OBSERVATIONAL STUDY PROTOCOL

TITLE	Implementation of Harmonized Depression Outcome Measures in a Health System to Support Patient-Centered Outcomes Research
PROTOCOL/STUDY NO.	N/A
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Table of Contents

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List of Abbreviations

ABFM	American Board of Family Medicine
AHRQ	Agency for Healthcare Research and Quality
APA	American Psychiatric Association
CFR	Code of Federal Regulations
CHRT	Concise Health Risk Tracking
EHR	Electronic health record
EMR	Electronic medical record
FDA	U.S. Food and Drug Administration
FIBSER	Frequency, Intensity, and Burden of Side Effects Ratings
GCP	Good Clinical Practice
GPP	Good Pharmacovigilance Practices
HAM-D	Hamilton Depression Score
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Committee on Harmonization
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
MDD	Major Depressive Disorder
MIPS	Merit-based Incentive Payment System
OMF	Outcome Measures Framework
PHQ-9	Patient Health Questionnaire – 9
PRO	Patient Reported Outcome
PsychPRO	Psychiatric Patient Registry Online
SAP	Statistical analysis plan

1. Background

A patient registry is defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves one or more pre-determined scientific, clinical, or policy purposes."[1] Patient registries fulfill different purposes for a wide range of stakeholders, as documented in the publication, Registries for Evaluating Patient Outcomes: A User's Guide.[1] Given their myriad purposes, it is unsurprising that a large number of registries exist – over 5,000 according to the ClinicalTrials.gov.

Together, these registries represent an enormous investment in research infrastructure and a tremendous data resource that could be used to address new research questions in a timely and efficient manner. Yet, linkage and comparisons of data across registries to address research questions is challenging, if not impossible, because of variation in both the concepts and definitions of the outcome measures used in registries within the same clinical area. Even when the outcome concept is the same (e.g., remission in depression), registries may define the measure differently (e.g., using the Hamilton Depression Rating Scale [HAM-D] vs. the Patient Health Questionnaire-9 [PHQ-9]) because very few standardized definitions exist. This limits the potential of registries to support new research and serve as a foundation for learning health systems and national health data infrastructure. This also introduces inefficiency in registry data collection. Many organizations, such as health systems, participate in multiple registries, but data must be captured differently for each registry. Incorporation of key data elements within electronic health record (EHR) systems would reduce the burden of registry data entry, but, for many organizations, the cost of incorporating each registry's unique data elements within the EHR system is too high.

To address these issues, patient registries must implement standardized outcome measures that can be captured consistently as part of routine clinical practice across care settings and seamlessly transferred into different registries. These outcome measures also must be useful in routine clinical practice for informing treatment decision and monitoring patients over time. The Agency for Healthcare Research and Quality (AHRQ) has supported the development of the Outcomes Measures Framework (OMF), a conceptual model for classifying outcomes that are relevant to patients and providers across most conditions.[2] Under this OMF project,[3, 4] minimum sets of standardized outcome measures suitable for use in registries and clinical practice were developed in five clinical areas, including depression.

While registries, clinicians, and other stakeholders expressed enthusiasm about standardized outcome measures, they identified several barriers to implementation in registries and in clinical practice during workgroup meetings for the previous project. First, stakeholders noted the difficulty of working with different EHRs to extract data for patient registries. Registry sites often use EHRs from different vendors; even when sites use the same vendor (e.g., Epic), they often have customized implementations that make extraction of data in a standardized manner difficult. In reviewing the standardized measures, stakeholders also expressed concerns about the burden on patients and clinicians of capturing patient reported outcomes (PROs) on a regular basis, particularly for long-term follow-up. Lastly, stakeholders noted the potential for disruptions to clinical care if clinicians are asked to document additional information in

structured fields (as opposed to notes). Many stakeholders emphasized the need for pilot testing to demonstrate the feasibility of implementing the harmonized measures and to show the value of the harmonized measures – both in terms of reduced burden of data entry and the ability to generate data of sufficient quality for registry-based research.

The proposed project will implement the harmonized outcome measures in a manner that addresses these barriers, using depression as a test case. Major depressive disorder (MDD) is a common mental disorder that affects an estimated 16.2 million adults and 3.1 million adolescents in the United States.[5, 6] Characterized by changes in mood, cognitive function, and/or physical function that persist for two or more weeks, MDD can reduce quality of life substantially, impair function at home, work, school, and in social settings, and result in increased mortality due to suicide.[7] MDD also is a major cause of disability, with an economic burden of approximately $210.5 billion per year in the United States.

Despite the burden of MDD and the availability of treatment, the condition is often undiagnosed and untreated. In 2016, the U.S. Preventive Services Task Force recommended screening for depression in the general adult population, including pregnant and postpartum women, and in adolescents.[7, 8] While routine screening is intended to improve diagnosis and treatment of MDD, many questions remain, such as about the comparative effectiveness of different treatment approaches, the incidence of adverse events, when to add medications for patients who do not respond to an initial course of treatment, how and why depression recurs, and how to classify and treat treatment-resistant depression.[9, 10] MDD patients also may receive care from different providers, such as primary care physicians, psychologists, and psychiatrists. Care coordination is important for improving patient outcomes but can be difficult to achieve even within the same health system.

Patient registries capture a wealth of data on depression treatment patterns and outcomes in the United States and could serve as the foundation for a national research infrastructure to address these and other research questions. Yet, as documented in the prior project, existing registries use different outcome measures (e.g., remission as defined by the PHQ-9 vs. HAM-D) and capture data at different timepoints. Similarly, data are not captured consistently across practice settings in routine clinical practice.

2. Rationale

Depression registries offer an excellent opportunity to demonstrate the feasibility and value of implementing the harmonized outcome measures. Existing registries, such as the American Psychiatric Association's (APA) Psychiatric Patient Registry Online (PsychPRO) and the American Board of Family Medicine's (ABFM) PRIME Registry, already capture some of the necessary data for the harmonized measures for quality reporting purposes, although at different timepoints; capture of these measures and the additional measures at consistent intervals will enable the registries to generate more robust data suitable for research purposes. A feasibility study will show that it is technically feasible for registries to collect the data elements necessary to calculate the harmonized outcome measures and to pool the de-identified data for research purposes.

A pilot study is necessary to show that is possible to capture the standardized outcome measures in the clinical workflow, without overburdening clinicians or patients; to provide the measure information back to clinicians to help inform patient care; and to submit the data to different patient registries.

3. Objectives

The purpose of this pilot study is to demonstrate feasibility and value of collecting a subset of the harmonized outcomes measures for MDD in the primary care and mental health setting.

Objectives:

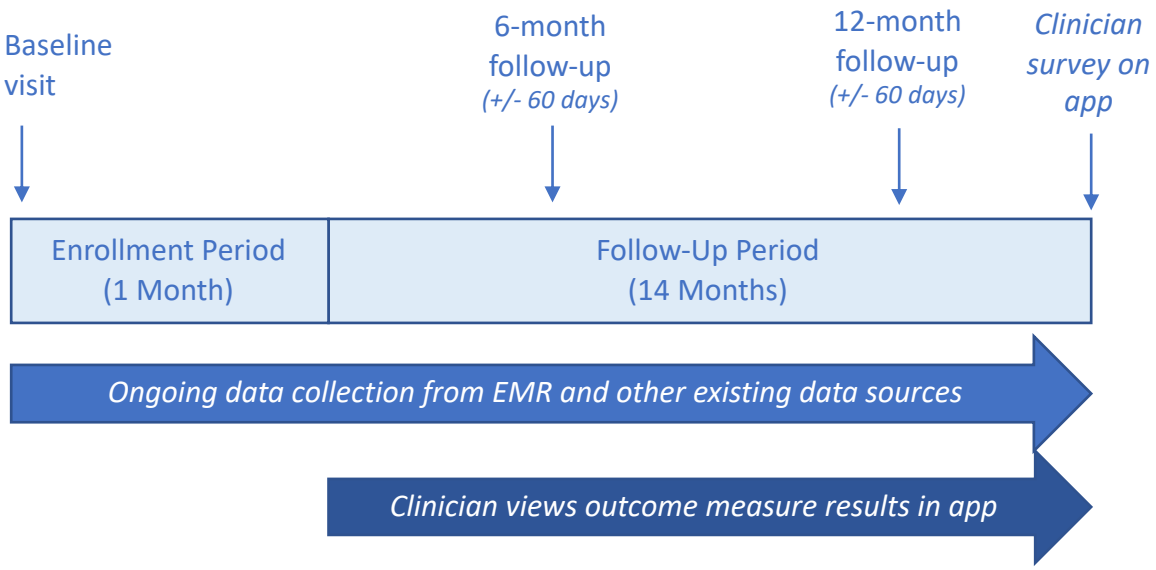
- Demonstrate that it is technically and operationally feasible to use an open-source app to extract the selected outcome measures, including PHQ-9 information, from existing clinical systems and provide the calculated measure results in the clinician's workflow.
- Assess burden of capturing the measures from patients (PHQ-9) and clinicians and value of providing the measure results.

4. Study Design

4.1 Study Description

The study is a longitudinal, observational pilot study that will assess the utility and value displaying the harmonized outcomes data to clinicians in the clinical workflow using an open-source, SMART on FHIR app. The app will connect with the site EHR, aggregate EHR and PRO data, calculate the outcome measure results, and return the results to the EHR so that they are viewable within the clinician workflow. Baseline data on patient characteristics, treatments, and symptoms will be combined with longitudinal data on outcomes during the study timeframe (see Figure 1). All data will be collected from institution electronic medical records (EMRs), PRO portals, and other existing data sources, as needed.

Figure 1. Study Design



4.2 Study Population

The study will collect data on approximately 50 patients from a total of five practices within the same health system.

4.2.1 Inclusion Criteria

The following criteria must be met in order to be enrolled in the study:

- Patients age 18 and older
- Diagnosis of major depression or dysthymia
- Willing and able to provide informed consent

4.2.2 Exclusion Criteria

There are no exclusion criteria for this study.

4.2.3 Study Enrollment

Both specialist (mental health) and general practice sites within the participating health system will be targeted for recruitment. Sites with the ability to implement a SMART on FHIR app will be prioritized. Selection criteria and basic site information (e.g., site size, site type) will be collected via a site qualification survey.

All eligible patients identified during the determined enrollment period at the site will be enrolled.

4.2.4 Patient Withdrawal

Patients may withdraw from the study for any reason at any time.

4.3 Exposure Definition and Measures

This is an observational pilot study focused on technical and operational feasibility in this patient population. This protocol does not recommend the use of any specific treatments, and all assessments are captured as part of routine clinical care.

4.4 Outcome Definitions and Measures

Outcome Measure	**Definition**
Death from suicide	Patient age 18 or older with a diagnosis of major depression or dysthymia who died from suicide, reported in 12-month intervals. This should be captured where feasible; however, this information may not be recorded accurately or available to all providers.
Improvement in Depressive Symptoms: Remission	Patient age 18 or older with a diagnosis of major depression or dysthymia and an initial PHQ-9 score > 9 who demonstrates remission defined as a PHQ-9 score less than 5. *Timeframe for measurement:* Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)
Improvement in Depressive Symptoms: Response	Patient age 18 or older with a diagnosis of major depression or dysthymia and an initial PHQ-9 score > 9 who demonstrates a response to treatment defined as a PHQ-9 score that is reduced by 50% or greater from the initial PHQ-9 score. *Timeframe for measurement:* Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)
Worsening in Depressive Symptoms: Recurrence	Patient age 18 or older with a diagnosis of major depression or dysthymia and an initial PHQ-9 > 9 who demonstrates remission (defined as a PHQ-9 score < 5) of at least two months' duration and subsequently experiences a recurrence of a depressive episode, defined as a PHQ-9 score > 9 OR hospitalization for depression or suicidality. *Timeframe for measurement:* Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)
Adverse Events	Depression treatment-related adverse events, captured using the Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER) scale and extracted from data routinely recorded in the EMR. *Timeframe for measurement:* Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)

Suicide Ideation and Behavior	Selection of 'several days', 'more than half the days' or 'nearly every day' option on PHQ-9 item 9 ("Thoughts that you would be better off dead or of hurting yourself in some way") and/or documentation of nonfatal suicide attempts/suicide attempt behaviors, planning/preparatory acts, or active suicidal ideation extracted from data routinely recorded in the EMR. *Timeframe for measurement:* Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days) *Note, supplemental assessments of suicide ideation and behavior should be completed for patients who screen positive for suicide ideation on the PHQ-9 or when a clinician has concerns about suicidality. Supplemental assessments should be completed using an appropriate, brief, validated instrument, such as the Concise Health Risk Tracking (CHRT) scale.*

4.5 Minimization of Bias

The study will enroll all eligible patients identified during the determined enrollment period at each site. The inclusion of all 'eligible' patients minimizes any potential for bias in the selection of patients for participation in this registry.

4.6 Data Collection

No data will be collected solely for the purposes of this study. All data elements will be collected from information routinely recorded in the EHR or other relevant data sources (e.g., a standalone PRO platform). No visits or examinations, laboratory tests or procedures are mandated as part of this study. In addition, the app will be implemented locally, meaning that no data will leave the health system IT systems. The app will have the ability to transmit data externally (e.g., to a patient registry), but this feature will not be activated during the pilot study.

The capture of PROs, specifically the PHQ-9, at regular intervals is critical for implementation of the depression outcome measures. Practices participating in this pilot project will capture the PROs at regular intervals (including outside of clinical visits with reminders sent to patients) using a standalone PRO system implemented within the health system. This is done as part of routine clinical care for patients with depression, and data captured in this manner are used to calculate quality measures for submission to the Centers for Medicare and Medicaid Services under the Merit-based Incentive Payment System (MIPS).[11, 12]

4.6.1 Data Elements

The following data will be collected for all patients (if available in the EMR or other existing data sources):

Patient Characteristics

- Sex
- Age

- Race/ethnicity
- Family history of depression and other major mental illnesses
- Socioeconomic status
- Pregnancy/Postpartum status

Disease

- Comorbidities
- Disease course
    - Type of depressive episode
    - Depressive severity at diagnosis
    - Duration of symptoms
    - Previous relapses/prior history of depression
    - Prior treatments, including number of medications and number of failed antidepressant treatment attempts
    - Lab tests (e.g., thyroid function, metabolic indices, inflammatory markers)
- Suicidality

Treatments

- Type
    - Medications (type, dose, duration, adherence)
    - Psychotherapy
    - Devices (type, dose, and duration)
    - Alternative
- Referral(s) for treatment

Outcomes

- Death from Suicide
- Improvement in depressive symptoms (assessed via PHQ-9 scores)
    - Response
    - Remission
- Worsening in depressive symptoms
    - Recurrence (PHQ-9 score, hospitalization data)
- Adverse events
- Suicide Ideation and Behavior (assessed via PHQ-9, diagnosis codes)

5. Qualitative Assessment

No formal statistical analysis is planned for this pilot study, and no sample size calculations were done. We anticipate that approximately 50 patients enrolled at five practices will be sufficient to address the objectives of this pilot study.

The purpose of this analysis is to assess the feasibility and value of the open-source app. Clinicians and other personnel (e.g., IT staff) at participating practices will be asked to complete a brief web-based survey at the conclusion of the data collection period to provide feedback on the app. The survey will contain approximately 20 questions assessing three domains: usability of the app, burden of using the app, and overall value of the app for informing patient care and improving engagement with patients. Results of the survey will be summarized in a final study report and in a publication. No patient data will be included in the assessment phase.

6. Study Management

This study will be performed by OM1 in close collaboration with the health system, with guidance, input, review, and approval of AHRQ. The health system team will lead the engagement and support activities for the participating practices, including development of site recruitment materials and training materials, with support from the OM1 team. To ensure the quality and integrity of research, this study will be conducted under the *Guidelines for Good Pharmacoepidemiology Practices* issued by the International Society for Pharmacoepidemiology (ISPE),[13] the principles outlined in the Declaration of Helsinki,[14] and any applicable national guidelines.

6.1 Data Management

All data will remain within the health system IT systems.

6.2 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will usually require submission to the relevant institutional review board (IRB) for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained. Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by at each participating site and will be submitted to the relevant IRB.

6.3 Study Governance

OM1 will be responsible for providing appropriate oversight of all scientific, technical, financial, and administrative matters related to this project, under the direction of Dr. Richard Gliklich as the Project Director.

6.4 Publication Policy

Any publication of the results from this study will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated December 2018.[15] The rights of the participating sites and of OM1 with regard to publication of the results of this study are described in the site contract.

7. Safety Reporting

Due to the observational nature of the study and the use of existing data sources, no adverse event reporting is required. No specific medicinal products or devices are being evaluated as part of the study and there are no objectives related to safety.

8. Ethical and Regulatory Considerations

8.1 Guiding Principles

The study will be conducted in compliance with the US Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 50 – Protection of Human Patients and Part 56 – Institutional Review Boards; the International Council for Harmonisation for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines E6R2 (November 09, 2016) as they apply to post-marketing, observational studies; the Guidelines for Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE); the Belmont Report; US Title 45 CFR Part 164 Subpart E – Privacy of Individually Identifiable Health Information and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule (2002); and any applicable national guidelines.

8.2 Required Documents

Prior to commencement of any study procedures, the protocol signature page, site contract, and IRB approval must be on file with OM1.

8.3 Patient Information and Informed Consent

All data elements will be collected from information routinely recorded in the electronic medical record or as part of the patient's participation in one of the registries. No visits or examinations, laboratory tests, or procedures are mandated as part of this study. Patients will be asked to provide consent for their data to be presented to clinicians within the context of the open-source app.

8.4 Patient Confidentiality

No patient data will leave the health system IT systems as part of this project. Neither OM1 nor AHRQ will have access to any patient data as part of this project. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law.

8.5 IRB

Consistent with local regulations and prior to commencement of any study procedures, the study protocol will be submitted to the responsible IRB for its review. Enrollment will not start at any site before OM1 has obtained written confirmation of a favorable opinion/approval from the relevant central or local IRB. The IRB will be asked to provide documentation of the date of the

meeting at which the favorable opinion/approval was given that clearly identifies the study and the protocol version.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB in a manner consistent with local regulations. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from their local IRB and provide documentation of approval to OM1. All correspondence with the IRB should be retained in the Investigator File.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the IRB of the early termination.

9. References

1. Gliklich R Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov.

2. Gliklich RE, Leavy MB, Karl J, et al. A framework for creating standardized outcome measures for patient registries. J Comp Eff Res. 2014;3(5):473-80. PMID: 25350799. DOI: 10.2217/cer.14.38.

3. Calkins H, Gliklich RE, Leavy MB, et al. Harmonized outcome measures for use in atrial fibrillation patient registries and clinical practice: Endorsed by the Heart Rhythm Society Board of Trustees. Heart Rhythm. 2019;16(1):e3-e16. PMID: 30449519. DOI: 10.1016/j.hrthm.2018.09.021.

4. Gliklich RE, Castro M, Leavy MB, et al. Harmonized outcome measures for use in asthma patient registries and clinical practice. J Allergy Clin Immunol. 2019. PMID: 30857981. DOI: 10.1016/j.jaci.2019.02.025.

5. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

6. National Institute of Mental Health. Major Depression: Prevalence of Major Depressive Episode Among Adults. [Internet]. Bethesda, MD; [updated 2019 Feb; cited 2019 Jun 19]. Available from: https://www.nimh.nih.gov/health/statistics/major-depression.shtml.

7. Siu AL, Force USPST, Bibbins-Domingo K, et al. Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(4):380-7. PMID: 26813211. DOI: 10.1001/jama.2015.18392.

8. Siu AL, Force USPST. Screening for Depression in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. Pediatrics. 2016;137(3):e20154467. PMID: 26908686. DOI: 10.1542/peds.2015-4467.

9. Mojtabai R. Universal Depression Screening to Improve Depression Outcomes in Primary Care: Sounds Good, but Where Is the Evidence? Psychiatr Serv. 2017;68(7):724-6. PMID: 28292224. DOI: 10.1176/appi.ps.201600320.

10. Gaynes BN, Asher G, Gartlehner G, et al. Definition of Treatment-Resistant Depression in the Medicare Population. Technology Assessment Program. Project ID: PSYT0816. (Prepared by RTI–UNC Evidence-Based Practice Center under Contract No. HHSA290201500011I_HHSA29032006T). Rockville, MD: Agency for Healthcare Research and Quality. February 2018. http://www.ahrq.gov/clinic/epcix.htm.

11. Centers for Medicare and Medicaid Services. Depression Remission at Six Months. Quality ID #411 (NQF 0711). https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2019_Measure_411_MIPSCQM.pdf. Accessed July 29, 2019.

12. Centers for Medicare and Medicaid Services. Depression Remission at Twelve Months. MH-1 (NQF 0710). https://qpp.cms.gov/docs/QPP_quality_measure_specifications/Web-Interface-Measures/2019_Measure_MH1_CMSWebInterface_UPDATED.pdf. Accessed July 29, 2019.

13. Ispe. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf. 2008;17(2):200-8. PMID: 17868186. DOI: 10.1002/pds.1471.

14. World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed July 29, 2019.

15. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. http://www.icmje.org. Accessed June 10, 2019.