative data on local context to inform these plans. Strategies to facilitate implementation and sustainment of MMBFM may include broadening inclusion criteria (e.g., recruiting all antenatal women with PHQ-9 scores <10 vs. those with histories of depression and residual symptoms; including antenatal women with moderate to high anxiety, i.e., GAD-7 scores ≥10, etc.), testing different recruitment methods (population-based vs. referral-based), and modifying the MMBFM coaching protocol (e.g., using digital vs. telephonic coaching), among others.

Implementation strategies will be evaluated using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) model to determine whether meaningful reach, adoption, implementation, and maintenance metrics are achieved. Descriptive and qualitative analyses (based on stakeholder interviews) will be done to assess representativeness of MMBFM participants and referring providers, reasons for the outcomes observed (e.g. patients' reasons for not participating in MMBFM or OB providers' reasons for not referring patients to MMBFM), and any adaptations made to increase values for the following implementation outcomes:

Reach: 25% of eligible women contacted or referred will participate in MMBFM.

Effectiveness: The primary effectiveness outcome will be assessment of differences between MMBFM vs. UC groups in symptoms of depression and rates of relapse, as described in Aim 1. Secondary outcomes will include group differences in anxiety symptoms, infant outcomes, and maternal function.

Adoption: 30% of OB providers within and across implementation sites where MMBFM is offered will refer eligible patients to the program after the initial recruitment phase for the trial is completed. Survey questions attached to the MMBFM program will ask participants about referring OB providers and clinics.

Implementation: 40% of patients who initiate MMBFM will complete at least 4 sessions of the program (minimal dose shown to be effective), as assessed by website usage statistics.

Maintenance: Implementation sites will decide to offer MMBFM as a preventive treatment option for women at risk for perinatal depression.

Efforts to broaden dissemination of the MMBFM program to the 13 MHRN healthcare systems will be undertaken if implementation study metrics are achieved and/or if stakeholders/decision makers in these healthcare systems express interest in adopting MBFM. Together, these healthcare systems account for over 100,000 births annually.

In addition, the results of this hybrid trial will be disseminated via academic publications and conference presentations.

Section 6 - Clinical Trial Milestone Plan (Study 278300)

6.1. Study Primary Completion Date	04/30/2024	Anticipated
6.2. Study Final Completion Date	06/30/2024	Anticipated
6.3. Enrollment and randomization		
Enrollment of the first subject	10/01/2020	Anticipated
25% of planned enrollment recruited by	01/01/2021	Anticipated
50% of planned enrollment recruited by	04/15/2021	Anticipated
75% of planned enrollment recruited by	08/10/2021	Anticipated
100% of planned enrollment recruited by	12/31/2021	Anticipated
6.4. Completion of primary endpoint data analyses	09/30/2022	Anticipated
6.5. Reporting of results in ClinicalTrials.gov	12/31/2022	Anticipated
6.6. Is this an applicable clinical trial under FDAAA?	❍ Yes ● No	

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
278301	Implementation Study of Digital Mindfulness-Based Cognitive Therapy for Prevention of Perinatal Depression	No	SP1_Delayed_Just_Implement_Study_218019_Final.pdf

The overall study is an Optimization, Effectiveness, and Implementation (OEI) hybrid effectiveness trial-implementation study. The effectiveness trial will be a two-arm randomized design comparing the intervention to usual care on change in the primary outcomes of depression symptom severity and relapse rates from baseline through 6-months postpartum for women at risk for recurrent depression.

For the implementation study, a single cohort design will be used to test the success of implementation strategies at the HP and KPGA sites. Guided by the OEI effectiveness trial, implementation study site investigators will identify key stakeholders from obstetrics, behavioral health, and health system administration, as well as women with lived experience of perinatal depression, to collaboratively develop site-specific implementation and sustainment plans for the MMBFM program. Key stakeholder interviews will be conducted to provide qualitative data on local context to inform these plans. Strategies to facilitate implementation and sustainment of MMBFM may include broadening inclusion criteria (e.g., recruiting all antenatal women with PHQ-9 scores <10 vs. those with histories of depression and residual symptoms; including antenatal women with moderate to high anxiety, i.e., GAD-7 scores ≥10, etc.), testing different recruitment methods (population-based vs. referral-based), and modifying the MMBFM coaching protocol (e.g., using digital vs. telephonic coaching), among others.

Enrollment and assessment procedures will be more limited than for the effectiveness trial in order to more closely resemble conditions for real-world implementation in healthcare systems. For example, baseline assessment of past depressive episodes will be done via a self-report question (“Have you ever had a period when you were feeling depressed or down most of the day nearly every day for two weeks or more or you were a lot less interested in most things or unable to enjoy the things you used to enjoy?”). In addition, participants will not be randomized to UC or collect data on perinatal or postpartum outcomes. Instead, outcome assessment using the PHQ-9 and GAD-7 (embedded in the MMBFM program) will be done following completion of MMBFM.

Study sites will include Kaiser Permanente Georgia and HealthPartners. The study will follow the same single IRB plan submitted for the Effectiveness Trial of Digital Mindfulness-Based Cognitive Therapy for Prevention of Perinatal Depression. This will be submitted prior to study initiation.

Since this study is not a Clinical Trial, the NIH’s Policy on the Dissemination of NIH-Funded Clinical Trial Information will not apply.

Section 1 - Basic Information (Study 278304)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Stakeholder perspectives on implementing suicide risk prediction models.

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	❍ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	❍ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 278304)

2.1. Conditions or Focus of Study

- Suicide

2.2. Eligibility Criteria

We propose to interview six administrators [approximately two per site] with interest in suicide prevention and/or authority to implement risk models. Interviewees will be identified by the site PIs, all of whom are embedded clinician-researchers with ability to identify relevant interview candidates. Interviewees may also nominate other key informants [snowball sampling]. We propose to identify approximately 30 clinicians [10 per site] to interview about their concerns and hopes for how suicide risk models would be deployed [KPNW] or about their experiences using a visit-based alert triggered by risk models [KPWA] or a patient registry for outreach to high risk patients [HP]. At KPNW we will randomly select clinicians from behavioral health, primary care, and emergency medicine as these departments are potential implementation settings. At KPWA, we propose to interview clinicians who are expected to interact with the visit-based alert during the implementation pilot study. It will be important to identify and focus some interviews on clinicians who interacted with patients identified by the risk flag who were not identified by other means - that is, patients who would have been missed if it were not for the risk flag. At HP, we will seek to sample the behavioral health care managers with the most experience doing these specific outreach calls. Across the three sites we will seek to interview 60 patients [20 per site]. Patients will be greater than or equal to 18 years old and identified either clinically or by the suicide risk models as at high risk for suicide. The goal will be to identify a representative sample of high risk patients, including those for whom traditional risk factors [e.g., depression diagnosis, previous suicide attempts, high PHQ-9 item 9 response] are not apparent and who might be surprised to learn they are identified as high risk.

2.3. Age Limits	Min Age: 18 Years	Max Age: 79 Years
2.4. Inclusion of Women, Minorities, and Children	PP1_Wom_Min_218019_Final.pdf	
2.5. Recruitment and Retention Plan	PP1_Recruit_Plan_218019_Final.pdf	
2.6. Recruitment Status	Enrolling by invitation	
2.7. Study Timeline	PP1_Timeline_218019_Final.pdf	

Interview participants will include approximately 6 administrators, 30 clinicians, and 60 patients in participating health systems. We will seek to enroll a representative sample. Both men and women will be included; we will seek to balance the sample by sex. Only adults [age ≥18] will be eligible to participate in this pilot study. First, we anticipate all administrators and clinicians will be adults. Second, we anticipate that when health systems initially implement suicide risk prediction models they will limit prediction to adult patients. Third, the limited pilot nature of this project does not allow us to explore the significant ethical complexities of identifying, consenting/assenting minor patients and their legal guardians, and interviewing minors. All racial and ethnic groups will be eligible to participate; we will seek to seek to enroll members of racial/ethnic groups consistent with the distributions of each group in these health systems.

We will first email or staff message administrators and clinicians with study information and a request to reply if interested in participation. We will follow up by email, staff message, and phone to recruit those who do not respond. We will make at least three contact attempts. Because gift cards and monetary compensation are subject to taxation, clinicians will receive an artisanal chocolate bar in appreciation of their participation. We have found this incentive to be well-received in previous studies.

Potentially eligible patient participants will be sent a recruitment letter and/or email providing details about the study, including a number to call to indicate interest in participation. We will phone individuals who do not respond, making up to 8 attempts at different times of the day on different days of the week over a 2-3 week period. We have successfully used this recruitment strategy in several studies and expect to outreach to about 180 patients to achieve our recruitment goal. Patients will receive a $50 gift card in gratitude for their participation in the single one-hour interview.

As shown in the timeline in the associated Research Plan, in year 1 we will gain IRB approval of the study protocol (we anticipate sites will cede IRB authority to KPNW); establish data use/transfer agreements with the participating sites; at KPNW, the analyst will create a program that will identify appropriate clinicians and patients for interviews; at KPNW, finalize and pilot test interview guides; at KPNW, lead training for interviewers at all sites; at participating sites, work with programmers to develop systematic way of identifying clinicians and patients per system's implementation plans; at all sites, conduct system administrator, clinician and patient interviews. In year 2, at all sites, continue with clinician and patient interviews; at KPNW, begin developing qualitative coding scheme; at KPNW, code all interviews, and double code subset for quality assurance; at KPNW, begin qualitative analyses. In year 3 (6 months), finalize qualitative analysis, disseminate findings to stakeholders including health system teams developing the EHR-based clinical tools, produce manuscripts.

.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 275669	Domestic	Oregon, Washington, Idaho, Minnesota, Wisconsin

Inclusion Enrollment Report 275669

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Oregon, Washington, Idaho, Minnesota, Wisconsin

Comments: Planned enrollment includes 6 administrators, 30 clinicians, and 60 patients.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	3	3	0	0	6
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	2	0	0	4
White	36	36	4	4	80
More than One Race	3	2	0	0	5
Total	45	43	4	4	96

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	1	0	0	0	0	0	1
Black or African American	0	0	0	0	0	0	0	0	0	0
White	4	2	0	0	0	0	0	0	0	6
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	1	0	0	0	0	0	0	0	0	1
Total	5	2	0	1	0	0	0	0	0	8

Section 3 - Protection and Monitoring Plans (Study 278304)

3.1. Protection of Human Subjects	PP1_Hum_Subj_218019_Fina.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ❍ No ❍ N/A
If yes, describe the single IRB plan	PP1_SIRB_218019_Final.pdf
3.3. Data and Safety Monitoring Plan	PP1_DSMP_218019_Final.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	PP1_Team_218019_Final.pdf

Risks to Human Subjects

Human Subjects Involvement, Characteristics, and Design

This pilot study will explore health system administrators', clinicians', and patients' expectations, concerns, suggestions regarding, and experiences with the use of suicide risk prediction models in clinical settings. At one site considering implementation of the suicide risk models in the next year (KPNW), qualitative interviews will focus on perceived benefits and risks associated with automated risk identification. Two other sites with imminent plans to conduct small implementation pilot studies during the study period (KPWA, HP) will afford opportunities to study the advantages and disadvantages of different implementation approaches.

We propose to interview six administrators (≈ two per site) with interest in suicide prevention and/or authority to implement risk models. Interviewees may also nominate other key informants (i.e., snowball sampling). Additionally, we propose to identify approximately 30 clinicians (10 per site) to interview about their concerns and hopes for how suicide risk models would be deployed (KPNW) or about their experiences using a visit-based alert triggered by risk models (KPWA) or a patient registry for outreach to high risk patients (HP). Across the three sites we will seek to interview 60 patients (20 per site). The goal will be to identify a representative sample of higher risk patients, including those for whom traditional risk factors (e.g., depression diagnosis, previous suicide attempts, high PHQ-9 item 9 response) are not apparent and who might be surprised to learn they are identified as high risk.

Study Procedures, Materials, and Potential Risks

Potential interview candidates will be contacted by letter, email, or staff message. Initial contacts will include study information and a number to call to indicate or decline interest in participation. We will follow up by email, staff message, or phone to those who fail to respond to the initial outreach. We will make at least three contact attempts to reach administrators and clinicians and up to 8 attempts to reach patients at different times of the day on different days of the week over a 2-3 week period. Interviews will take place in-person whenever possible and by phone when that is the preference of the interviewee. We anticipate administrator and clinician interviews will be approximately 20 minutes duration; patient interviews will be 60 minutes. Willing clinicians may be interviewed twice—at the beginning and near the end of the interview window to assess changes over time in their attitudes, knowledge, and comfort with the suicide risk prediction tools—patients will be interviewed once only. Administrators and clinicians will receive an artisanal chocolate bar and patients a $50 gift card as appreciation for their participation.

Semi structured interview guides will be developed by the team at KPNW. Administrator and clinician questions will be guided by the Consolidated Framework for Implementation Research (CFIR) and will assess, for example, familiarity with and value of risk prediction models; vision and leadership support for use of these models and how they will be implemented; any preparation, communication, and training planned for clinicians; concerns about burdening clinicians with additional risk assessment and safety planning work; broad familiarity with how models derived from machine learning produce risk estimates; whether clinicians expect to see predictors that put their patients at risk and whether not having that information is problematic; and clinician preferences for implementation of risk models and associated processes and tools. Interviews at KPWA and HP will be framed to elicit clinicians' actual experiences using the visit-based alert or patient registry and will inquire about their own experiences and their perceptions of their patients' experiences of risk conversations. Interviews with administrators and clinicians will conclude with an opportunity for interviewees to express concerns about anticipated liabilities that might accompany use of suicide risk prediction tools.

Examples of patient interview questions include "What do you think about computers predicting a person's risk of suicide?" "How would you feel about your health information being used to calculate a suicide risk score?" "If your doctor told you that you were at high risk for suicide, what other information, if any, would you like to know from him/her?" "How might that affect the clinical visit or your relationship with your doctor?" "Would you rather your doctor/counselor alert you to this risk or would you be comfortable receiving a call from another health professional tasked with following up with high risk patients?" "Do you think this kind of outreach is caring and compassionate or creepy and intrusive?" Interviews will explore concerns about risk information being released (e.g., to employer, insurance) or used to justify coercive or restrictive treatments. Interviews at KPWA and HP will be anchored to the patient's recent experience with their clinician and the actual conversation which took place regarding their suicide-related risks.

The primary risks to participants are discomfort discussing suicide risk, inconvenience, and potential loss of

Adequacy of Protection Against Risks

Informed Consent and Assent

The process of informed consent will assure that participants understand the nature of the research and adequately comprehend their involvement, including risks and benefits. Participants choice to participate will be voluntary. All participants will be asked to review an IRB-approved consent document and provide consent.

Protections Against Risk

Discomfort discussing suicide risk. Interviews will be conducted by trained qualitative interviewers experienced in conducting interviews regarding sensitive information. Interviewers are trained to assess risk of suicide if these concerns are disclosed in patient interviews, and participants will be connected to mental health services immediately if needed, including by medical transport to the nearest emergency department if warranted. We have an established, IRB-approved protocol for assessing suicide risk which includes consultation with licensed professional staff regarding appropriate disposition.

Inconvenience. Clinician interviews will be conducted at the clinician's convenience, in the setting and by the mode of their choice. They will be offered an artisanal chocolate bar in appreciation. Patient interviews are limited to about one hour and will be conducted only once, in the setting and by the mode of the patient's choice; interviewers are sensitive to participants' needs for breaks, and interviews can be completed in more than one session if needed. Patients will receive a $50 gift card to compensate them for travel, interview time, and inconvenience.

Loss of confidentiality. Investigators and study staff will reduce any risk of disclosure of confidential information, maintaining subjects' privacy through secure data storage and the removal or obscuring of patient names or identifying features during data acquisition or analysis phases. Participants' privacy and confidentiality will be assured by transporting encrypted interview digital recording materials in locked containers. Investigators and study staff will also securely store data in password-protected files and directories on computers within firewall-protected networks. We will ensure that unmodified interview answers (containing identifying data or features) are accessible only to interviewers working under the direction of the investigators for the duration of the project; all identifiers will be eliminated from interviews during transcription.

Vulnerable Subjects, if relevant to your study

Not relevant.

Potential Benefits of the Proposed Research to Research Participants and Others

This study is designed to deepen our understanding of health system administrators', clinicians', and patients' expectations, concerns, suggestions regarding, and experiences with the use of suicide risk prediction models in clinical settings. The potential benefits of risk prediction models are dependent on making sure that these kinds of tools are deployed in a manner that does not harm patients, supports clinical care management, and is sustainable for health care delivery systems. Qualitative interviews with administrator, clinician, and patient stakeholders will benefit participants because they will have an opportunity to voice their opinions about the use of these risk mitigation tools, how they should be designed and deployed. While there is an emerging literature supporting the promise of predictive models in health care, implementation factors and patient impacts have been largely ignored. The results of this study will have important clinical implications and inform ongoing health system-level efforts to reduce suicide prevalence.

Importance of the Knowledge to be Gained

The long-term goal of this pilot project is to prevent suicides by optimizing the use of suicide risk prediction tools through a rigorous and systematic pre-implementation evaluation. Results of this study will inform large-scale implementation in MHRN health systems and other systems across the U.S.

The Kaiser Permanente Northwest (KPNW) IRB will serve as the single IRB for this pilot study. The three sites participating in this study have used IRB reliance agreements developed by the broader Health Care Systems Research Network and are accustomed to ceding for studies. Our sites are currently involved in a study led by KPNW where the KPNW IRB is the IRB of record and KP Washington and HealthPartners, the two other sites participating in this pilot, are ceding review to KPNW's IRB. Sites communicate with the KPNW IRB liaison/ study project manager who communicates directly with the IRB administrator.

We do not believe that a data and safety monitoring plan is necessary for these qualitative interviews; this pilot study is not a clinical trial and we will have established safety monitoring procedures in place for dealing with critical incidents such as disclosure of suicide risk. As described in the Human Subjects Protection section, interviewers are trained to assess risk of suicide if these concerns are disclosed in patient interviews and an IRB-approved safety protocol will be invoked when necessary.

Dr. Yarborough will oversee all research activities for the project, including human subjects requirements, development of study materials including consents and interview guides, recruitment of participants, the overall qualitative analysis, interpretation of the analyses, and lead manuscript preparation and dissemination activities. Site PIs will oversee all study activities at their respective sites. The KPNW project manager will manage the IRB submission and oversee the process of having participating sites cede IRB approval to KPNW; site project managers will usher this process. Project managers at all sites will monitor progress on the study and perform all reporting activities. The research analysts will work with the site PIs to execute a clinician and patient recruitment selection process. The qualitative research analyst will work with Dr. Yarborough to develop the final interview guides, train the qualitative interviewers, oversee data collection, develop the coding guide, apply codes in Atlas.ti and manage the preliminary analyses. The qualitative interviewers will perform all interviews of health system leaders, clinicians and patients.

Section 4 - Protocol Synopsis (Study 278304)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Section 6 - Clinical Trial Milestone Plan (Study 278304)

6.1. Study Primary Completion Date
6.2. Study Final Completion Date
6.3. Enrollment and randomization

Enrollment of the first subject	02/01/2020	Actual
25% of planned enrollment recruited by		
50% of planned enrollment recruited by		
75% of planned enrollment recruited by		
100% of planned enrollment recruited by		

6.4. Completion of primary endpoint data analyses
6.5. Reporting of results in ClinicalTrials.gov
6.6. Is this an applicable clinical trial under FDAAA? ❍ Yes ❍ No

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
278303	Effect of glutamate receptor modulator drugs on suicidal ideation and behavior	No	SP2_Delayed_Just_218019_Final.pdf

We propose to use health system records to evaluate the effect of anticipated glutamate-receptor modulator drugs (i.e. ketamine-like drugs) on suicidal ideation and behavior in real-world practice. The first of these drugs, esketamine, is expected to be approved in mid-2019. This project is expected to begin in approximately month 27 of the overall network award (i.e. approximately January 2022. By that time, a large enough sample of patients using one or more of these new drugs will have accumulated. While we are able to specify key aspects of the study design (see attached Research Plan), we are not able to specify key aspects related to protection of human subjects until data regarding actual medication use are available. Specifically:

- Study sites – While we anticipate that this project will include three or more of the larger MHRN health systems, selection of sites will depend on actual patterns of use for these new drugs in 2020 and 2021.
- Planned enrollment – The number of patients to be included will depend both on actual patterns of use and on work regarding sample size estimation that currently underway in Dr. Shortreed's recently funded methods grant.
- Inclusion of women, minorities, and children – Inclusion of women and minorities will depend on actual patterns of use of new drugs. Based on patterns of use for existing treatments, we would predict that women will make up approximately 65% of the sample. We do not expect that these new drugs will be approved for use in children under age 18 during the study period, so we do not expect that children under 18 will be included.

We can be certain, however, that this project will not be a clinical trial (i.e. will not involve prospective assignment of treatments by researchers) and that it will not involve any direct interaction with or collection of study-specific data from patients (i.e. all study data will be extracted from existing records).

Note: Under the Revised Common Rule, research limited to existing records may be considered exempt from IRB review. Washington State law, however, still requires IRB review of records-based research. Consequently, we anticipate requesting and being granted a waiver of informed consent (rather than an exemption) to conduct this records-based research.

Section 1 - Basic Information (Study 278307)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Outreach to Reduce Disparities in Depression Treatment Initiation

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	❍ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	❍ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 278307)

2.1. Conditions or Focus of Study

- Initiation of depression treatment after a new diagnosis of depression in primary care

2.2. Eligibility Criteria

New diagnosis of major depressive disorder or dysthymic disorder at a primary care visit ("new" defined as no depression diagnosis, psychotherapy visit or filled antidepressant prescription in the prior year; Continuously enrolled in the participating health system for 365 days prior to the eligible diagnosis (to assure capture of prior diagnoses or treatments); PHQ-9 depression score of 10 or more within 14 days before to 7 days after the eligible diagnosis; No filled prescription for any antidepressant medication OR psychotherapy visit attended within 30 days of the eligible diagnosis; No recorded PHQ-9 depression score less than 5 since the eligible diagnosis.

2.3. Age Limits	Min Age: 18 Years	Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	PP2_Wom_Min_218019_Final.pdf	
2.5. Recruitment and Retention Plan	PP2_Recruit_Plan_218019_Final.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	PP2_Timeline_218019_Final.pdf	

Inclusion of women – We anticipate that approximately two-thirds of participants will be women, reflecting the epidemiology of new diagnoses of depression in primary care.

Inclusion of minorities – This trial focuses specifically on failure to initiate indicated depression treatment in under-served minority groups. Enrollment will be limited to specific minority groups: Asian, Native Hawaiian/Pacific Islander, Black of African American, and Hispanic.

Inclusion of children – Children under 18 will not be included. Trial design is determined by treatment guidelines specific to adults, assessment tools specific to adults, and EHR functionalities only available to adult health system members.

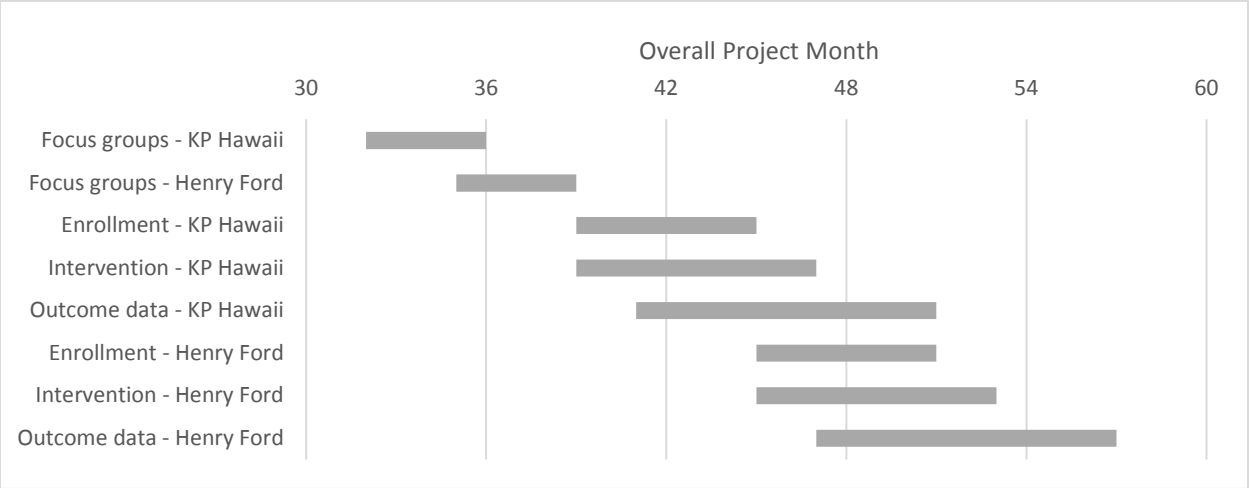
Recruitment and Retention Plan

Recruitment - Participants will not be specifically recruited. All participants meeting study eligibility criteria will be automatically identified using health system records and randomly assigned to either continued usual care (no contact) or to attempted outreach.

Retention in Intervention – All participants assigned to the intervention condition will be offered outreach and (as clinically appropriate) care facilitation. We anticipate that some participants will decline these services, and (following principles of pragmatic or effectiveness trials) rate of intervention participation is a study outcome.

Retention in Outcome Data Collection – Outcomes will be ascertained from health system records. Participants will not be contacted regarding study outcomes. Based on data from past and ongoing MHRN research, we anticipate that fewer than 0.5% (i.e. one in 200) participants will disenroll from the participating health system (so that complete outcome data will not be available) during the 60-day follow-up period for the primary trial outcome.

Pilot Project #2 is scheduled to begin in approximately month 30 of the 5-year overall network timeline. Expected times for specific activities are shown below.



Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 275673	Domestic	Kaiser Permanente Hawaii, Henry Ford Health System

Inclusion Enrollment Report 275673

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Kaiser Permanente Hawaii, Henry Ford Health System

Comments: Enrollment will be limited to patients enrolled in the two participating health systems

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	67	33	0	0	100
Native Hawaiian or Other Pacific Islander	67	33	0	0	100
Black or African American	67	33	0	0	100
White	0	0	67	33	100
More than One Race	0	0	0	0	0
Total	201	99	67	33	400

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 278307)

3.1. Protection of Human Subjects	PP2_Hum_Subj_218019_Final.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	● Yes ❍ No ❍ N/A
If yes, describe the single IRB plan	PP2_SIRB_218019_Final.pdf
3.3. Data and Safety Monitoring Plan	PP2_DSMP_218019_Final.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	PP2_Team_218019_Final.pdf

Human Subjects Involvement, Characteristics, and Design

This pilot trial will evaluate a low-intensity outreach program to increase rates of treatment initiation among racial and ethnic minority patients receiving new diagnoses of depression in primary care. Enrollment will be limited to specific racial and ethnic groups with low rates of treatment initiation. Participants assigned to the intervention condition will be offered outreach services. Those assigned to the usual care condition will not be contacted. Outcomes (initiation of depression treatment, documentation of depression response or remission) will be assessed using health system records.

Study Procedures, Materials, and Potential Risks

Participants will be identified automatically using health system records and then randomly assigned to either the intervention or usual condition. Participants assigned to the intervention condition will be contacted by online messaging (via EHR patient portals) and asked to complete an initial assessment. Those who report continued significant symptoms of depression will be contacted to facilitate engagement in care. Participants not responding to online messaging will be contacted by phone.

Participants assigned to the usual care condition will not be contacted. No additional treatment will be provided, but no treatment or other health service usually available will be restricted or denied. Consequently, each usual care participant will receive the same treatment she or he would have received if the study were not occurring. The only risk to usual care participants would be breach of confidentiality by accidental disclosure of health information.

Potential risks to participants assigned to the intervention condition include:

- Breach of confidentiality breach due to inadvertent disclosure of health information
- Upset precipitated by outreach and care facilitation contacts
- Potential adverse effects of depression treatment (medication or psychotherapy) prompted by the outreach intervention

Adequacy of Protection Against Risks

Informed Consent

- We propose a waiver of consent to use records data to identify potential participants. Such a waiver is justified because:
  - Use of existing records for this purpose does not involve more than minimal risk
  - It would not be practicable (or even possible) to identify patients failing to initiate depression treatment without use of records.
  - Use of records for this purpose will not affect patients' rights, privileges, or access to any effective treatments.
- We propose a waiver of consent to randomly assign eligible participants to intervention or usual care conditions. We believe such a waiver is justified because:
  - This assignment does not involve more than minimal risk. Each participant assigned to the usual care condition will receive the treatment she or he would have received if the study were not occurring. Participants assigned to the intervention condition will be encouraged to pursue treatment consistent with well-supported and widely accepted treatment guidelines, but will be free to refuse participation or any treatment.
  - It would not be practicable to contact eligible patients to request consent prior to random assignment. A trial of outreach to promote treatment initiation that was limited to motivated volunteers would have no scientific or public health value.
  - Assignment to either condition would not affect patients' rights, privileges, or access to any effective treatments.
- We propose a modification or partial waiver of consent to offer or provide outreach and care facilitation services to participants assigned to the intervention group. Specifically, outreach messages will include specific elements of informed consent (i.e. this outreach is part of research, participation is voluntary, and

patients are free to withdraw at any time if outreach contacts are unhelpful or bothersome). We believe that a modification or partial waiver of consent is justified because:

- The offer of outreach and care facilitation does not involve more than minimal risk. Participants assigned to the intervention condition will be encouraged to pursue treatment consistent with well-supported and widely accepted treatment guidelines, but will be free to refuse participation or any treatment.
- It would not be practicable to use a traditional consent procedure prior to offering outreach and care facilitation. The consent procedure itself would be both more intrusive and more intensive than the outreach contact.
- Assignment to either condition would not affect patients' rights, privileges, or access to any effective treatments.

Protection Against Risk

While severe depression and/or suicidal ideation are not risks of study participation, it is possible that study clinicians will discover severe depression or suicidal ideation in patients not receiving treatment. In these cases, study clinicians will follow standard procedures to assess risk, encourage engagement in care, and notify responsible primary care physicians. As described in the accompanying Data and Safety Monitoring Plan, responses to these high risk situations will be tracked and reviewed by site investigators.

Potential Benefits of the Proposed Research to Research Participants and Others

Participation will not have any direct benefit to participants assigned to the usual care condition.

While it is reasonable to expect that promoting initiation of treatment would offer benefit to people with significant symptoms of depression, we cannot be sure of benefits to any individual. Consequently, initial messages to intervention group participants will not promise any specific benefit.

Importance of the Knowledge to be Gained

Failure to initiate treatment is a major gap in depression care, and some minority racial and ethnic groups are a particularly high risk. The proposed pilot study will assess feasibility of low-intensity outreach programs to address this care gap and inform the design of a subsequent full-scale pragmatic trial.

It is not yet determined if both sites will implement the same intervention protocol, and this will only be determined after the formative research described in the Research Plan. If both sites implement the same protocol, then the Henry Ford IRB can serve as IRB for both sites. If sites implement separate protocols, then each site's IRB will review and approve a site-specific protocol.

Overview – We do not propose to create a formal Data and Safety Monitoring Board. Given the short enrollment periods at each site, data regarding study outcomes or potential adverse events would not be available soon enough to inform decisions regarding study continuation. Consequently, no interim analyses regarding effectiveness or safety are proposed. We describe below specific procedures regarding monitoring for adverse events, responding to urgent clinical needs, and monitoring data quality and integrity. Lead investigators at each site will have primary responsibility for adherence to these procedures. Dr. Simon (lead investigator for the MHRN Administrative Core) will serve as independent safety monitor, with responsibilities described below.

Monitoring for Adverse Events – While study participants could experience adverse events such as suicide attempts or psychiatric hospitalization, we do not propose to review these events to determine "relatedness" to study intervention. These events are expected in a small proportion of patients receiving treatment for depression, and we do not believe it would be possible to determine whether or not any event was related to study outreach messages or telephone contacts. We also do not propose to compare rates of such events in the intervention and control groups. Based on previous MHRN research, the expected number of psychiatric hospitalizations and the expected number of suicide attempts in this population (people with new diagnoses of depression in primary care) over 90 days would be less than one per group. Any comparison would lack precision to support any meaningful conclusions regarding intervention effects.

We do, however, identify some adverse events that might require evaluation and corrective action. Any of the following adverse events will be reported to the independent safety monitor (Dr. Simon) and the responsible Institutional Review Board:

- Breach of confidentiality (e.g. inadvertent disclosure of protected health information by the outreach clinician to someone other than the participant)
- Violation of study protocol (e.g. failure or significant delay in sending outreach messages)
- Participant complaint (e.g. participant complains that study is a misuse of health data or that messages are bothersome)

The safety monitor and IRB will review reports of each of these events and recommend any appropriate change in study procedures or other corrective action.

Response to Suicide Risk or Other Urgent Clinical Needs – Suicidal ideation or severe depression discovered during initial outreach contacts would not be considered an adverse effect of study participation or study interventions, but study staff must still be prepared to respond appropriately to urgent clinical need. Any response of "More than half the days" or "Nearly every day" to item 9 of the PHQ-9 (regarding thoughts of death or self-harm) will activate a structured response used successfully in the MHRN Suicide Prevention Outreach Trial:

- The Outreach Clinician will respond immediately by online messaging AND initiate telephone outreach to administer the Columbia Suicide Severity Rating Scale (CSSRS).
- The Outreach Clinician will then recommend and facilitate follow-up care with type and timing of care recommendation depending on CSSRS score:
  - CSSRS score 5 = Specialty mental health or emergency department visit within 2 days
  - CSSRS score 4 = Specialty mental health visit within 7 days
  - CSSRS score 3 = Specialty mental health visit within 2 weeks
  - CSSRS score 1 or 2 = Specialty mental health or primary care visit within 4 weeks

Assessment findings and disposition will be recorded in the electronic health record with a copy to the primary care physician recording the eligibility diagnosis.

Any PHQ-9 total score of 20 or greater will also prompt immediate online messaging and telephone outreach by the Outreach Clinician to assess urgent need and to advise and facilitate specialty mental health follow-up care within 7 days.

Outreach clinicians will record outreach efforts, assessment findings, and disposition for each of these events. At each site, these records will be reviewed the principal investigator to assure adequate outreach efforts and appropriate clinical recommendations. Records from both sites will be reviewed by Dr. Simon, the independent safety monitor.

Monitoring Data Quality and Integrity – All study outcomes will be extracted from health system records. Accuracy and completeness of data elements contributing to the primary study outcome (filled antidepressant prescriptions, psychotherapy visits) are monitored quarterly as part of MHRN's routine data quality and descriptive analyses. Data elements and processes contributing to secondary outcomes (NCQA/HEDIS indicators of depression response and remission) are routinely monitored by participating health systems' public quality reporting processes.

Study staff at each site will include:

- A lead investigator responsible for all study operations, including liaison with local providers and health system leaders, supervision of outreach clinicians, and initial review of study staff response to urgent clinical situations
- A project manager responsible for communications, fiscal management, and regulatory compliance
- A programmer/analyst responsible for extracting relevant data from health system records and developing/implementing study tools in electronic health records systems
- A focus group interviewer responsible for recruiting focus group participants and conducting focus groups

The study will be supported by central MHRN resources at the KP Washington site:

- Dr. Simon, a practicing psychiatrist and lead of the MHRN Administrative Core, will serve as independent safety monitor.
- Site programmer/analysts will rely on MHRN's extensive library of computable EHR phenotypes and standard data extraction programs.

Section 4 - Protocol Synopsis (Study 278307)

4.1. Brief Summary

This pilot trial will evaluate a low-intensity outreach intervention to address frequent failure to initiate indicated depression treatment among underserved racial/ethnic minority groups.

4.2. Study Design

4.2.a. Narrative Study Description

Pilot Trial Design: Each week, the computable EHR phenotype described above will be used to identify patients meeting criteria for failure to initiate depression treatment during the prior week. All eligible participants will be randomly assigned either to continued usual care (i.e. no contact from study staff) or to an outreach intervention described below. Engagement in care and recorded clinical outcomes over the subsequent 60 days will be assessed using health system records. Eligibility and Exclusion Criteria: Criteria for failure to initiate indicated depression treatment (the primary eligibility criterion) are listed above. The KP Hawaii site will limit enrollment patients self-identified (based on EHR data) as Asian or Native Hawaiian or Pacific Islander. The Henry Ford site will limit enrollment to patients self-identified as Black or Hispanic. Potential participants will be excluded because of: Diagnosis of schizophrenia or bipolar disorder in the prior 2 years Not registered to use EHR patient portal Previously requested to not be contacted for research Intervention Assignment: All eligible patients will be randomly assigned (1:1 ratio) to either continued usual care or attempted outreach using a masked table of computer-generated random assignments. Assignment will be stratified by study site and implemented with randomly selected block sizes ranging from 4 to 12. Waiver/Modification of Consent: We propose a waiver of the usual requirement for informed consent to identify potential participants and assign patients to either continued usual care or attempted outreach. We believe that this approach (waiver of consent in such a modified Zelen or randomized encouragement design to evaluate a low-risk outreach intervention) satisfies regulatory requirements and ethical standards for waiver of consent. Use of this approach in similar previous MHRN trials has been vetted with the DHHS Office for Human Research Protections and approved by MHRN health system institutional review boards. For participants assigned to outreach, the initial outreach message will include abbreviated informed consent information, including: Description of the outreach program Notification that outreach is part of a research project Advice that participation is voluntary and instructions on declining further participation Outreach Intervention: The structured outreach and care facilitation intervention will adapt procedures and tools developed and proven successful in the current MHRN automated outreach project as well as several other outreach and care management interventions developed and tested by MHRN investigators. Specific components include: Initial outreach messages - Outreach messages including attached questionnaires (described below) will be sent via health system EHR (Epic) patient portal messaging systems. This system supports secure and confidential two-way exchange of free-text messages, tracking of read/unread messages, and attachment of standard questionnaires (including immediate feedback tailored according to questionnaire responses). Text for initial outreach messages will be based on messages developed and refined in the ongoing MHRN automated outreach project, further refined using formative feedback from focus groups described above. Online messaging and telephone follow-up - Following procedures developed and tested in the messaging collaborative care trial and the ongoing Suicide Prevention Outreach trial, outreach clinicians will follow a structured protocol for outreach if there is no response to the initial message: If initial message is read but no response - initial reminder by online message followed by up to three telephone outreach attempts If initial message is not read - up to three telephone outreach attempts Based on previous experience, we expect that most telephone outreach would involve leaving telephone message reminders regarding patient portal messages rather than live contact with participants. Structured assessment of symptoms, perceived needs, and barriers - The initial assessment questionnaire will include structure assessment of current depression symptoms (PHQ-9) and structured assessment of perceived need for treatment as well as perceived barriers to or drawbacks of treatment. Questionnaire content will be based on tools developed and tested in the previous secure messaging collaborative care trial and the ongoing MHRN automated outreach project. Those existing assessments will be further refined using formative feedback from focus groups described above. In case of live telephone contacts during telephone reminders (see above), outreach clinicians will offer to complete assessments by telephone. Tailored feedback - Using standard EHR (Epic) functionality, participants completing the patient portal questionnaire will receive immediate tailored feedback based on questionnaire responses. Feedback will be generated by algorithms developed and tested in the previous secure messaging collaborative care trial and the ongoing MHRN automated outreach project. Those existing algorithms will be further refined using formative feedback from focus groups described above. To illustrate the general form of feedback messages, a respondent reporting a PHQ-9 score of 12 and low perceived need for treatment would receive a message similar to "Thanks for answering those questions. Based on your answers, you might be experiencing significant symptoms of depression or stress. You did say that you are not now interested in treatment for stress or depression, but I would still like to talk with you about your options. I'll try to reach you directly in the next few days." Participants completing the initial assessment by telephone would receive tailored feedback by telephone, proceeding immediately to care facilitation (described below). Care facilitation - Participants who report satisfactory outcome (response or remission by PHQ-9) will receive immediate feedback without subsequent care facilitation. Participants who report unsatisfactory outcome (no response or remission by PHQ-9 will be contacted by

online message and/or telephone for subsequent care facilitation. Outreach clinicians' actions to facilitate care will also be determined by participants' responses regarding symptoms, perceived needs, and barriers. For participants with PHQ-9 score less than 15 and a response <2 to PHQ-9 item 9, initial contact will be by online message. For participants with PHQ-9 score >=15 or response to item 9 >=2, initial contact will be by telephone. Using motivational interviewing scripts and tools developed in previous research, outreach clinicians will assess readiness and respond with appropriate tailored interventions focused on either motivational enhancement or action planning. Depending on clinical need, outreach clinicians will also assess risk of self-harm, initiate safety planning, and facilitate urgent mental health care - using procedures developed in the MHRN Suicide Prevention Outreach Trial. Monitoring initiation and adherence - Based on experience in the MHRN Suicide Prevention Outreach Trial and Automated Outreach project, Outreach clinicians will track reading and response to outreach messages as well as initiation of and early adherence to depression treatment (either medication or psychotherapy) using EHR-based population management tools (Epic Registry and Reporting Workbench functionality). Outreach clinicians - Outreach clinicians will be either registered nurses or masters-prepared mental health clinicians. Following a typical model for implementation of collaborative care or care management programs, outreach clinicians will receive approximately 8 hours of initial training and will participate in bi-weekly supervision teleconferences during the period of active intervention delivery. Estimates of necessary outreach clinician effort levels are based on staffing and caseload levels in the MHRN automated outreach project. Trial Outcomes: The primary trial outcome will be initiation of formal depression treatment within 60 days of randomization, defined as either at least one filled prescription for any antidepressant medication or attending at least one individual psychotherapy visit. Two secondary outcomes (recording of depression remission or response) will be defined and assessed using NCQA/HEDIS Electronic Clinical Data Systems specifications for depression response and remission. Those specifications identify recorded response (i.e. 50% or greater decrease in PHQ-9 score from baseline) and remission (i.e. any recorded PHQ-9 score of less than 5) among all patients with new diagnoses and baseline PHQ9 scores of 10 or higher.

4.2.b. Primary Purpose: Health Services Research

4.2.c. Interventions

Type	Name	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Outreach and care facilitation	Adult patients failing to initiate indicated depression treatment will be identified using health system records. Those assigned the outreach intervention will be contacted by online messaging via the EHR patient portal (with telephone follow-up for those no responding). Those contacted will be asked to complete a brief structured assessment of depression symptoms, perceived need for treatment, and barriers to initiating treatment. Participants will receive immediate tailored feedback after completion of the online assessment. Those reporting persistence of significant depressive symptoms will be contacted (by online message and/or telephone) to assess/enhance motivation for treatment, address barriers, and facilitate initiation of appropriate treatment (medication or psychotherapy).

4.2.d. Study Phase: Phase 2

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ● No

4.2.e. Intervention Model: Parallel

4.2.f. Masking: ● Yes ❍ No

❑ Participant ❑ Care Provider ☑ Investigator ☑ Outcomes Assessor

4.2.g. Allocation: Randomized

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

Primary	Rate of treatment initiation	60 days after randomization	Filled prescription for any antidepressant medication OR attending at least one psychotherapy visit - assessed by health system records
Secondary	Depression remission and response	180 days after randomization	Recorded PHQ-9 depression score demonstrating response (i.e. 50% decrease from baseline) or remission (i.e. score <5) defined according to NCQA HEDIS ECDS quality measures for depression

4.4. Statistical Design and Power — PP2_Stat_Power_218019_Final.pdf

4.5. Subject Participation Duration — Intervention activities (outreach and care facilitation) may continue for up to 60 days after randomization.

4.6. Will the study use an FDA-regulated intervention? — ❍ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan — PP2_Diss_Plan_218019_Final.pdf

Data Analysis Plan

Descriptive analyses will examine baseline participant characteristics (age, sex, baseline PHQ-9 score, history of prior depression treatment) and examine uptake or acceptance of specific intervention activities, including:

- Proportion of intervention participants reading initial outreach messages
- Proportion responding to initial outreach and completing outreach assessment
- Proportion of those not responding to online messages who respond to subsequent telephone outreach
- Distribution of PHQ-9 responses, perceived need for treatment, and perceived treatment barriers among those completing outreach assessment (by online messaging or telephone).
- Proportion initiating any treatment or specific type of treatment (medication or psychotherapy) according to response to outreach, PHQ-9 score at initial assessment, perceived treatment need at initial assessment, and perceived barriers to treatment at initial outreach.

Sample size permitting, each of these analyses will be stratified by race/ethnicity group.

Analyses of primary outcomes will compare rate of treatment initiation within 60 days (defined above) among all patients originally assigned to the intervention condition to rate among those assigned to continued usual care, regardless of acceptance of or participation in the outreach intervention (i.e. complete intent-to-treat analysis). Unadjusted analyses will compare rates using chi-square statistics and adjusted analyses will use logistic regression with adjustment for age group, history of prior depression treatment (medication or psychotherapy) and baseline PHQ9 score. Analyses of secondary outcomes (depression remission and response by HEDIS specifications) will follow the same scheme.

We do not propose any “as treated” or “per protocol” analyses limited to patients who accept or respond to outreach interventions. Because it is not possible to identify usual care patients who would have declined intervention services, any comparison of intervention “accepters” to the full usual care sample would be fundamentally and irreparably biased.

Statistical Power / Sample Size

Based on previous MHRN research, we presume that 10% of participants assigned to usual care will initiate treatment within 60 days of randomization (after not initiating treatment in the first 30 days after diagnosis). A sample size of 200 per group at both sites will afford 90% power (with 2-sided type 1 error of 5%) to detect an increase from 10% to 22% in those assigned to the outreach intervention. Within any specific racial or ethnic group, the anticipated sample size of approximately 50 per group would afford 80% power to detect an increase from 10% to 33% in those assigned to the outreach intervention. In other words, this pilot study will have adequate power to detect moderate to large increases in treatment initiation and will not have adequate power to examine effects on ultimate clinical outcomes (i.e. HEDIS response and remission rates).

Results will be disseminated via academic publications and conference presentations. We do not believe findings of this pilot trial will clearly support implementation of this outreach program. Instead, we anticipate that results this pilot study will inform a full-scale pragmatic trial of outreach to reduce disparities in depression treatment initiation. Such a trial would be adequately powered to evaluate impact on ultimate clinical outcomes (HEDIS response and remission rates) and would explicitly examine effects on disparities, including both minority and non-Hispanic white patients and examining interaction between racial-ethnic disparities and assignment to outreach intervention or usual care.

Section 6 - Clinical Trial Milestone Plan (Study 278307)

6.1. Study Primary Completion Date	05/01/2024	Anticipated
6.2. Study Final Completion Date	06/30/2024	Anticipated
6.3. Enrollment and randomization		
Enrollment of the first subject	09/01/2022	Anticipated
25% of planned enrollment recruited by	12/01/2022	Anticipated
50% of planned enrollment recruited by	03/01/2023	Anticipated
75% of planned enrollment recruited by	06/01/2023	Anticipated
100% of planned enrollment recruited by	09/01/2023	Anticipated
6.4. Completion of primary endpoint data analyses	05/01/2024	Anticipated
6.5. Reporting of results in ClinicalTrials.gov	06/01/2024	Anticipated
6.6. Is this an applicable clinical trial under FDAAA?	❍ Yes ● No	