MINNESOTA

# Psychedelic Medicine Task Force

## Scientific research methods protocol

The following is an outline of the steps in a systematic scientific review. A significant amount of preparation is needed in developing the methods to be used, and task force input on steps 1-6 is needed before steps 7-10 can occur. Information highlighted in yellow is what task force input is needed on. All of this information will be presented during the meeting on December 4th, 2023.

1. Consider scientific review type
    a. Meta-analysis: An objective scientific method of combining and analyzing results from multiple scientific studies, typically randomized controlled trials (which generally have the highest level of evidence). Meta-analyses use statistical methods on estimates from two or more studies to form a pooled estimate.
    b. Systematic review: A systematic review is an objective, reproducible method to find answers to specific research questions by collecting all available studies and analyzing their results
    c. Rapid review: A rapid review is similar to a systematic review, though the questions are typically narrower and the search strategies are more limited in the interest of saving time. Oregon utilized a rapid review strategy.
    d. Type(s) of report

2. Define the boundaries of research
    a. Legislative Duties, Subdivision 5. The task force shall:
        i. survey existing studies in the scientific literature on the therapeutic efficacy of psychedelic medicine in the treatment of mental health conditions, including depression, anxiety, post-traumatic stress disorder, bipolar disorder, and any other mental health conditions and medical conditions for which a psychedelic medicine may provide an effective treatment option;
        ii. compare the efficacy of psychedelic medicine in treating the conditions described in clause (1) with the efficacy of treatments currently used for these conditions
    b. Efficacy vs effectiveness
        i. Efficacy: The performance of the treatment only under ideal and controlled circumstances, such as those in a clinical trial vs Effectiveness: How the drug performs in "real world conditions."
        ii. Efficacy would only include drugs that have been rigorously tested in phase 2/3 clinical trials, and as an extension of that would then only cover conditions that these drugs have treated in phase 2/3 clinical trials.
            1. Currently only MDMA has completed phase 3 trials (2 completed, 1 currently recruiting, 1 getting ready to recruit, and one that is an extension of another completed trial)

2. Psilocybin has 4 currently registered phase 3 trials, none of which are complete.
    a. Two trials for treatment resistant depression
        i. Single dose phase 3 trial
        ii. Repeated dose phase 3 trial
    b. One trial for caregiver burnout
    c. One trial for a cancer study - technically a phase 2b/3 trial
3. LSD - only phase 2 trials have been done
4. Cluster headaches
5. Existential anxiety and depression for life threatening illness (AKA palliative care)
6. Other conditions
7. Also used in Switzerland as a legal form of therapy since 1988.

iii. "Efficacy" excludes LSD from our research, since it hasn't gone through any phase 3 trials, nor are any registered. Phase 3 trials are required for the FDA to approve the treatment as well as sending recommendations to the DEA to reschedule the drug.
    1. Something to note is the difficulty in studying these drugs in a clinical setting in terms of blinding and placebo. It is immediately obvious to both patient and provider which condition the patient is in (drug or placebo).

iv. "Effectiveness" would broaden the scope and allow us to look at studies of drugs that are being tested in phase 2 trials, as well as other types of studies, including population health studies and Indigenous sources.
    1. However, including effectiveness means the task force needs to create strict boundaries around what is or is not acceptable to include in the scientific report.
    2. Effectiveness also covers lived experiences, so the task force would need to think about whether sources like those from non-scientifically moderated places are considered in-bounds.

c. Efficacy or effectiveness? Bounds of scientific research.

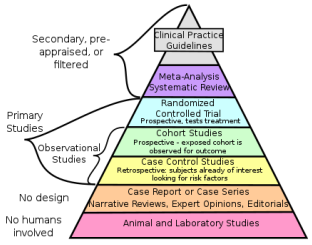
3. Define the research questions
    a. Based on the language in the legislation (particularly the part about "any other condition..."), it's best to have questions that are suitably broad so as not to unintentionally exclude any conditions.
    b. Potential to divide the two explicit duties in the legislation (see 2A above) into questions per drug, e.g.:
        i. MDMA
        ii. Duty 1: What are the conditions that MDMA shows efficacy/effectiveness in treating?
        iii. Duty 2: What is the efficacy/effectiveness of MDMA in treating the above-named conditions as compared with the current gold-standard treatments?
        iv. Psilocybin
        v. Duty 1: What are the conditions that psilocybin shows efficacy/effectiveness in treating?
        vi. Duty 2: What is the efficacy/effectiveness of psilocybin in treating the above-named conditions as compared with the current gold-standard treatments?
        vii. LSD
        viii. Duty 1: What are the conditions that LSD shows efficacy/effectiveness in treating?

ix. Duty 2: What is the efficacy/effectiveness of LSD in treating the above-named conditions as compared with the current gold-standard treatments?

c. An agreement or refinement of the above questions.

4. Identify the databases
    a. Academic: Includes literature from traditional academic or commercial publishing sources, often peer-reviewed.
        i. PubMed—peer-reviewed scientific articles, focusing on STEM including clinical trials, meta-analyses, and systematic reviews. Includes psychology articles, as well as survey studies and population statistics.
        ii. Indigenous research sources
    b. Gray literature: Include literature produced by individuals or organizations outside of commercial and/or academic publishers. This includes clinical trial registries, patent databases, company and industry-wide repositories, regulatory agency digital archives, abstracts of paper and poster presentations on meeting/congress websites, industry investor reports and press releases, and institutional and personal websites.
        i. ClinicalTrials.gov—registered clinical trials, including those currently in process
        ii. Cochrane Library—library of systematic reviews and randomized controlled trials (RCTs)
        iii. BioArXiv/medArXiv—preprints (not peer-reviewed) articles focusing on biology and medicine, includes newest research and negative results
    c. Any other databases from which we should search.
        i. Specific Indigenous sources.
        ii. Drug user forums like the Shroomery or Erowid?
        iii. Books?

5. Levels of Evidence
    a. What types of studies would present data that would be convincing.



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    b. What level(s) of evidence would be convincing?

6. Develop a search strategy
    a. Using specific Boolean search queries based on the above information.

7. Develop comprehensive inclusion and exclusion criteria
    a. Date: While many reviews include all possible ranges, something to note is that IRB approval wasn't part of the process until the 1970s. Though research into psychedelics occurred before that time, this may raise ethical considerations around consent and methodology. On the other hand, recent studies have shown evidence replicating those findings, suggesting that the results are still sound.

        i. Include or exclude studies that occurred before IRB approval was instated?
    b. Exposure of interest: The most inclusive criteria would be having taken the drug of interest in the context of treatment for any health condition. This raises the question of what constitutes treatment? What constitutes a health condition? Does a formal diagnosis need to be made?
        i. How to frame exposure of interest?
    c. Geographic location? E.g., does the task force want to limit studies by location?
        i. Explicitly include or exclude any geographic locations?
    d. Language of publication?
        i. Limit studies to only those in particular languages?
    e. Population: While not explicit in the legislation, it's implied that we're investigating their efficacy/effectiveness in an adult population. Building on the exposure of interest question, do we want to investigate in an adult population with [any] health condition? And again, what constitutes a health condition? Is this a formal diagnosis from a health care provider (HCP)?
        i. What are the population considerations for the research?
    f. Peer-reviewed only?
        i. If the task force lands on efficacy, then only peer–reviewed studies would be included. Gray literature would be excluded.
            1. Peer-review only?
    g. Types of reported outcomes?
        i. Within clinical trials, do we only want to include primary outcomes, or should secondary outcomes be included as additional supporting evidence?
            1. In clinical trials, only include primary outcomes?
    h. Therapeutic Setting:
        i. Is there a particular therapeutic setting that we are interested in? For example, within a registered clinical trial? In a therapy setting? At home? Are there any specific settings to exclude?
            1. Are there any settings to explicitly exclude?
    i. Study design(s)
        i. Do we only want randomized controlled trials? Will we allow surveys? What about open label trials?
            1. Are there study designs to explicitly exclude?
    j. Types of publication?
        i. Do we include systematic reviews? Meta-analyses? Legislative reports? What are the types of indigenous reports? Do we include technical reports? Do we allow dissertations? Do we allow message boards? Should we exclude non-systematic reviews?
            1. What types of publications are acceptable?
    k. Apart from the above considerations, are there any other criteria that should/should not be considered?

8. Perform the search
    a. Use a citation manager and manual research log to record the search parameters.

9. Assess the quality of the studies based on critical appraisal tools (CATs)
    a. JBI (Joanna Briggs Institute) provides comprehensive critical appraisal tools for many of the peer-reviewed publications we're interested in.
    b. Will need to devise a CAT for gray literature (see Evaluating Grey Literature)

10. Analyze results
    a. In a methodological way, pull out the relevant data from the accepted studies that fit the search criteria and log the findings.

11. Write the scientific report
    a. Summarize the above methodological steps, provide search strategies, and provide a narrative response.

# Proposed timeline:

| **Week of** | **Research Task** |
|---|---|
| December 4, 2023 | Task force provides input to methods by December 8, 2023 |
| December 11, 2023 | Task force suggestions are incorporated, methods refined & finalized by December 15, 2023 |
| December 18, 2023 | Formal literature search of academic databases |
| December 25, 2023 | Formal literature search of gray databases |
| January 1, 2024 | Formal literature search of gray databases |
| January 8, 2024 | Presentation of search results to task force |

| **Month** | **Research Task** |
|---|---|
| January–March 2024 | In-depth analysis of literature on MDMA |
| April–June 2024 | In-depth analysis of literature on psilocybin |
| July–September 2024 | In-depth analysis of literature on LSD |
| October 2024 | Preparation of final research report |
| November 2024 | Task force review of research report |
| December 2024 | Task force finalizes research report |