SPECIFIC AIMS

Mortality and morbidity related to suicidal behavior and opioid use disorder (OUD) have increased significantly over the past decade. These two public health crises are intertwined at multiple levels:

- People with a range of mental health conditions are at high risk for both suicidal behavior and OUD.
- Opioid use and OUD increase risk of developing a mood or anxiety disorder.
- Chronic pain is associated with increased risk of mood or anxiety disorder and suicidal behavior.
- The boundary between unintentional and intentional opioid overdose is far from distinct.
- Shared social and environmental factors increase risk of OUD and suicidal behavior.
- Withdrawal from or forced tapering of opioids may increase risk of suicidal behavior.

Medications for OUD, especially buprenorphine, have the potential to decrease illicit opioid use and reduce the multiple negative consequences of OUD, including fatal and nonfatal overdose, criminal justice involvement, infectious complications, and misuse of other substances. In addition, several small randomized trials of buprenorphine treatment in treatment-resistant depression (with or without co-occurring OUD) suggest that buprenorphine may reduce depressive symptoms and suicidal ideation. No conceivable randomized trial, however, would be large enough to assess effects of buprenorphine on suicidal behavior.

Consequently, we propose a large observational study to evaluate the effects of initiating buprenorphine treatment on subsequent suicidal behavior among people with OUD, including those with and without co-occurring mental health conditions or other known risk factors for suicidal behavior.

We propose to assemble data from four MHRN health systems serving a combined member/patient population of approximately 11 million. This work will take advantage of methods successfully implemented in previous MHRN research and research by our HCSRN Addictions Research Network, including:

- Methods and tools to assess mental health diagnoses and treatments using health system records
- Use of health records data to assess OUD diagnoses and treatments
- Population-based ascertainment of suicidal behavior
- Development of machine learning models to predict suicidal behavior
- Methods for causal inference from observational designs

Valid causal inference will require appropriate methods to account for confounding by indication (i.e. people with OUD treated with buprenorphine have higher or lower pre-existing risk of suicidal behavior than people not treated with buprenorphine). Choice of the optimal method will depend on patterns observed in actual data (e.g. rates and correlates of buprenorphine use), but we anticipate considering the following:

- Propensity-score matching using machine learning-derived propensity scores
- Propensity-score weighting using machine learning-derived propensity scores
- Disease risk score adjustment using machine learning-derived suicide risk prediction scores

Using this data resource and these analytic methods, we will address the following specific questions:

1) Overall effect: Among people with recognized OUD, how does initiation of buprenorphine treatment affect risk of suicidal behavior over the following 90 days compared to risk among otherwise similar people with OUD not initiating buprenorphine treatment?
2) Heterogeneity of effect: Does any effect of initiating buprenorphine vary according to:
   a. Means or mechanism of suicidal behavior (opioid overdose vs. other overdose vs. self-injury)?
   b. Presence/absence of co-occurring mood disorder or severe mental illness?
3) Specificity of effect: Are effects observed for buprenorphine also observed for alternative medications for treatment of OUD (e.g. naltrexone)?

No previous research has examined the effect of buprenorphine (or other treatments for OUD) on suicidal behavior. In addition, this work will take advantage of newly available tools and methods, including:

- Standard assessments of depression, suicidal ideation, and substance use in MHRN health systems
- Translation of risk prediction models to use for causal inference regarding therapeutics
- Use of real-world health system data to evaluate off-target therapeutic effects