

## OBSERVATIONAL STUDY PROTOCOL

TITLE	Implementation of Harmonized Depression Outcome Measures in a Primary Care Registry and a Mental Health Registry to Support Patient-Centered Outcomes Research
PROTOCOL/STUDY NO.	N/A
VERSION	1.0 15-August-2019
SPONSOR	Agency for Healthcare Research and Quality 5600 Fishers Lane Rockville, MD 20857
CONDUCTED BY	OM1, Inc. 800 Boylston Street, Suite 1410 Boston, MA 02199

## Table of Contents

<i>Sponsor Signature Page</i> .....	4
<i>List of Abbreviations</i> .....	5
<b>1. Background</b> .....	6
<b>2. Rationale</b> .....	7
<b>3. Objectives</b> .....	7
<b>4. Study Design</b> .....	8
<b>4.1 Study Description</b> .....	8
<b>4.2 Study Population</b> .....	8
4.2.1 Inclusion Criteria.....	8
4.2.2 Exclusion Criteria.....	8
4.2.3 Study Enrollment.....	9
4.2.4 Patient Withdrawal.....	9
<b>4.3 Exposure Definition and Measures</b> .....	9
<b>4.4 Outcome Definitions and Measures</b> .....	9
<b>4.5 Minimization of Bias</b> .....	10
<b>4.6 Data Collection</b> .....	10
4.6.1 Determination of Eligibility.....	11
4.6.2 Data Elements.....	11
<b>5. Statistical Methods</b> .....	12
<b>5.1 Sample Size</b> .....	12
<b>5.2 Data Analyses</b> .....	12
5.2.1 General Considerations.....	12
5.2.2 Planned Analyses.....	12
<b>5.3 Data Reporting</b> .....	13
5.3.2 Annual/interim Analyses and Reporting.....	13
5.3.3 Final Analyses and Reporting.....	13
<b>6. Study Management</b> .....	13
<b>6.1 Data Management</b> .....	13
<b>6.2 Changes to the Protocol</b> .....	13
<b>6.3 Study Governance</b> .....	13
<b>6.4 Publication Policy</b> .....	13
<b>7. Safety Reporting</b> .....	14
<b>8. Ethical and Regulatory Considerations</b> .....	14
<b>8.1 Guiding Principles</b> .....	14
<b>8.2 Required Documents</b> .....	14
<b>8.3 Patient Information and Informed Consent</b> .....	14

**8.4 Patient Confidentiality.....14**  
**8.5 IRB.....15**  
**9. References.....16**

## Sponsor Signature Page

Reviewed and Approved by:

_____ <Sponsor>	_____ Signature	_____ Title	_____ Date
--------------------	--------------------	----------------	---------------

_____ <Sponsor>	_____ Signature	_____ Title	_____ Date
--------------------	--------------------	----------------	---------------

Principal Investigator

_____ OM1, Inc	_____ Signature	_____ Title	_____ Date
-------------------	--------------------	----------------	---------------

## 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.”<sup>1</sup> 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*.<sup>1</sup> 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. 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.<sup>2</sup> Under this OMF project,<sup>3,4</sup> minimum sets of standardized outcome measures suitable for use in registries and clinical practice were developed in five clinical areas, including depression.

While registries and stakeholders expressed enthusiasm about standardized outcome measures, they identified several barriers to implementation 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.<sup>5, 6</sup> 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.<sup>7</sup> 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.<sup>7, 8</sup> While routine screening is intended to improve diagnosis and treatment of MDD, many questions remain, such as 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.<sup>9, 10</sup>

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.

## **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.

## **3. Objectives**

The purpose of this pilot project is to demonstrate feasibility and value of collecting a subset of the harmonized outcomes measures for MDD in two registries and combining the data to support patient-centered outcomes research.

Objectives:

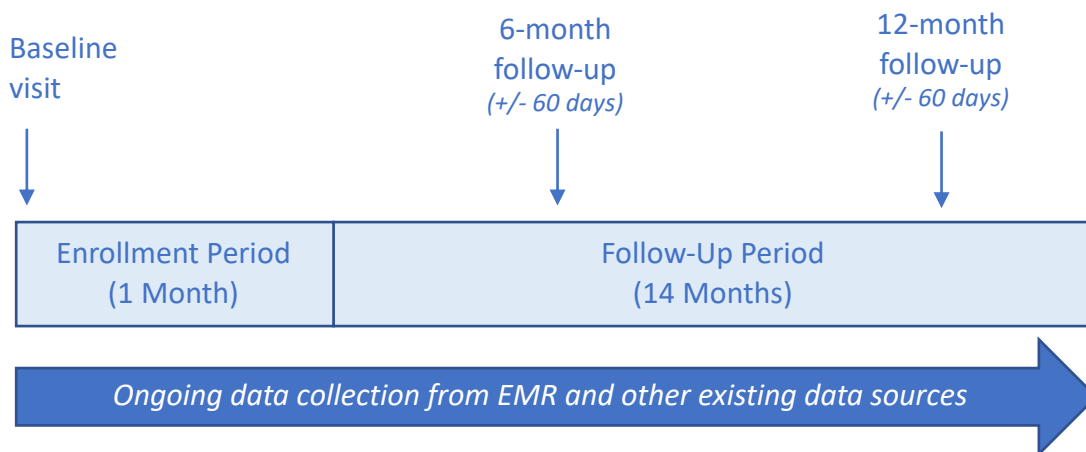
- To demonstrate that it is technically feasible for two patient registries to collect the data elements necessary to calculate six harmonized MDD outcome measures.
- To demonstrate that the harmonized de-identified data can be combined across the two registries to address new research questions in a timely and cost-efficient manner.

## 4. Study Design

### 4.1 Study Description

The study is a longitudinal, multi-center observational feasibility study that will include data on eligible patients with a diagnosis of MDD. Retrospective data on previous disease status and patient characteristics will be collected and combined with longitudinal data from these data sources 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 200 patients from a total of two registries in the United States. All eligible patients will be included.

#### 4.2.1 Inclusion Criteria

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

- $\geq 18$  years of age
- Diagnosed with major depression or dysthymia

#### 4.2.2 Exclusion Criteria

There are no exclusion criteria for this study.



### 4.2.3 Study Enrollment

Two registries (PsychPRO and the PRIME Registry) will participate in this feasibility study. A total of 20 sites participating in the registries (10 from each registry) will be recruited to participate in this study. To participate, sites must see adult patients with major depression or dysthymia and be willing to collect the PHQ-9 on a regular basis. Sites will have the option of using the Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER) scale to capture information on adverse events, but use of the FIBSER is not required.

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

### 4.2.4 Patient Withdrawal

Not applicable. Due to the use of routinely recorded existing data, patient informed consent is not required for this study and therefore there is no consideration for withdrawal of eligible patients.

### 4.3 Exposure Definition and Measures

This is an observational feasibility study in this patient population. This protocol does not recommend the use of any specific treatments.

### 4.4 Outcome Definitions and Measures

<b>Outcome Measure</b>	<b>Definition</b>
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.  <i>Timeframe for measurement:</i> 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.  <i>Timeframe for measurement:</i> Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)

Worsening in Depressive Symptoms: Recurrence	<p>Patient age 18 or older with a diagnosis of major depression or dysthymia and an initial PHQ-9 &gt; 9 who demonstrates remission (defined as a PHQ-9 score &lt; 5) of at least two months' duration and subsequently experiences a recurrence of a depressive episode, defined as a PHQ-9 score &gt; 9 OR hospitalization for depression or suicidality.</p> <p><i>Timeframe for measurement:</i> Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)</p>
Adverse Events	<p>Depression treatment-related adverse events, captured using the FIBSER scale where available and extracted from data routinely recorded in the EMR.</p> <p><i>Timeframe for measurement:</i> Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)</p>
Suicide Ideation and Behavior	<p>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.</p> <p><i>Timeframe for measurement:</i> Baseline, 6 months post baseline (+/- 60 days), 12 months post baseline (+/- 60 days)</p> <p><i>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.</i></p>

#### 4.5 Minimization of Bias

The study will enroll all eligible patients. 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 registry or other relevant existing data sources. No visits or examinations, laboratory tests or procedures are mandated as part of this study.

Sites participating in the patient registries use an existing process to extract data from the EHR and send data to the registry on a regular basis. Data will continue to be sent to the registry using the existing processes for this study. In addition, the registry data dictionaries have been compared to the outcome measure definitions, and some additional data elements will be extracted from participating site EHRs (if routinely documented) to support calculation of the outcome measures. These additional data elements include death, suicide ideation and behavior,

and adverse events related to depression treatment. The duration of ongoing prospective data collection for the purposes of this study will be approximately 12 months.

The capture of PROs, specifically the PHQ-9, at regular intervals is critical for implementation of the depression outcome measures. Sites participating in the registries will capture the PROs at regular intervals (including outside of clinical visits with reminders sent to patients) using the registry patient portal. 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).<sup>11, 12</sup> The patient portal is already available in the PsychPRO registry, and the PRIME Registry is adding the patient portal as part of this project to facilitate capture of the MIPS measures related to depression.

#### **4.6.1 Determination of Eligibility**

The following data will be used to determine patient eligibility for inclusion in the registry:

- Age  $\geq$ 18 years
- Diagnosis of major depression or dysthymia as documented in the patient's EMR

#### **4.6.2 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. Statistical Methods

### 5.1 Sample Size

For this observational feasibility study, no sample size calculations were done, and all eligible patients will be included. We anticipate that approximately 200 patients will be sufficient to address the objectives of this pilot analysis.

### 5.2 Data Analyses

#### 5.2.1 General Considerations

The specific nature of the analysis will be determined following selection of a research question by a Stakeholder Panel. The study will include, at minimum, descriptive analyses to gain an understanding of the study population (e.g., demographics, depression severity as indicated by PHQ-9 scores) and any subgroups of interest. In general, continuous variables will be reported as mean (and standard deviation) and median (interquartile range) where appropriate. Categorical variables will be summarized as number and proportion of the total patients enrolled and by subgroups of interest. All computations and generation of tables, listings, and data for figures will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA). Analytic methods and tools will be described in detail in the statistical analysis plan (SAP).

#### 5.2.2 Planned Analyses

One pilot analysis is planned to demonstrate the feasibility of combining data from separate registries for pooled analysis. The objectives for this descriptive analysis will be determined after the initial feasibility work is completed and will be described in a separate analytic plan.

### **5.3 Data Reporting**

#### **5.3.2 Annual/interim Analyses and Reporting**

No interim analysis is planned for this study.

#### **5.3.3 Final Analyses and Reporting**

A final study report will be generated after all data collection is complete. The final report will encompass all planned analyses, including a description of the complete study population and study results, as described above.

## **6. Study Management**

This study will be performed by OM1 in close collaboration with the APA and ABFM registry teams, with guidance, input, review, and approval of AHRQ. The APA and ABFM teams will lead the engagement and support activities for the participating registry sites, including development of site recruitment materials, training materials, and data management activities, 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),<sup>13</sup> the principles outlined in the Declaration of Helsinki,<sup>14</sup> and any applicable national guidelines.

### **6.1 Data Management**

All data will be extracted from the patient's EMR or other relevant existing data sources and sent to the patient registries using the procedures already established and in use for the patient registries. The patient registries have existing data management and data quality assurance plans in place and will continue to follow those procedures for this study.

### **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.<sup>15</sup>

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**

No direct contact with patients will occur as part of this study, and all data elements will be collected from information routinely recorded in the electronic medical record. No visits or examinations, laboratory tests, or procedures are mandated as part of this study. A waiver of informed consent will be obtained for this observational study as the following elements have been met:

1. The study involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i));
2. The waiver will not adversely affect the rights and welfare of the subjects;
3. The study could not practicably be carried out without the waiver

There should be no adverse effects to patients as a result of waiver of informed consent as there are no study related procedures.

### **8.4 Patient Confidentiality**

Medical record number or other local reference identifiers will not be collected as part of the study database. De-identification will be performed in a manner consistent with the Health

Information Portability and Accountability Act (HIPAA). All study analyses performed will use the statistically de-identified data. All parties will ensure protection of patient personal data and will not include patient identifiable information 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/ce.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. HHS290201500011I\_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](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](https://qpp.cms.gov/docs/QPP_quality_measure_specifications/Web-Interface-Measures/2019_Measure_MH1_CMSWebInterface_UPDATED.pdf). Accessed July 29, 2019.
13. Ipe. 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.