Norwegian Medical Products Agency

Protocol for Health Technology Assessment

Intravenous ketamine for treatment-resistant depression

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Summary

Major depressive disorder is among the most common mental health disorders worldwide and is often characterised by depressive mood symptoms such as dysphoria, sadness, and loss of interest. Treatment often involves psychotherapy, pharmacotherapy, and/or electroconvulsive therapy (ECT). A lack of response after treatment with at least two antidepressants given at an adequate dose and for an adequate duration is often defined as treatment-resistant depression. Due to low response to treatment and high rates of (co)morbidity and mortality among people with treatment-resistant depression, there is a need for new treatment strategies. The anaesthetic drug ketamine is a potential therapy option for treatment-resistant depression in subanaesthetic doses. In Norway, ketamine is currently only being offered off-label, i.e. outside approved indication for use for this patient group, at one public hospital

For assessment of clinical efficacy and safety, we will perform a systematic search for literature in relevant databases. References will be screened for title, abstract and full-text, and included in accordance with predetermined selection criteria. We will extract and analyse data from the included studies, and the results will be compiled and presented in a report written in English. The methodological quality of the included studies will be assessed, as will the certainty of the evidence, i.e., our confidence in the results. We will also perform a health economic evaluation of intravenous ketamin/esketamin compared to standard care, considering national priority criteria and including a five-year budget impact analysis.

The work of this health technology assessment (HTA) will be focused on adults with severe treatment-resistant depression, treated with intravenous ketamine 0,5-1 mg/kg, or intravenous esketamine. Relevant comparators include placebo, ECT, and esketamine nasal spray. The primary efficacy outcome will be objective response rate based on depression rating scale scores. Outcomes for safety will among others include serious adverse events. We will mainly include randomised controlled trials, but also cohort studies for long-term efficacy and safety outcomes and for older, i.e., geriatric populations.

Title:
Intravenous ketamine for treatment-resistant depression: a protocol for Health Technology Assessment

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Commissioner:
The Ordering Forum in the national system for managed introduction of health technologies within the specialist health care service

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18.03.2024

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Approved by:
Martin Lerner, *unit director*, NoMA

Sammendrag

Depressiv lidelse er blant de vanligste psykiske lidelsene i verden, og er blant annet karakterisert ved dysfori, nedstemthet, eller interesse- og gledesløshet. Behandling involverer ofte psykoterapi, farmakoterapi og/eller elektrokonvulsiv terapi (ECT). Manglende respons etter behandling med minst to antidepressiva gitt i adekvat dose og varighet, omtales ofte som behandlingsresistent depresjon. Som følge av lav respons på behandling og høy grad av (ko)morbiditet og mortalitet, blant personer med behandlingsresistent depresjon er det et stort behov for nye behandlingsstrategier. Det anestetiske legemidlet ketamin er et potensielt behandlingsalternativ for behandlingsresistent depresjon i subanestetiske doser. I Norge tilbys ketamin «off-label», dvs. utenfor godkjent indikasjon, for denne pasientgruppen kun ved ett sykehus.

For vurdering av klinisk effekt og sikkerhet, skal vi gjennomføre et systematisk litteratursøk i relevante databaser. Referanser vil screenes basert på tittel, sammendrag og fulltekst, og vil inkluderes i henhold til forhåndsbestemte seleksjonskriterier. Vi planlegger å ekstrahere og analysere data fra de inkluderte studiene, og resultatene vil sammenfattes og presenteres i en rapport skrevet på engelsk. Vi vil vurdere metodologisk kvalitet i de inkluderte studiene, i tillegg til vår tillit til resultatene. Vi kommer også til å gjennomføre en helseøkonomisk evaluering og en femårig budsjettkonsevensanalyse.

Dette metodevurderingsarbeidet kommer til å fokusere på voksne med alvorlig behandlingsresistent depresjon, behandlet med intravenøs ketamin 0,5-1 mg/kg, eller intravenøs esketamin. Relevante komparatorer inkluderer placebobehandling, ECT, og esketamin nesespray. Hovedutfallsmål for effekt kommer til å være objektiv responsrate basert på score fra verktøy for rangering av depresjonssymptomer. Utfallsmål for sikkerhet inkluderer blant annet alvorlige uønskede hendelser. Vi kommer hovedsakelig til å inkludere randomiserte kontrollerte studier, men også kohort studier med hensyn på langtidseffekter, samt for eldre (geriatrisk populasjon).

Tittel:
Intravenøs ketamin ved behandlingsresistent depresjon: en prosjektplan for fullstendig metodevurdering.

Oppdragsgiver:
Bestillerforum for nye metoder

Bestillingsdato:
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Leveringsfrist:
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Martin Lerner, enhetsleder, DMP

Commission

On 6th January 2022, Østfold Hospital HF submitted a proposal for a new national health technology assessment (HTA) regarding the use of intravenous ketamine for treatment-resistant depression and acute suicide risk or suicidal ideation. The Regional Health Authorities (RHA) Ordering Forum assessed the proposal on 21st March 2022 and commissioned The Norwegian Institute of Public Health (NIPH) to perform a mapping review to assess the available documentation, to use as a basis for further evaluation of the proposal. This review was submitted in August 2022. In accordance with the mapping review, the RHA Ordering Forum decided on 29th August 2022 not to commission a national HTA at the present time, and rather revisit the proposal and documentation in the start of 2024. In February 2024 the Norwegian Medical Products Agency (NoMA) was asked by the RHA Ordering forum to reassess the documentation for ketamine treatment for treatment-resistant depression and acute suicide risk or suicidal ideation. Based on this assessment, on 18th March 2024, the RHA Ordering forum commissioned NoMA to conduct a national HTA of intravenously administered ketamine for treatment-resistant depression. The commission specifies that the HTA should include long-term effects and also assess the effect of intravenous administration of esketamine for the same population. The HTA is intended to act as a basis for decision-making for the RHA Decision forum. The work on this HTA was officially initiated in June 2024.

The HTA-work will be a collaboration between NoMA, clinical experts from the RHA, and patient representatives, and the Norwegian Hospital Procurement Trust (Sykehusinnkjøp) that will issue a price note based on the HTA report.

Project group

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Internal project group at NoMA:	Ingrid Kristine Ohm Annette Vogt Flatby Anna Stoinska-Schneider Elisabet Hafstad
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Patient representatives:	Patient representative A Patient representative B

Glossary and abbreviations

Term/abbreviation	Explanation
CI	Confidence interval
CNS	Central nervous system
ECT	Electroconvulsive therapy
HDRS	Hamilton Depression Rating Scale
HTA	Health technology assessment
ICD-10	International Classification of Diseases and related health problems, 10th edition (ICD-10)
MADRS	Montgomery And Åsberg Depression Rating Scale
MeSH	Medical Subject Headings
NIPH	Norwegian Institute of Public Health
NoMA	Norwegian Medical Products Agency
NMDA receptor	N-methyl-D-aspertate receptor
PICOS	Population, Intervention, Comparator, Outcomes, Study design
SSRI	Selective serotonin reuptake inhibitors
tDCS	transcranial Direct Current Stimulation

1. Introduction

1.1 Major depressive disorder

1.1.1 Symptoms

Major depressive disorder is a mood disorder consisting of at least one major depressive episode with several depressive symptoms, lasting for at least two weeks (1). The disorder is characterised by disturbances in emotions and gives rise to symptoms such as dysphoria (depressed mood), intense sadness, and emotional numbness and distress (2). Other symptoms may include disturbances in ideation or cognition (e.g., loss of interest, reduced or impaired concentration, social distancing or isolation), and somatic function (e.g., sleep disturbances, changes in appetite, fatigue, or loss of energy) (2;3). As depression is a heterogenous disorder with several subtypes, clinical symptoms may vary greatly between patients (2).

According to the International Classification of Diseases and related health problems, 10th edition (ICD-10), which is currently used in Norway, the severity of depression can be categorised as follows (4;5):

- Mild depressive episodes: 4 depressive symptoms
- Moderate depressive episodes: 5-6 depressive symptoms
- Severe depressive episodes: ≥7 depressive symptoms

1.1.2 Epidemiology

Depression disorders are among the most common mental health disorders worldwide and affect around 50% more women than men (6). In Norway, the 12-month prevalence and lifetime prevalence were shown as 4-7% and 8-18% respectively, which are comparable to that of other countries in Europe and North America (7).

1.1.3 Aetiology

Major depressive disorder was previously thought to be mainly caused by disturbances in neurotransmitters, such as serotonin and dopamine (8). However, the aetiology of depression is now recognised to be a more complex multifactorial disorder, involving biological, genetic, environmental and psychosocial factors, that may influence the neuroregulatory systems of the brain (3;8).

Risk factors for depression include challenging life circumstances or traumatic events, such as illness, unemployment, divorce, or death of loved ones, as well as struggles with drug and/or alcohol addiction (3;8).

1.1.4 Treatment

The goal of treating major depressive disorder is to eliminate depressive symptoms, improve daily functioning and quality of life, all while minimising adverse effects of the treatment, and avoiding relapse (3;9). The treatment for depression should be tailored to the individual patient's needs and preferences (3;9;10). There are several treatment options available, often used in combination with each other, including psychotherapy, pharmacotherapy, and various electrical therapies, including electroconvulsive therapy (ECT) (3;9).

Psychotherapy, which may include cognitive behavioural therapy and interpersonal therapy, is a first-line option for treating mild and moderate depression (3;9). However, the effect of this therapy alone diminishes with increasing severity of the depressive episode (4;9).

Pharmacological therapy is often considered a first-line option for treating moderate and severe depression (1;9). Although there are several classes of antidepressive drugs, selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, fluoxetine, and sertraline) are the clear first choice (4;9). SSRIs act by increasing the concentration of serotonin in synaptic gaps in the brain (3). Usually, the antidepressive effect will be evident first after a few weeks of treatment (11). As the risk of suicide

often increases in the early period of treatment, it is important to be aware of this risk and to ensure close follow-up of the patient (9;12;13).

ECT is mainly used for treating severe depression when other treatments have failed (9;14). A small electric current is used to produce a generalized cerebral seizure, while the patient is under general anaesthesia (14;15). ECT treatment is typically given 2-3 times a week, and usually consists of 6-12 treatments in total (9;14). Recommendations regarding the use of ECT treatment in Norway, are presented in a national guideline published by the Norwegian Directorate of Health (16). Other treatments for depression include transcranial Direct Current Stimulation (tDCS), repeated Transcranial Magnetic Stimulation (rTMS) and Vagus Nerve Stimulation (VNS) (4). In 2022, tDCS treatment was implemented in Norwegian specialist health care as a treatment option for patients with moderate or severe unipolar depression (17).

Although most people with depression experience remission, relapse is still common (3;4). The recurrence rate increases with time, and has been reported to be up to 40% after two years, up to 60% after five years, and almost 90% after 15 years (3;9).

1.1.5 Treatment-resistant depression

Many people with depression do not respond to the initial treatment and will require other therapies, e.g., other antidepressants, a combination of treatments, etc (9;18). However, some patients, especially those with severe depression, do not respond to treatment even after trying several different therapies (18;19). Although there is no universal definition of treatment-resistant depression, it is usually defined as a lack of response after treatment with at least two antidepressants given at an adequate dose and for an adequate duration (18;20). Due to the unclear definition, there is a wide range of prevalence estimates for treatment-resistant depression (20-22). Many sources, however, seem to report a prevalence of around 30% of all patients with depression (18;22). As people with treatment-resistant depression tend to have low response to treatment and high rates of (co)morbidity and mortality, there is a need for novel treatment strategies (23).

1.2 Ketamine

Ketamine is a well-known, highly effective anaesthetic drug that has been commercially available since the 1970s (24;25). Due to its rapid onset effect, short half-life and general lack of clinically significant respiratory depression, ketamine has remained as a desirable anaesthetic, especially for emergency surgical procedures (24-26). Additionally, ketamine has also been known to have both analgesic and antidepressive effects, and subanaesthetic doses of ketamine have now (re)emerged as a potential therapy option for treatment-resistant depression (24;27). However, due to the dissociative effects with distortion of sensory perception and thought processes at even low doses, and a potential for abuse, ketamine remains as a somewhat controversial treatment option for treatment-resistant depression (26;28).

The anaesthetic effect of ketamine is primarily attributed to it acting as a noncompetitive antagonist blocking N-methyl-D-aspartate (NMDA) receptors (25;26). Though several theories presume similar mechanism for the antidepressive effect, the full picture is still largely unknown (28).

1.2.1 Ketamine in Norway

Ketamine is only authorised for use in Norway as an anaesthetic for brief diagnostic and/or surgical procedures, and as a supplement to other anaesthetics (29). However, ketamine in subanaesthetic doses is being used off-label as analgesia, especially for treating severe pain, e.g. in palliative care (25;27;30;31). Ketamine as an antidepressive agent for treatment-resistant depression is a fairly new treatment option and is currently only being offered at one public hospital in Norway, in addition to some private clinics.

In 2020, the S-enantiomer of ketamine: esketamine, was awarded marketing authorisation in Norway for treating adults with treatment-resistant depression, used in combination with other antidepressive drugs (32). However, the drug Spravato® (esketamine nasal spray) has currently not been approved

for financing by the Norwegian specialist health care in the RHA Decision Forum, due to low quality evidence and high costs (33).

1.3 Why it is important to do this HTA

As previously described, the commission for this HTA was based on a proposal from Østfold Hospital HF, where ketamine treatment for treatment-resistant depression is provided. They argue that ketamine is a low-cost drug, with significant therapeutic effect and few side effects, and that it is a valuable alternative to ECT (34). According to the Act relating to specialist health care (Spesialisthelsetjenesteloven), the regional health authorities must organize their service in line with priority criteria relating to benefit, resource use and severity (35). All new medicines and indications for use that the Norwegian specialist healthcare service are expected to finance, must first be assessed in an HTA relating to the priority criteria. As such, it is important to assess the efficacy and safety, as well as to perform a health economic evaluation of treatment with ketamine for this patient group.

1.4 Aim

The aim of this HTA is to systematically identify, assess and analyse available research regarding efficacy and safety of intravenously administered ketamine for treating treatment-resistant depression in adults. The HTA will assess the efficacy of intravenously administered esketamine for the same population. We will also evaluate the methods against the priority setting criteria by conducting a health economic evaluation of the relevant treatment alternatives.

1.5 External project group

Before the work on this HTA was officially initiated, we recruited external project group members consisting of clinical experts appointed by Nye metoder, as well as patient representatives. The external project group will contribute to the work by giving their input and suggestions on information regarding Norwegian clinical practice, inclusion criteria (i.e. PICOS) based on the research question drafted in the commission, suggestions of relevant publications, as well as reading and giving their input on the report draft.

2. Efficacy and safety - method

We plan to conduct the work in our HTA in accordance with the handbook “Slik oppsummerer vi forskning”, by the National Institute of Public Health (36) and Cochrane handbook (37).

2.1 Selection criteria

Our framework, i.e., inclusion and exclusion criteria, for searching for and selecting relevant literature for our HTA is outlined in *Table 1*.

Table 1: *Selection criteria (PICOS)*

PICOS	Inclusion criteria	Exclusion criteria
Population	Adults ≥18 years with moderate or severe depression (e.g. MADRS score ≥20) that is treatment-resistant	Psychosis, mild depression (e.g. MADRS score <20) that is treatment-resistant
Intervention	Intravenous ketamine: 0,5-1 mg/kg, single and multiple administrations Intravenous esketamine	
Comparator	Inactive placebo: saline Active placebo: midazolam, ketamine <0,5 mg/kg Electroconvulsive therapy (ECT)	Antidepressive drugs, e.g. SSRIs. Other administration forms of ketamine or esketamine
Outcome	**Efficacy**: 1) Primary: objective response rate e.g. based on MADRS score and Hamilton score. 2) Secondary: response on treatment defined as 50% reduction rate, mean reduction in e.g. MADRS and HDRS scores, remission rate, relapse rate, time to relapse, quality of life, hospitalisation, duration of hospitalisation, use of resources, e.g. direct cost and personnel time, long-term effect on efficacy on the above outcomes. **Safety**: adverse events, serious adverse events, reports of abuse, long term effect on safety on the above outcomes.	
Study design and publication type	Randomised controlled trials Cohort studies for long-term efficacy and safety and in geriatrics.	Case studies, case series, animal studies, conference abstracts*, preprints*, systematic reviews†

MADRS: Montgomery And Åsberg Depression Rating Scale, HDRS: Hamilton Depression Rating Scale
** To be screened by one person (but not formally included) to give a general view of potential nonpublication rate*
† Systematic reviews will be screened for relevant primary studies

We will predominantly include randomised controlled trials (RCT). However, we will also include other study designs, such as cohort studies, to address long-term efficacy and safety of ketamine treatment, as specified in the commission. If we do not find sufficient data on long-term effect of ketamine for treatment-resistant depression, we may choose to include studies on long-term effect of ketamine for other indications, such as analgesia.

Papers written in other languages than English, or any of the Scandinavian languages will be excluded. A list of publications excluded based on language alone will be listed separately.

2.2 Literature search

The librarian responsible for the search (EH) will, in collaboration with the project team and in line with best practice in the field (38;39), plan information retrieval with the aim of finding completed and ongoing research that meets the predefined selection criteria for the assignment. The plan and search strategies will be peer reviewed by a librarian colleague in line with the Peer Review of Electronic

Search Strategies (PRESS) (40) before the searches are executed. Thorough documentation of the search process and results will be attached to the HTA-report.

As a first step, while working on the protocol, we will search for ongoing and completed HTAs in the International HTA database supplemented with relevant HTA organisations' websites. We will also search the Epistemonikos database for published systematic reviews on the topic. For the main search, we will then use the following sources:

- Cochrane Central Register of Controlled Trials (Wiley)
- Embase (Ovid)
- MEDLINE (Ovid)
- Clinicaltrials.gov (National Institutes of Health)
- International Clinical Trials Registry Platform (World Health Organization)

The search strategies for the electronic bibliographic databases will be adapted to the interface of each individual database. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords, for the population and intervention concepts. Search terms will be combined with the Boolean logical operator "OR", and the search concepts with "AND". The treatment-resistant aspect of depression and number and dosage of infusions will not be specified in the search but operationalised during screening. We will not restrict the search by language or publication year. We will exclude case reports and animal studies in the search strategy, but not otherwise use a separate concept to limit the search to certain study designs or publication types. However, we will keep records of conference abstracts, preprints and study registrations apart and screen them separately.

We will also ask the experts involved in this HTA work if they know of relevant publications and check the studies/study reports included in selected reviews and HTAs published since 2022. Furthermore, we will conduct citation searches (backwards and forwards) in lens.org (via citationchaser (41)) and/or OpenAlex (via EPPI-Reviewer (42)) on publications meeting eligibility criteria after full-text review.

The project team will consider the need for supplementary searches to provide further data on health economic evaluations, quality of life and health utility weights or complications, long-term side effects and other safety aspects when the main inclusion and data extraction processes are complete. If necessary, we will consult with the experts before deciding whether more information is needed or not.

We will export the search results from the bibliographic databases and study registries to the reference management tool EndNote. Here, we remove duplicates by a standardized and semi-automated method mainly based on Bramer 2016 (43), before unique records are exported to EPPI-Reviewer (44) for assessment of relevance against the selection criteria.

2.3 Selection of studies

We will select studies found in the literature search in a two-step selection strategy:

1) Screening: two researchers (AVF and IKO) will independently screen titles and abstracts (where available) using the EPPI Reviewer software (44;45) to include or exclude articles based on their relevance to our research question. When in doubt, the references will be included. We will screen systematic reviews, conference abstracts, preprints and records from trials registries separate from the journal articles.
2) Full-text assessment: two researchers (AVF and IKO will independently read the full-text articles of the references included in step 1, to assess which will be included in our HTA.
3) Both steps will adhere to the eligibility criteria listed above (*Table 1*). Disagreements in either of the two steps will be resolved through discussion, or by consultation with a third researcher.

We will use machine learning in the first step, in order to screen titles and abstracts more efficiently. Machine learning involves algorithms that makes the computers able to "learn" from and develop decision support based on empirical data. In the process of screening titles and abstracts, we use "priority screening", which is a ranking algorithm in the EPPI Reviewer software (44;45). The algorithm

is trained by the researchers' decisions on the inclusion and exclusion of references at the title and abstract level. References deemed more relevant by the algorithm are pushed forward in the “queue”. This way, we get a quicker overview of the number of references that possibly meet the inclusion criteria compared to reading the references in a random order. When a clear flattening of the inclusion curve in the software is observed, and more than 200 studies have been screened without finding a relevant study, we will stop manual screening based on the assumption that the remaining references are likely to be irrelevant.

2.4 Assessment of risk of bias

Two researchers (AVF and IKO) will independently assess the risk of bias for primary outcomes reported in the included RCTs by using the Cochrane Risk of Bias Tool for RCTs 2 (37;46). For non-randomised studies, all relevant outcomes will be assessed using the Cochrane Risk of Bias in Non-randomised Studies of Interventions tool (ROBINS-I) (47). Any potential differences will be resolved through discussion between the researchers, or by consultation with a third researcher.

2.5 Data extraction

Relevant data will be extracted from the full-text articles to a self-made Excel-sheet, by one researcher. The extracted data will be verified by a second researcher. Any potential disagreements will be resolved through discussion, or by consultation with a third researcher. If necessary (e.g., if data are unintelligible, etc.), we will attempt to contact the authors for them to provide us with sufficient information to use in our HTA. Information to be extracted is presented in *Table 2*.

Table 2: *Data to be extracted from included studies*.

About	Information to be extracted
The study	Authors, publication year, study design, country, clinical identification number, eligibility criteria, follow-up time, funding
The participants	Numbers of participants in each group, age, diagnosis, ethnicity, previous antidepressive treatment, baseline depression rating, e.g. MADRS or HDRS score
The interventions and comparators	Treatment name, information related to posology, e.g. dosage, administration, treatment cycles, etc.
The outcome	All outcome-data relevant for our HTA (see Outcome in *Table 1*)

MADRS: Montgomery And Åsberg Depression Rating Scale, HDRS: Hamilton Depression Rating Scale

2.6 Analysis

The data synthesis will depend on the data provided in the included articles. If we include both RCTs and non-RCTs, they will be analysed separately. If possible, we will synthesise the data in one or more meta-analyses (48). As we cannot assume populations, interventions and outcomes to be identical across the included studies, we will use a random-effects model in our meta-analyses. If the included studies present both adjusted and non-adjusted effect estimates, we will use the adjusted estimates. If meta-analyses cannot be performed (e.g., if we have too heterogeneous studies, too few studies, etc.) we will present the data in a narrative synthesis. Regardless, all outcomes will be presented in forest plots (where possible) and summary-of-findings tables. We will use effect measures such as relative risk or odds ratio for analyses of dichotomous outcomes, and hazard ratios for time-to-event outcomes. Uncertainty will be presented as 95% confidence intervals (CI). Continuous data outcomes will be presented as absolute or relative mean difference between groups. If the included studies are using different scales to measure the same outcome, we will use standardised mean difference, with 95% CI. Where possible, each primary outcome will be subjected to subgroup (e.g., age group, etc.) or sensitivity analysis, with respect to risk of bias and disease severity. Heterogeneity will be assessed by computing I^2 (48). All data will be analysed using the Review Manager software (49).

2.7 Assessment of certainty of evidence

We will assess the certainty of evidence for each selected outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (50). In brief, the GRADE system evaluates the certainty of evidence through assessment of several criteria (50). Downgrading may be applied due to a) study limitations (risk of bias), b) inconsistency of results, c) indirectness of evidence, d) imprecision, and e) publication bias. For non-randomized studies of interventions, upgrading the certainty of evidence may be applied due to a) large magnitude of effect, b) dose-response gradient, and c) plausible residual confounding (50). The GRADE approach results in an assessment of the certainty of evidence in one of four grades, as presented in *Table 3*.

Table 3: *Certainty of evidence classification*

GRADE level	Symbol	Definition
High certainty	⨁⨁⨁⨁	We are very confident that the true effect lies close to that of the estimate of the effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty	⨁⨁⨁◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty	⨁⨁◯◯	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty	⨁◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Two researchers will GRADE effect estimates for each outcome extracted. Any potential disagreements will be resolved through discussion, or by consultation with a third researcher.

3. Health economics - method

The priority setting in Norwegian health care system is based on three principles: health benefit, resource use, and severity (50). Health technology assessments, and particularly economic evaluation are instrumental in quantification of these criteria.
To assess the cost-effectiveness of intravenous treatment with ketamine/esketamine for the treatment of patients with treatment-resistant depression, we will estimate and describe all costs and health effects related to this treatment option and all the comparator(s) relevant in the Norwegian context. Efficacy estimates will be based on the results of the systematic literature review, and we will make final decisions about the appropriate methods and the time horizon for the health economic evaluation once the efficacy results become available. Structure, assumptions, and other input parameters in the health economic analysis will be based on feedback from clinical experts, Norwegian cost databases, national registers, and literature. All cost data will be expressed in Norwegian kroner. If we are able perform a cost-utility analysis, we will calculate the absolute shortfall for patients with treatment resistant depression. We will explore uncertainty related to the analyses in a sensitivity analysis. Further, in collaboration with the clinical experts, we will perform a budget impact analysis of a potential introduction of intravenous ketamine treatment as a treatment option for patients with treatment-resistant depression in Norway. In the analyses, we will use an extended healthcare perspective, which entails inclusion of consequences for the entire health service (both the specialist health service and the primary health and care service), but exclusion of broader effects, for example production losses. This perspective is relevant for the prioritization of interventions within a fixed healthcare budget, in line with the guidance from the Priority-setting White Paper (51).

4. Other assessments

4.1 Involvement of patient representatives

The patient representatives recruited as external project participants will provide their input on aspects on ketamine therapy for the treatment of resistant depression, that are important for patients. We will collect this information through a survey that will be sent by e-mail. Similarly to clinical experts and other external team members, the patient representative(s) will be given the opportunity to read and comment on the protocol and the HTA report before submitting it to the commissioner.

4.2 Involvement of clinical experts

The clinical experts recruited, as external project participants, will provide their input on clinical aspects of ketamine treatment. Their involvement extends to all stages of the project, in particular the establishment of PICO(S), and review of the protocol and HTA report drafts. If potential clinical disagreements regarding this treatment become apparent, we will attempt to elucidate the differing opinions.

5. Deliverables and publication

5.1 Delivery

The end product of this project will be an HTA report, intended as a decision-making support for the national system for managed introduction of health technologies within the specialist health care service (Nye Metoder). However, the finished report will also be published and available to the public and should therefore be readable for a larger audience. The report will be written in clear English, with a Norwegian summary and key points. We will publish the report on the web pages of NoMA (www.dmp.no), as well as on the web pages of Nye metoder (www.nyemetoder.no). We are also open to publish the whole or parts of the report as one or more articles in scientific journals. Abstracts may be submitted to relevant conferences. The approved protocol will be published on the web pages of NoMA (www.dmp.no) along with a short description of the commission, as well as in the INAHTA database.

5.2 Peer-review

5.2.1 Protocol

A finalised draft of the protocol will be sent to the external project members, i.e., clinical experts and patient representatives, for input, before being submitted to internal peer-review by co-workers at NoMA. The protocol will then be approved by our unit contact and the head of the unit for HTA medical devices at NoMA.

5.2.2 HTA report

When the report draft is finalised, it will be sent to the entire external project group for input and submitted to internal peer-review. The report may be subjected to external peer-review. The report will subsequently be approved by our unit contact and the head of the unit for HTA medical devices at NoMA.

5.3 Time frame

Start date: 28.06.2024
End date: 28.06.2025

Step	**From date**	**To date**
Protocol	21.05.2024	01.10.2024
Literature search	12.08.2024	13.09.2024
Screening references	16.09.2024	04.10.2024
Assessment of risk of bias	07.10.2024	18.10.2024
Data extraction	07.10.2024	25.10.2024
Analysis	28.10.2024	29.11.2024
Assessment of certainty of evidence	25.11.2024	20.12.2024
Preparatory work for health economic evaluation / data collection	03.06.2024	11.10.2024
Health economic analyses	14.10.2024	28.03.2025
Draft report	26.08.2024	28.03.2025
Peer-review	31.03.2025	13.06.2025
Assess and complete report draft	25.04.2025	23.06.2025
Approval of report	19.06.2025	20.06.2025
Send to commissioner	23.06.2025	23.06.2025
Publish	30.06.2025	30.06.2025

5.3.1 Measures to be taken in the event of delays/unforeseen developments

If conditions arise that may affect the deadline for the HTA report more than the framework for this project allows for, we will implement relevant measures, e.g.:

- Increased staffing.
- Replacing project members upon long-term disease or absence.
- Limiting the selection criteria.
- Extending the deadline, after agreement with the commissioner.

Examples of such conditions may include, but are not limited to, unforeseen long-term absences among the project members, larger number of hits to screen following the literature search, or larger number of included studies to extract data from.

5.4 Related projects or publications at NoMA or NIPH

NIPH has previously performed a mapping review (2022) on this topic:

- Intravenous ketamine for treatment-resistant depression and acute suicide risk/ideation: a single technology assessment – mapping (52).

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