Medicinrådet

Bilag til Medicinrådets vurdering af esketamin til behandling af behandlingsresistent depression

Vers. 3.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. esketamin
2. Forhandlingsnotat fra Amgros vedr. esketamin
3. Ansøgers endelige ansøgning vedr. esketamin

Johnson&Johnson

24. oktober 2025

Vedr. Medicinrådets udkast til vurdering af esketamin NS (Spravato) til patienter med behandlingsresistent depression (TRD)

Vi takker for udkastet til vurderingsrapporten og muligheden for at gennemgå og kommentere revurderingen af esketamin NS. Vi anerkender det grundige arbejde der er lagt i gennemgangen af de nye data og udarbejdelsen af rapporten.

Vi sætter pris på muligheden for at få sagen revurderet på baggrund af nye data, der imødekommer de usikkerheder, der er fremhævet i tidligere vurderinger fra Medicinrådet. Vi håber, at denne sidste og endelige ansøgning vil resultere i, at en ny behandling stilles til rådighed for patienter med TRD - en patientpopulation med stort behov for effektive alternativer.

Grundlaget for revurderingen adskiller sig væsentligt fra de tidligere vurderinger på flere punkter:

- Patientpopulationen er indsnævret til patienter, der har fejlet miniumum *tre* tidligere behandling.
- Vurderingen baseres på et styrket evidensgrundlag med ESCAPE-TRD, et stort og længerevarende fase 3-studie, hvor esketamin NS er sammenlignet med en aktiv og relevant komparator, quetiapin XR.
- Langtidsdata fra SUSTAIN-3, hvor patienter er fulgt i op til 6,5 år, bidrager til vurderingen af esketamin NS' sikkerhedsprofil.

Dosering af quetiapin XR

I rapporten rejses der bekymring vedrørende doseringen af quetiapin XR i ESCAPE-TRD, og om lavere doser i studiet sammenlignet med dansk praksis kan have ført til en overvurdering af den relative effekt af esketamin NS vs quetiapin XR.

I ESCAPE-TRD blev patienterne titreret til 150-300 mg/dag og den gennemsnitlige dosis var 193 mg/dag. Dette er i overensstemmelse med produktresuméet og anbefalingerne på pro.medicin.dk, som specificerer et interval på 150-300 mg/dag for tillægsbehandling i MDD[1-2]. Doser over 300 mg/dag er ikke godkendt til MDD.

Som beskrevet i ansøgningen viser danske registerdata, at den gennemsnitlige daglige dosis er [redacted] mg/dag for quetiapin XR i MDD/TRD, hvilket yderligere viser, at doseringen i ESCAPE-TRD afspejler den anvendte dosering i Danmark[3].

Ingen RCT'er, vejledende anbefalinger eller myndighedsgodkendelser understøtter brugen af quetiapin XR ved doser over 300 mg/dag til tillægsbehandling i MDD. Højere doser er forbeholdt skizofreni og bipolar lidelse. Der er en veldokumenteret sammenhæng, der viser, at jo højere dosis med quetiapin XR, des flere bivirkninger og flere patienter der ophører behandling på grund af bivirkninger. Både EMA og FDA anerkender dette og anbefaler at anvende den laveste effektive dosis hos voksne for at afbalancere effekten med tolerabilitet[1-2,4-7].

Såfremt doser op til 900 mg/dag alligevel anses som relevant sammenligningsgrundlag for denne indikation, bør det indgå i vurderingen, hvilke compliance- og sikkerhedsmæssige konsekvenser det har at sammenligne esketamin NS med quetiapin XR i så høje doser. Dette aspekt er ikke behandlet i rapporten og bør afspejles i vurderingen.

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Baseret på ovenstående argumenter, mener vi ikke, at bekymringen for potentiel overvurdering af den relative effekt af esketamin NS på grund af "for lav" dosering af quetiapin XR er underbygget af dokumentation.

Vi håber, at Medicinrådet vil lade det samlede evidensgrundlag være udslagsgivende for en positiv beslutning der kan give flere behandlingsmuligheder til patienter med behandlingsresistent depression – i tråd med psykiatriplanens ambitioner for mennesker med svær psykisk sygdom.

Referencer:

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7. Dubath C, et al. Effect of Quetiapine from Low to High Dose, on Weigh and Metabolic Traits: Results from a Prospective Cohort Study. Pharmacopsychiatry 2021, 54(6): 279-286

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23.10.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	19.11.2025
Leverandør	Johnson & Johnson
Lægemiddel	Spravato (esketamin)
Ansøgt indikation	I kombination med en SSRI eller SNRI til voksne med behandlingsresistent moderat til svær depression, som ikke har responderet på mindst to forskellige behandlinger med antidepressiva under den igangværende moderate til svære depressionsepisode.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse, revurdering

Prisinformation

Amgros har forhandlet følgende pris på Spravato (esketamin):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke /pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Spravato	28 mg / 2 stk. næsespray	2.667,28	[redacted]	[redacted]	[redacted]	[redacted]
Spravato	28 mg / 3 stk. næsespray	3.952,76	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

[redacted]. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på Spravato og komparator quetiapin jævnfør Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke / pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Spravato*	28 mg / 3 stk. næsespray	**Uge 1-4.** Startdosis: 56 mg. Efterfølgende doser: 56 eller 84 mg to gange ugentligt **Uge 5-8.** 56 mg eller 84 mg én gang ugentligt **Uge 9 +** 56 mg eller 84 mg hver anden uge eller én gang ugentligt	[redacted]	Ved minimumsdosis per år: [redacted] Ved maksimal dosis per år: [redacted]
Quetiapin "Krka"	100 mg /100 stk., tabletter	193 mg dagligt**	[redacted]	[redacted]

*Baseret på Spravato produktresume.
** Jævnfør Medicinrådets vurderingsrapport.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Ikke anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Spravato (esketamine) for adults with treatment-resistant Major Depressive Disorder

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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Abbreviviations: N/A = not applicable.

Table of contents

Tables and Figures

Abbreviations

Abbreviation	Definition

AD	Antidepressant
AE	Adverse event
ANCOVA	Analysis of covariance
AP	Antipsychotic
BMI	Body mass index
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CFB	Change from baseline
CGI-C	Clinical Global Impression – Change
CGI-S	Clinical Global Impression – Severity
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
C-SSRS	Columbia-Suicide Severity Rating Scale
DRG	Diagnostic-related groups
DMC	Danish Medicines Council
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECT	Electroconvulsive therapy
EMA	European Medicines Agency
EQ-VAS	European Quality of Life Group visual analogue scale
EQ-5D-5L	European Quality of Life Group, 5-Dimension, 5-Level
GP	General practitioner
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LSM	Least squares mean
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major depressive disorder
MDE	Major depressive episode
MMRM	Mixed model for repeated measurements
MSM	Maudsley Staging Model
NRI	Non-responder imputation
NS	Nasal spray
N/A	Not applicable
OAD	Oral antidepressants
OR	Odds ratio

PHQ-9	Patient Health Questionnaire 9-item
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RCT	Randomised controlled trial
rTMS	Repetitive transcranial magnetic stimulation
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STA	Single technology assessment
TEAE	Treatment-emergent adverse events
TRD	Treatment resistant depression
TLR	Target literature review
VAS	Visual Analogue Scale
XR	Extended-release

1. Regulatory information on the medicine

Table 1 Overview of the medicine

Overview of the medicine	
Proprietary name	Spravato®
Generic name	Esketamine nasal spray (ESK NS)
Therapeutic indication as defined by EMA	Spravato, in combination with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), is indicated for adults with treatment-resistant Major Depressive Disorder (MDD), who have not responded to at least two different treatments with antidepressants (ADs) in the current moderate to severe depressive episode.
Marketing authorization holder in Denmark	Janssen-Cilag A/S, a Johnson & Johnson company Østbanegade 123 DK-2100 København Ø
ATC code	N06AX27
Combination therapy and/or co-medication	Yes (in combination with a SSRI or SNRI)

Overview of the medicine	
(Expected) Date of EC approval	19/12/2019
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	ESK NS, co-administered with oral antidepressants (OAD) therapy, is indicated in adults with a moderate to severe episode of MDD, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency.
Other indications that have been evaluated by the Danish Medicines Council (DMC) (yes/no)	Yes (the following indication: ESK NS + OAD is indicated in adults with a moderate to severe episode of MDD, as acute short-term treatment, for the rapid reduction of depressive symptoms, which according to clinical judgement constitute a psychiatric emergency)
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? **Yes** Is the product suitable for a joint Nordic assessment? **No** If no, why not? **ESK NS has already been assessed in Finland, Iceland, Norway, and Sweden and is recommended in all of these countries except from Norway.**
Dispensing group	AP4BG
Packaging – types, sizes/number of units and concentrations	Spravato (esketamine) 28 mg nasal spray (solution), 2 devices Spravato (esketamine) 28 mg nasal spray (solution), 3 devices

Abbreviations: AD, antidepressant; DMC, Danish Medicines Council; EMA, European Medicines Agency; ESK, esketamine; JNHB, Joint Nordic HTA Bodies; MDD, major depressive disorder; OAD, oral antidepressants; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.Sources: European Medicines Agency, 2024[1]; European Medicines Agency, 2024[1]; Danish Medicines Council, 2023[2]; Danish Medicines Agency, 2024[3].

2. Summary table

Table 2 Summary table

Summary	
Indication relevant for the assessment	The ESCAPE-TRD randomised controlled trial (RCT) included patients with TRD, who had failed two to six consecutive treatments in the current major depressive episode. Approximately 39% of the population included in the ESCAPE-TRD clinical trial had failed ≥3 prior treatments.

Summary	
	For this submission the patient population has been refined based on prior DMC submissions to include only those patients with inadequate response to three or more prior AD treatments deemed suitable for adjunctive treatment such as with an antipsychotic, in accordance with current practices in Denmark. I.e., the indication relevant for the assessment is more targeted compared to the EMA indication, as the EMA indication includes a broader treatment resistant depression (TRD) segment who have not responded to at least two different treatments with ADs.
Dosage regiment and administration	**Patients younger than 65 years of age** Induction phase, Weeks 1-4: The starting day 1 dose is 56 mg. Subsequent doses are 56 mg or 84 mg twice a week. Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment. Maintenance phase, Weeks 5-8: 56 mg or 84 mg once weekly. Maintenance phase, from Week 9: 56 mg or 84 mg every two weeks or once weekly. The need for continued treatment should be re-examined periodically. **Patients at least 65 years of age** Induction phase, Weeks 1-4: The starting day 1 dose is 28 mg. Subsequent doses are 28 mg, 56 mg, or 84 mg twice a week. Evidence of therapeutic benefit should be evaluated at the end of induction phase to determine need for continued treatment. Maintenance phase, Weeks 5-8: 28 mg, 56 mg, or 84 mg once weekly. Maintenance phase, from Week 9: 28 mg, 56 mg or 84 mg every two weeks or once weekly. The need for continued treatment should be re-examined periodically. All dose changes should be in 28 mg increments.
Choice of comparator	SSRI or SNRI augmented with quetiapine (QTP) extended release (XR), which is different from the previous application for assessment of ESK NS in which SSRI/SNRI was the comparator[4].
Prognosis with current treatment (comparator)	The development of TRD increases morbidity and all-cause mortality in a relatively young population. Patients with TRD have a mean episode duration approximately three times longer, significantly higher rates of comorbidities, higher risk of suicide, and a seven-fold increase in suicide attempts compared to patients with non-TRD MDD[5-7]. Additionally, a 2021 study utilising the Danish National Prescription Registry found that 154,513 patients with TRD had a life expectancy shorter by 1.21 years for men and 1.24 years for women compared to other patients with depression[8].
Type of evidence for the clinical evaluation	Head-to-head study.
Most important efficacy endpoints (Difference/gain compared to comparator)	In the subgroup of patients with 3+ prior treatment failures from the ESCAPE-TRD head-to-head study, [redacted] participants in the ESK NS arm and [redacted] participants in the QTP XR arm achieved remission at Week 8. The odds ratio (OR) (unadjusted) was [redacted]

Summary	
	[redacted] participants in the ESK NS arm and [redacted] participants in the QTP XR arm reached remission by Week 8 and remained relapse free at Week 32 after remission. The OR (unadjusted) was [redacted]
Most important serious adverse events for the intervention and comparator	Few serious treatment-emergent adverse events (TEAEs) were observed in the group of patients with 3+ prior treatment failures in ESCAPE-TRD. No individual serious TEAE were recorded in ≥ 5% of study subjects. Only 'Psychiatric disorders' as a group of serious TEAEs (a system organ class) was observed in ≥ 5% of study subjects with [redacted] in the QTP XR + OAD arm and [redacted] in the ESK NS + OAD arm.
Impact on health-related quality of life	Clinical documentation: The health-related quality of life (HRQoL) was assessed via the EQ-5D-5L instrument and the EQ visual analogue scale (VAS). The HRQoL results generally favoured the ESK NS arm compared with the QTP XR arm. Health economic model: Treatment with ESK NS + OAD is associated with a QALY-gain compared to QTP XR + OAD, which is driven by an overall increase in HRQoL.
Type of economic analysis that is submitted	Cost-utility analysis based on a Markov cohort model.
Data sources used to model the clinical effects	ESCAPE-TRD[9] individual-level patient data collected from the pre-defined subgroup (i.e., 3+ prior treatment failures) were mainly used to derive health state transition probabilities.
Data sources used to model the health-related quality of life	EQ-5D-5L data collected in ESCAPE-TRD trial[9]. Health-state utility value (HSUV) estimates were based on the pre-defined subgroup (i.e., ≥ 3 treatment failures) with Danish preference weights.
Life years gained	0.01 years (discounted)
QALYs gained	0.39 QALY (discounted)
Incremental costs	113,114 DKK
ICER (DKK/QALY)	293,491 DKK/QALY
Uncertainty associated with the ICER estimate	Deterministic: The most important uncertainty of the incremental cost-effectiveness ratio (ICER) estimate was the time horizon.
Number of eligible patients in Denmark	Incidence: annually, approximately 86 patients Prevalence: approximately 760-780 patients are treated for TRD annually.
Budget impact (in year 5)	8,362,018 DKK (year 5)

Abbreviations: AD, antidepressant; AP, antipsychotics; CI, confidence interval; DMC, Danish Medicines Council; EMA, European Medicines Agency; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; ESK, esketamine; HSUV, health-state utility value; MDD, major depressive disorder; NS, nasal spray; OAD, oral antidepressants; OR, odds ratio; QALY, quality-adjusted life years; QTP, quetiapine; RADS, Rådet for Anvendelse af Dyr Sygehusmedicin; RCT, randomised controlled trial; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse events; TRD, treatment resistant depression; VAS, visual analogue scale; XR, extended-release.

Sources: European Medicines Agency, 2024[1].

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Major depressive disorder (MDD) or unipolar depression is a common and debilitating psychiatric disorder with an estimated prevalence of 3% in Denmark, affecting approximately 150,000 individuals[10]. In 2018, the World Health Organization ranked the medical condition third in terms of disease burden, with projections indicating it will become the leading cause by 2030[11].

The current classification of depression into MDD and unipolar depression is based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and the International Classification of Diseases, 10th Revision (ICD-10), respectively. According to DSM-5 MDD is defined by at least one discrete major depressive episode (MDE) (single or recurrent) lasting a minimum of two weeks and characterised by core symptoms of frequent depressed mood, and/or loss of interest or pleasure (anhedonia) in activities, leading to significant distress or functional impairment[12-14].

MDD is accompanied by other symptoms such as sleep disturbances, fatigue, change in appetite, psychomotor agitation or retardation, difficulty concentrating, and feelings of worthlessness[12,13]. The severity of MDD is classified as mild, moderate or severe based on the number of symptoms, the level of distress caused by the intensity of the symptoms, and the degree of impairment in social and occupational functioning.

As well as the morbidity and mortality associated with the disease itself, this disorder is often accompanied by psychiatric and physical comorbidities and increases the risk of developing or exacerbating cardiovascular disease, metabolic disorders, diabetes, and substance use disorders. Notably, individuals with MDD face a 20-fold higher risk of suicide compared to the general population and with a greater suicide risk than most mental disorders[15].

[11]Clinical trials have demonstrated that 30-40% of depressed patients fail to respond to first-line antidepressant treatment despite adequate compliance, dose and duration. Moreover, 10-30% exhibit treatment-resistant symptoms leading to impaired social and occupational function, decline in physical health, more suicidal thoughts, and increased health care utilization[16]. Consequently, MDD imposes a significant economic burden on the healthcare system, with treatment and care costs surpassing 9.7 billion DKK, alongside societal costs of 25.7 billion DKK due to loss of productivity and premature death[17].

Treatment Resistant Depression (TRD)

TRD represents a severely debilitating subgroup of MDD. While there is no universally accepted definition of TRD[10,18], the most widely recognised definition involves the failure to respond to two or more AD treatments, despite adequate dosage, duration, and adherence. This definition is endorsed by the Food and Drug Administration and European Medicines Agency (EMA)[19] and is commonly used in research based on the observation from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study of rapidly declining response rates after the failure of two adequate antidepressant treatments[18,20].

Patients with TRD exhibit the same clinical features and symptoms as those with non-TRD MDD (non-TRD); however, their symptoms are often of greater severity and persist longer due to inadequate responses to AD therapies[21]. On average, episodes in patients with TRD last approximately three times longer than in patients with non-TRD, which underlines that illness duration is highly associated with TRD[6,18,22].

TRD is a complex condition often associated with various comorbidities, a two-fold increased risk of hospitalisation, longer admissions, a seven-fold increase in suicide attempts and a high risk of suicide, a greater likelihood of exiting the workforce prematurely, and a diminished HRQoL compared to patients with non-TRD[5-7,23-28]. Additionally, a recent Danish registry study found that TRD was associated with a reduction in life expectancy of 1.21 years for men and 1.24 years for women in comparison to other patients with depression[8]. This reduction further contributes to the twofold mortality rate associated with MDD compared to the general population[8].

Whilst multiple distinct treatment options are available, including SSRIs, SNRIs, tricyclic antidepressants and atypical ADs, many patients with MDD still experience inadequate or partial response. The STAR*D study highlighted this issue, revealing a decline in remission rates with each successive line of treatment. Only 13.7% and 13.0% of patients achieved remission following third- and fourth-line AD therapy, respectively, which underlines that a substantial proportion of TRD patients do not respond adequately to multiple antidepressant interventions[20]. This finding is supported by a Danish register-based cohort study involving 211,689 patients with depression, as approximately 14% of patients developed TRD (second shift in AD treatment during the first 12 months after diagnosis) within the first year following their initial hospital contact[27-29].

Furthermore, whilst STAR*D demonstrated decreasing remission rates with each additional line of AD treatment, it also showed that time to relapse was shortened with increasing treatment lines[30]. Additionally, the risk of relapse increases with each unsuccessful treatment attempt, and the severity of depressive episodes tends to escalate with subsequent relapses, making effective intervention more difficult in TRD[31]. Shorter remission periods and growing resistance to AD therapy further contribute to poor prognoses and an increased risk of chronicity underscoring the necessity for effective treatments to achieve remission as early as possible[32-34].

These findings highlight the significant burden that TRD places on the healthcare system, as well as the profound personal impact on patients. There is a need for additional treatment options to effectively tackle this challenging condition and alleviate its extensive ramifications of both individuals and society.

3.2 Patient population

Background to submission: TRD patient population

In the previous DMC assessment report on ESK NS for TRD[4], it was noted that the definition of TRD in Danish clinical practice may vary from the definitions discussed in section 3.1. The scientific committee questioned whether patients with two prior treatment failures would be characterised as treatment resistant in Danish practice e.g., due to pseudo-resistance, incorrect diagnosis and unrecognised comorbidities. Additionally, there was uncertainty whether the duration of the episodes would be sufficient for the patients to be considered treatment resistant. The committee emphasised that patients with TRD typically experience a depressive episode lasting at least one year, and often even longer[35].

The DMC requested data demonstrating the efficacy of ESK NS using the Maudsley Staging Model (MSM) for the previous DMC assessment. The MSM is a multidimensional framework to stage the degree of resistance by incorporating illness duration, symptom severity and treatment attempts including adjunctive treatments. However, the multidimensional approach allows for multiple pathways to achieve the same MSM score, complicating the definition of a well-defined patient population for health technology assessment. The heterogeneity of an MSM based definition can be illustrated by considering a patient with severe MDD with psychosis, currently enduring symptoms for less than 12 months and having ECT, but no prior ADs. This patient achieves the same MSM score as another individual with mild MDD, lasting over 2 years, who has undergone treatment with 3-4 prior antidepressants and augmentation strategies.

The clinical trials of ESK NS are designed in accordance with strict regulatory guidelines from the FDA and EMA, which define TRD as the failure to respond to at least two or more AD treatments. Consequently, clinical investigations of medicinal products are not designed to investigate the efficacy of ESK NS according to MSM scores or resistance categories. While the MSM score's potential applicability and relevance are acknowledged, it is important to recognize that it is seldom utilized in RCTs, regulatory agencies or in routine clinical practice, making it infeasible for health technology assessment purposes[18,36,37].

Patient population for submission: TRD patients with inadequate response to three or more AD treatments and is eligible for adjunctive therapy

To address these uncertainties and align with Danish clinical practice, this submission focuses on a refined patient population that demonstrates inadequate response to three or more AD treatments and is eligible for adjunctive therapy (e.g., antipsychotic treatment, lithium, or repetitive transcranial magnetic stimulation [rTMS]) as per the current RADS guidelines for unipolar depression[38]. This is reflected in a pre-defined subgroup from the ESCAPE-TRD study, which has a mean duration of the current depressive episode of 94.4 weeks (standard deviation [SD]: 90.47)[39].

Patient numbers

The prevalence is estimated as follows. In the Danish population 80.9% of the population are adults[40] and among these, the point prevalence of MDD is 3%[10,41]. Further, 65% are diagnosed or treated for MDD[10,42] and 14% of adults with MDD are estimated to have TRD (defined as two or more AD failures)[10,29]. Among these patients with TRD, 59.7% of patients have moderate to severe TRD[26], and 12% of patients with 3 or more ADs initiate adjunctive treatment within a year[43], 81.9% of which initiate second-generation antipsychotics or lithium as adjunctive treatment[43]. These figures are applied to the Danish mid-year population size in 2020, 2021, 2022, 2023, and 2024, respectively[40]. For instance, the prevalence in 2024 is estimated as
5,972,420*0,809*0,03*0,65*0,14*0,597*0,12*0,819 = 980 patients.

The incidence of TRD is estimated from Gronemann et al. 2021[26], which is a Danish register-based cohort study including all citizens in Denmark aged 18 or above registered for the first time with an MDD diagnosis at a Danish hospital between January 1, 1996, and December 31, 2015. In the publication, TRD is defined as two shifts in treatment for MDD. In this period, the TRD incidence was 29,212. To estimate the yearly incidence 29,212 was divided by 20. This estimate was multiplied with 59.7%, 12%, and 81.9% as described above to estimate patients with moderate to severe TRD with 3 or more prior ADs, who initiate augmentation treatment with second-generation antipsychotics or lithium as adjunctive treatment applied[43-45].

Table 3 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	86	86	86	86	86
Prevalence in Denmark	755	758	766	770	774
Global prevalence *	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A, not applicable.

Notes: * For small patient groups, also describe the worldwide prevalence.

Source: Gronemann et al. 2021[26]; Danmarks Statistik 2024[40]; Videbeck & Deleuran 2016[41]; Dansk Psykiatrisk Selskab & Region Hovedstadens Psykiatri 2020[10]; Substance Abuse and Mental Health Services Administration 2017[42]; Gronemann et al. 2018[29]; Janssen 2024[43].

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Regardless, the estimates will be associated with uncertainty. Johnson & Johnson estimate that ESK NS will replace the current treatment for approximately 5% of eligible patients within the first year, increasing to 27% by year five. The 27% market share is aligned with the DMC's estimated market share for the patients in need of acute short-term treatment with ESK NS[46]. A constant incidence was assumed, with approximately 86 patients discontinuing treatment each year while 86 new patients-initiated treatment. Additionally, the prevalence was expected to increase by 4 patients annually compared with the reported prevalence obtained from literature (reported in Table 4), which is based on retrospective data.

Table 4 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	759	848	856	860	864

Source: DMC[47]

3.3 Current treatment options

While multiple treatment options are currently available for treatment of TRD, adjunctive treatment with antipsychotics or lithium are staged as the preferred option after 3 prior treatments according to Danish national guidelines. In the treatment guidelines from RADS, it is recommended that patients who have not responded to two prior AD treatments (administered at optimal doses) should be referred to a psychiatrist or admitted to a psychiatric department. The guidelines do not explicitly state which treatments are recommended for patients, that are not hospitalised after two failed treatments, but for hospitalised patients with nonpsychotic depression tricyclic ADs, selective serotonin-noradrenaline reuptake inhibitors, or mirtazapine should be considered. If the patient does not improve after 2-4 weeks at optimal dose (representing a failure of 3 prior treatments), lithium or an antipsychotic (e.g., quetiapine or aripiprazole) can be used as an adjunctive treatment. Again, if the patient does not improve after 2-4 weeks at optimal dose, patients should be considered for electroconvulsive therapy (ECT)[38]. It is assumed that the pathway for patients referred to a psychiatrist for outpatient treatment would be similar. Recently, the Danish Health Technology Council also recommended rTMS as a treatment option for TRD. rTMS is mainly considered as an adjunctive treatment alongside standard pharmacological treatment in Danish clinical practice. Patients who are given the option of rTMS might have been considered for ECT but are reluctant due to side effects of ECTs. Also, it may be offered to less severe patients without acute suicidal risk and/or psychotic symptoms[10,48].

A register-based cohort study has assessed the real-world patterns of antidepressant treatment among Danish patients with TRD. In this study, a treatment change was defined as any switch in antidepressants, a shift to ECT or adding an additional antidepressant (combination therapy). Consistent with the national guidelines, the findings indicated that patients most commonly initiated their first AD treatment for MDD with an SSRI, followed by an SNRI as second treatment. Moreover, 81.5% of patients were prescribed either an SSRI or SNRI as their third AD, while SNRIs of different chemical classes remained the most frequent AD options as fourth and fifth treatments. Within 12 months of meeting TRD criteria, 31.9% of patients were treated with a tricyclic antidepressant, whereas only 1.1% received a monoamine oxidase inhibitor[26]. Despite, the availability of neuromodulation techniques such as ECT and rTMS, real world data indicate that they are not utilized for the majority of patients with TRD[45,49-51]. Specifically, Danish registry data reported that only 5.4% of all patients diagnosed with MDD were treated with ECT, and just 10.6% received ECT within 12 months of meeting TRD criteria[52]. Furthermore, while comprehensive national data on rTMS is lacking, a recent survey of Danish rTMS clinics found that 383 patients with moderate to severe MDD were

treated with this technique in 2023[53]. However, the study does not specify what proportion of these patients were classified as having TRD.

While antidepressant therapies, particularly, SSRIs and SNRIs, are a cornerstone in the treatment of both MDD and TRD, augmentation strategies, such as antipsychotics, are frequently added to ADs in line with Danish national guidelines. A recent unpublished cohort study utilizing Danish register data revealed that antipsychotics were the predominant adjunctive treatment to ADs in MDD, accounting for [redacted]% of cases, with QTP being the most prevalent antipsychotic choice at [redacted]%. The mean daily dose of QTP was [redacted] mg in line with its MDD label[43]. These observations are consistent with existing Danish registry data on treatment patterns for TRD, indicating a significant reliance on antipsychotic augmentation, particularly QTP. Specifically, 30.2% of patients receiving a fourth-line antidepressant treatment were prescribed an antipsychotic, and nearly 45% of patients with TRD had undergone antipsychotic augmentation within 12 months after two prior antidepressant treatments. In comparison, only 3.4% of patients with TRD were treated with lithium as a fourth-line option, highlighting its limited use in Danish practice[26].

3.4 The intervention

ESK NS was approved by EMA in 2019 and is currently reimbursed for the TRD indication in 32 countries in the Europe, the Middle East, and Africa region (please see Appendix O) and has a long-term multi-year establishment of efficacy and safety. Importantly, ESK NS is recognized by the World Psychiatric Association as the most rigorously evaluated pharmacologic strategy in the acute and maintenance treatment of TRD. Furthermore, it is the only treatment approved by EMA for TRD and the only antidepressant treatment extensively evaluated in RCTs of patients with lack of response to two prior antidepressant treatment trials. To date, ESK NS has been administered to more than 140,000 patients worldwide[18,54].

ESK is the S-enantiomer of racemic ketamine. It is a non-selective, non-competitive, antagonist of the N-methyl-D-aspartate receptor, an ionotropic glutamate receptor. Through N-methyl-D-aspartate receptor antagonisation, ESK produces a transient increase in glutamate release leading to increases in stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and subsequently to increases in neurotrophic signalling which may contribute to restoring the synaptic function in these brain regions involved with the regulation of mood and emotional behaviour. The restoration of dopaminergic neurotransmission in brain regions involved in reward and motivation, along with decreased stimulation of brain regions involved in anhedonia, may contribute to the rapid response[1].

ESK NS is administered as a nasal spray and primarily targets the glutamate pathway. It is the first and only fast-acting (within 24 hours) AD approved for the treatment of TRD in combination with an OAD[22,55,56]. Treatment with other ADs usually take weeks to months to achieve their full effects[57]. In addition, ESK NS is intended to be administered by the patients themselves under healthcare professional (HCP) supervision to monitor the primarily transient side effects associated with ESK NS and to minimise risks[22,56,58].

It is important to recognise that ketamine, arketamine, and ESK-NS are distinct pharmaceuticals, and their efficacy and safety cannot be directly compared[59]. This difference is highlighted by ESK NS exhibiting a 4-fold greater affinity for the NMDA receptor compared with ketamine, as well as a recent placebo-controlled pilot study on arketamine in TRD, which did not show superiority over placebo[60,61].

Table 5 Overview of esketamine

Overview of intervention (esketamine)	
Indication relevant for the assessment	For this submission the patient population has been refined to include only those patients with 3+ prior treatment failures deemed suitable for adjunctive treatment such as with an antipsychotic. I.e., the indication relevant for the assessment is more targeted compared to the EMA indication, as the EMA indication include a broader patient population who have not responded to at least two different treatments with ADs.
Advanced Therapy Medicinal Product (ATMP)	No
Method of administration	Nasal use. The NS device is a single-use device that delivers a total of 28 mg of ESK, in two sprays (one spray per nostril). Thus, one device should be used for a 28 mg dose, two devices for a 56 mg dose, or three devices for an 84 mg dose, with a 5-minute rest between use of each device.
Dosing	Overall, it is recommended to maintain the dose the patient receives at the end of the induction phase (week 0-4) in the maintenance phase (week 5 and onward). During the maintenance phase, ESK NS dosing should be individualised to the lowest frequency to maintain remission/response. The dosing is further described in the summary table in section 2 (the row "dosage regiment and administration").

Dosing in the health economic model (including relative dose intensity)	ESK NS, average number of devices (4-week cycle):
	• Induction phase (first 4 weeks):
	  ○ Average number of sessions per week: 1.853
	  ○ Average number of devices per session: 2.261
	• Maintenance phase (weeks 5 to 8):
	  ○ Average number of sessions per week: 0.992
	  ○ Average number of devices per session: 2.591
	Maintenance phase (week 9 to 9 months):
	  ○ Average number of sessions per week: 0.856
	  ○ Average number of devices per session: 2.667
	• Maintenance in recovery (after 9 months):
	  ○ Average number of sessions per week: 0.675
	  ○ Average number of devices per session: 2.571
	The average number of devices is based on data from ESCAPE-TRD, except of the maintenance in recovery phase, where the estimate is based on data from SUSTAIN-1.

Overview of intervention (esketamine)	
	Relative dose intensity: 100%
Should the medicine be administered with other medicines?	Yes (in combination with a SSRI or SNRI).
Treatment duration / criteria for end of treatment	The SmPC states that after depressive symptoms improve, treatment is recommended for at least 6 months. In the health economic model, it was assumed that all patients discontinue treatment within the first two years after achieving remission (i.e. two years after the acute treatment period). See Section 4.2.
Necessary monitoring, both during administration and during the treatment period	ESK NS is intended to be self-administered by the patient under the direct supervision of an HCP. A treatment session consists of administration of ESK NS and a post-administration observation period. The risk management plan for ESK NS includes that patient's risk for abuse or misuse before prescribing ESK NS should be assessed and possible development of abuse or misuse while on therapy should be monitored. Transient dissociative states and perception disorders as well as disturbances in consciousness are other identified risks to be managed. This includes instructing patients prior to ESK NS administration to not engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a vehicle or operating machinery, until the next day following a restful sleep. Finally, increased blood pressure has been identified as a risk to be managed. After dosing with ESK NS, blood pressure should be reassessed at approximately 40 minutes and subsequently as clinically warranted (described in the SmPC[1]).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A
Package size(s)	Spravato (ESK) 28 mg nasal spray (solution), 2 devices Spravato (ESK) 28 mg nasal spray (solution), 3 devices

Abbreviations: AD, antidepressant; ATMP, advanced therapy medicinal product; EMA, European Medicines Agency; ESK, esketamine; N/A, not applicable; NS, nasal spray; RADS, Rådet for Anvendelse af Dyr Sygehusmedicin; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Sources: European Medicines Agency, 2024[1]; European Medicines Agency, 2024[1]; Danish Medicines Agency, 2024[3].

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

ESK NS will be included in the treatment algorithm in what corresponds to fourth line of the RADS guideline, as the guideline recommends that augmentation treatments

generally are introduced after three failed attempts with monotherapy[38]. As such, ESK NS offers another treatment option (in addition to lithium or an antipsychotic (e.g., QTP)) in fourth line.

3.5 Choice of comparator(s)

As described above, various strategies are available for treating TRD, including switching, combining or augmenting current therapies. Each approach requires careful consideration of the patient's clinical profile, comorbidities, tolerability, adherence, and preferences[62].

QTP is deemed to be the most appropriate comparator for this application aimed at TRD patients with 3+ prior treatment failures for the following reasons:

- In Denmark, the national guidelines recommend adjunctive treatment with antipsychotics (e.g. QTP and aripiprazole) and lithium as preferred treatment options in patients who have failed three prior ADs[38].
- Antipsychotics are the most frequently utilized adjunctive treatment for TRD in Denmark, with 30.2% of patients treated with this strategy in fourth line, primarily with QTP[45]. QTP is further the only antipsychotic EMA-approved as an add-on in MDD[63].
- Lithium augmentation is, despite being one of the oldest available treatment choices, prescribed to less than 5% of patients with TRD in Denmark from the third to fifth line. It further seems clinical inferior and less cost-effective than QTP augmentation as observed in a recent 12-month RCT study of patients with TRD[45,64].
- ECT is generally considered a later treatment option in TRD management after augmentation strategies per RADS guidelines, as underscored by Danish registry data showing that less than 11% of TRD patients are treated with the strategy, except in specific clinical situations such as acute suicidal ideation and psychotic features as outline in the national guideline[38,45].
- rTMS was recently recommended by the Danish Health Technology Council as a treatment option for TRD, but its inconsistent implementation and absence from the current RADS guidelines limit its clinical use, making it a less optimal comparator[45,48,53].

Table 6 Overview of quetiapine extended-release

Overview of comparator (quetiapine extended-release)	
Generic name	Quetiapine
ATC code	N05AH04
Mechanism of action	QTP and its active human plasma metabolite norquetiapine affect a wide range of neurotransmitter receptors. QTP and norquetiapine exhibit affinity for serotonin (5HT2) receptors and dopamine D1 and D2 receptors in the brain. The combination of receptor antagonism with a higher selectivity for 5HT2 receptors compared to D2 receptors is believed to contribute to the clinical antipsychotic properties and the low propensity to induce extrapyramidal side effects associated with QTP, compared to typical antipsychotics. QTP and norquetiapine show high affinity for histaminergic and adrenergic alpha1 receptors and moderate affinity for adrenergic alpha2 receptors.

	QTP has little to no affinity for muscarinic receptors, while norquetiapine exhibits moderate to high affinity for several muscarinic receptors, which may explain its anticholinergic (muscarinic) effects. Norquetiapine's inhibition of the norepinephrine transporter and partial agonism at 5HT1A sites may contribute to QTP's therapeutic effect as an AD.
Method of administration	Oral
Dosing	The initial dose is 50 mg on days 1 and 2 and 150 mg on days 3 and 4. In short-term studies, the AD effect was observed at daily doses of 150 and 300 mg when the medication was used as an adjunctive treatment in MDD. There is an increased risk of side effects at higher doses. Therefore, clinicians should ensure that the lowest effective dose starting at 50 mg/day is used in treatment. The need to increase the dose from 150 to 300 mg daily should be based on an individual evaluation of the patient.
Dosing in the health economic model (including relative dose intensity)	QTP XR average dosage per administration: 193 mg once daily every week[65]. Relative dose intensity: 100%. This dosage was largely consistent with the dosages observed in a non-interventional Danish study on adjunctive treatment patterns in patients with MDD/TRD[66]. Stopping rule: in the health economic model, it was assumed that all patients discontinue treatment within two years. See Section 4.2.
Should the medicine be administered with other medicines?	Yes, as adjunctive treatment to AD therapy.
Treatment duration/ criteria for end of treatment	If signs and symptoms of tardive dyskinesia appear, consideration should be given to whether the dose of QTP should be reduced or the treatment discontinued. Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including QTP. Clinical symptoms include hyperthermia, altered consciousness, muscle rigidity, autonomic disturbances, and elevated creatine phosphokinase. In such cases, treatment with QTP should be discontinued, and appropriate medical treatment should be initiated.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	QTP 150 mg tables, 30 XR tablets QTP 50 mg tables, 60 XR tablets QTP 50 mg tables, 100 XR tablets QTP 150 mg tables, 100 XR tablets QTP 200 mg tables, 100 XR tablets QTP 300 mg tables, 100 XR tablets QTP 400 mg tables, 100 XR tablets

Abbreviations: AD, antidepressant; MDD, major depressive disorder; N/A, not applicable; QTP, quetiapine; XR, extended-release.

Sources: Danish Medicines Agency, 2024[67]; Danish Medicines Agency, 2024[3].

3.6 Cost-effectiveness of the comparator(s)

QTP has not been evaluated by the DMC. However, QTP can reasonably be assumed to be cost-effective, as it is extensively used in Danish clinical practice and is relatively inexpensive[3,43,45].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The primary goal of treatment for MDD is remission, with maintenance treatment aimed at preventing relapse. Remission and response are included as efficacy outcomes, as the DMC has previously included these endpoints in the protocol for ESK NS for TRD[68]. Both outcomes can be assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) score. In addition, change from baseline (CFB) in MADRS total score is included as an efficacy outcome, as this is the mean benefit that can be expected by the individual patient. Furthermore, the endpoint relapse-free after remission is included[48].

Non-Responder Imputation (NRI) for binary endpoints and Baseline Observation Carried Forward (BOCF) for continuous endpoints were applied after study treatment discontinuation in order to enable a full intention-to-treat (ITT) analysis. For the outcomes of remission at week 8 and relapse free after remission at week 32, sensitivity analyses where for participants who stopped study intervention, but were still followed in the study, no imputation was performed, and their observed status was used for the analyses. The results of these analyses are available in table S5 in the supplementary materials from Reif et al. 2023[69]

Binary endpoints were analysed using Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for both randomisation stratification factors (age: 18 to 64 years / 65 to 74 years; total number of treatment failures: 2/3+) in analyses on the full population (no adjustment in subgroup analyses as number of prior treatment failures no longer applicable (all patients have 3+ failures in the subgroup analyses) and insufficient number of elderly patients).

Continuous endpoints were analysed using analysis of covariance (ANCOVA) models adjusting for both randomisation stratification factors and baseline score in analyses on the full population (adjusted only on baseline score in subgroup analyses).

Table 7 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Remission [Included in ESCAPE-TRD]	Week 8 and 32	Achieving a MADRS total score of ≤10[Ω], without discontinuation of any component of study intervention before Week 8.	The MADRS was assessed by a qualified independent site rater, who was blinded to the participant's treatment and who was

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Response rate [Included in ESCAPE-TRD]	Week 8 and 32	≥50% improvement in MADRS total score from baseline or MADRS ≤10.	not involved in any other study assessments or treatment decisions for a given study participant. Analyses are based on the NRI approach.
CFB in MADRS total score [Included in ESCAPE-TRD]	Week 32	CFB assessed with MADRS as a continuous variable.	
Relapse-free after remission [Included in ESCAPE-TRD]	Week 32	Remission at Week 8 visit (i.e., MADRS total score of ≤10 at the end of Week 8) and no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit.	A relapse was defined by worsening of depressive symptoms (MADRS total score ≥22 confirmed by one additional assessment of MADRS total score ≥22 within the next 5 to 15 days); psychiatric hospitalisation for worsening of depression, suicide prevention, or due to a suicide attempt; or suicide attempt, suicide, or any clinical event determined per the investigator's clinical judgement to be indicative of a relapse, but for which the participant was not hospitalised. The analysis is based on the NRI approach.

Abbreviations: CFB, change from baseline; DMC, Danish Medicines Council; MADRS, Montgomery-Asberg Depression Rating Scale; NRI, non-responder imputation.

Notes: * Time point for data collection used in analysis (follow up time for time-to-event measures). Ω This definition is stricter than in the previous application to the DMC in which the cut-off for remission was ≤12[70]. Further, this definition is also stricter than the definition provided by the DMC in the protocol for the previous appliction, in which remission was defined as a MADRS score of ≤11[68].

Sources: Janssen EMEA, 2023[65].

Validity of outcomes

The MADRS is a validated instrument in depression that measures the change in symptoms and can quantify the severity of the depressive disorder. The scale consists of 10 items, each of which is scored from 0 (symptom not present or normal) to 6 (severe or continuous presence of the symptom), for a total possible score of 60. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (anhedonia, loss of interest), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability[71]. The DMC has previously assessed that the minimal clinically relevant difference is 15 percentage points[68].

4. Health economic analysis

A cost-utility analysis was conducted based on an Excel-based cost-effectiveness model (CEM). The objective of the CEM is to assess the cost-effectiveness of ESK NS + OAD

versus QTP XR + OAD in TRD. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained.

4.1 Model structure

A Markov cohort model was developed to track the disease pathway and costs experienced by the patient cohort treated with ESK NS + OAD and QTP + OAD throughout the model time horizon. Figure 1 illustrates the model structure.

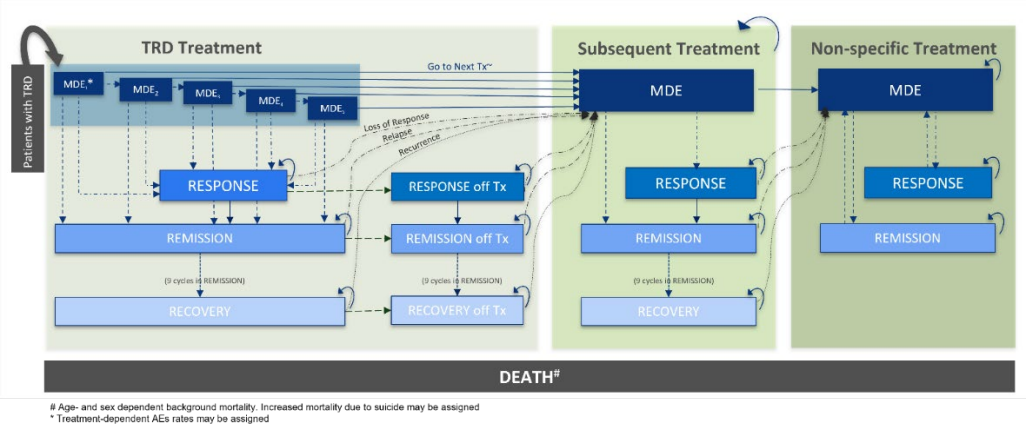


Figure 1 Markov cohort model flow diagram

Abbreviations: AD, antidepressant; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; TRD, treatment resistant depression; Tx, treatment

The patient cohorts enter the model in the acute phase with a MDE after 3+ prior treatment failures. The following definitions are used for the health states and the derivation of transition probabilities:

- Response: during the acute phase, response is defined as ≥50% improvement from baseline in the MADRS score, while still having a MADRS score >10
- Remission: a patient is considered to achieve remission when the MADRS score is ≤10
- Recovery: a patient who has stayed in uninterrupted remission for nine cycles (supported by data on relapse among stable remitters from the SUSTAIN-1 trial, where patients in both treatment arms showed considerable reduction in risk of relapse after 36 weeks)[72].
- Relapse (as defined in the ESCAPE-TRD trial):
  - Worsening of depressive symptoms as indicated by MADRS total score ≥22, confirmed by one additional assessment of MADRS total score ≥22 within the next five to 15 days. The date of the second MADRS assessment is used for the date of relapse.
  - Psychiatric hospitalization for worsening depression, suicide prevention, or due to a suicide attempt. For any of these events, the start date of hospitalization is used for the date of relapse.

Based on results from ESCAPE-TRD, after five cycles there is little additional remission or response gain. As such, the maximum number of cycles a patient can stay in MDE on initial treatment is set as 5 in the base case, with flexibility to vary this from 1 to 5.

Patients can transition to the absorbing death health state from any health state in the model.

At the end of each cycle in MDE on initial treatment (i.e., acute phase), patients are evaluated in the model, and they may:

- Respond to treatment and move into the response or remission health states.
- Fail to respond to treatment and stay in the MDE health state. When the maximum number of cycles in MDE on initial treatment is not yet reached, patients stay on initial treatment. When no response to treatment is observed at the end of the maximum cycle on initial treatment they move on to the next treatment in the sequence (i.e., OADs from two classes: a SSRI (escitalopram, sertraline, paroxetine, fluoxetine, citalopram, or fluvoxamine), or a SNRI (duloxetine or venlafaxine XR).
- Discontinue treatment early (i.e. due to all-cause drop out risk) and stay in the MDE health state but move on to the subsequent treatment in the sequence (or to the non-specific treatment mix when the maximum number of subsequent treatments have been attempted).

Those patients who responded to treatment may:

- Transition into the remission health state and start the continuation/maintenance phase of the same treatment.
- Relapse and transition to the MDE state in the next treatment sequence (or the non-specific treatment mix when the maximum number of subsequent treatments have been attempted).
- Discontinue treatment and remain in response.

Patients who achieve remission may:

- Achieve recovery after nine cycles of uninterrupted remission.
- Relapse and transition to the MDE state in the next treatment sequence (or the non-specific treatment mix if a single course of treatment is being evaluated, or the maximum number of subsequent treatments have been attempted).
- Discontinue treatment and remain in remission.

Patients achieving recovery and continuing in the maintenance treatment phase may:

- Experience a recurrence event, return to the MDE health state, and move on to the next treatment in the sequence. In a scenario analysis re-treatment with the same treatment originally assigned is investigated, see description of the re-treatment scenario below and in Appendix L.
- Discontinue treatment and remain in recovery.

Patients that fail on the initial treatment, move to MDE in the subsequent treatment health state. In the subsequent treatment health states, patients may receive up to three lines of subsequent treatment, before moving to the non-specific treatment health state. In the non-specific treatment health state, the patients may transition between MDE,

response and remission. The division of subsequent treatment lines and non-specific treatment (which both contain the same treatments, OADs) is made to capture the difference in probability of achieving response and remission in earlier vs later treatment lines as well as the increased risk of relapse in the later lines.

Retreatment scenario model

In the previous assessment, the DMC requested the inclusion of a re-treatment scenario analysis for ESK NS alongside the base case model. This scenario has also been implemented into the current model, providing an option to account for cases where a patient may undergo re-treatment with ESK NS before transitioning to subsequent treatment. The re-treatment with QTP was not requested due to a lack of data on its effectiveness and is not implemented as an option in the model. See Appendix L for details on the re-treatment scenario model.

4.2 Model features

Table 8 describes the model features.

Table 8 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with ≥ 3 treatment failures)	To reflect a patient population aligned with the DMC's positioning of ESK NS in the treatment algorithm[35,39].
Perspective	Limited societal perspective	According to DMC guidelines[73].
Time horizon	5 years	TRD is a disorder that may, for some patients, last a lifetime and is recurring in nature. However, long-term evidence of ESK NS and comparators is too uncertain to justify substantial modelled benefit over a longer period of time. The DMC have previously used this time horizon for the same indication[35].
Cycle length	4 weeks	Consistent with the SmPC[67] (i.e., patients who show improvement in their depressive symptoms within 4 weeks should continue treatment with ESK NS for at least 6 months).
Recovery	Recovery is defined as a patient who has stayed in uninterrupted remission for nine cycles	This definition of recovery is supported by data on relapse among stable remitters from SUSTAIN-1[72], which was discussed and validated by four UK clinicians in an advisory board[39]. In SUSTAIN-1, after 24 weeks of maintenance therapy (corresponding to 36 weeks after the acute treatment phase), patients from both treatment arms showed a considerable reduction in risk of relapse, indicating that patients have achieved stable remission of the disease.

Model features	Description	Justification
Stopping rule(s)	ESK NS is discontinued when patients relapse and is continued for patients in response or in remission. Upon reaching recovery (after 9 months in remission), 35.4% of patients discontinue ESK NS. For the remaining patients who reach recovery, it was assumed that they discontinue ESK NS by a maximum period of two years (applied as 24.9% per four-week cycle) after the acute treatment period (i.e., two years after first achieving remission). The same assumptions were applied in the QTP XR arm following a conservative approach.	For treatment discontinuation upon recovery, the risk was sourced from SUSTAIN-1[74]. Moreover, national and international guidelines recommend continuing treatment for at least 6–12 months after remission to reduce the risk of relapse[38,75,76].
Half-cycle correction	Yes	To adjust for the distribution of costs and benefits accrued throughout each cycle.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5% for all years
Intervention	ESK NS in combination with OAD	Intervention of interest
Comparator(s)	QTP XR in combination with OAD	Refer to Section 3.5
Outcomes	Time in MDE, response, remission, and recovery, and life years.	Main outcomes of interest for cost-effectiveness analysis.

Abbreviations: DMC, Danish Medicines Council; ESK, esketamine; MDE, major depressive episode ; NICE, National Institute for Health and Care Excellence; NS, nasal spray; OAD, oral antidepressants; SmPC, summary of product characteristics; TRD, treatment resistant depression; UK, United Kingdom; XR, extended-release.

Model limitations

TRD is an episodic condition, and due to the nature of the disorder, modelling life-time costs and effects for any treatment is associated with uncertainty. Thus, in base case analysis the time horizon is set to 5 years which is assumed to be sufficient duration to cover the length of one MDE and account for all the treatment-related costs and effects attributable to ESK NS + OAD. Assumptions relating to the natural history and course of the disease are needed.

Given their positive outcome, it is expected that patients who initially respond to ESK NS and achieve complete recovery from their TRD will undergo re-treatment with ESK NS in the event of a relapse. However, the available data on the efficacy of re-treatment with ESK NS is limited. These uncertainties are tested through a sensitivity analysis where the possibility of re-treatment is included.

5. Overview of literature

5.1 Literature used for the clinical assessment

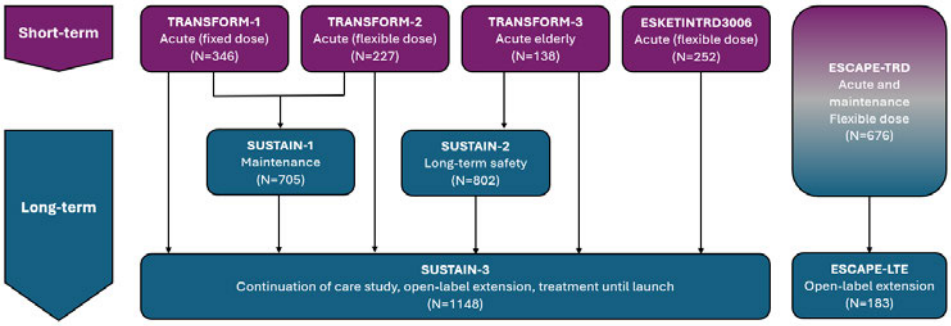
This application is primarily based on the ESCAPE-TRD head-to-head study with QTP XR as comparator. Therefore, no systematic literature review (SLR) has been conducted for this application. For the previous submission to the DMC (prior to the publication of the ESCAPE-TRD results), an SLR was conducted and no other direct evidence of ESK NS vs QTP XR was identified.

To provide additional insights into the safety profile of ESK NS, the open-label long-term phase 3 safety study, SUSTAIN-3, is included. SUSTAIN-3 provides the best source to inform on ESK NS's safety profile, as it is a safety study with the longest exposure time (median 45.8 months) and most patients enrolled (1,148). Further, it includes additional information on long-term efficacy for relevance for this application.

ESK NS clinical programme

Besides ESCAPE-TRD and SUSTAIN-3, the TRD study programme of ESK NS is substantial, consisting of multiple phase 2 and 3/4 studies, including the short term-trials TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, and ESKETINTRD3006, and the long-term trials SUSTAIN-1 and SUSTAIN-2, see Figure 2. These studies investigate ESK NS in combination with other treatments. More studies have investigated ESK NS as a monotherapy, example the ESKTINTRD4005 trial. For the purpose of this application, the results of the studies have not been included, however a brief overview is included to show the extent to which ESK NS has been studied. 3,620 patients with TRD have been treated with ESK NS as part of a clinical trial (phase 2-4) in the clinical development programme.

Figure 2 ESK NS clinical programme for TRD



Abbreviations: ESK, esketamine; NS, nasal spray.

A single-arm 2-year open-label long-term extension (LTE) to ESCAPE-TRD has also been conducted. Patients in ESCAPE-TRD, who completed ESK NS treatment in combination with an SSRI/SNRI to week 32, and where commercial ESK NS was not accessible to them in their country, were eligible to be enrolled in the LTE trial. Data for the intention-to-treat (ITT) population showed a consistent safety profile and maintained efficacy for most patients over 136 weeks. Of the 149 patients that experienced remission in ESCAPE-TRD, only 9 patients experienced relapse from point of remission and throughout

ESCAPE-LTE, and 118 (79.2%) remained in remission. As analyses for the 3+ prior treatment failures subgroup have not been conducted, data from the LTE trial is not presented in this application.

Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Full paper. Reif et al. Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. N Engl J Med. 2023 Oct 5;389(14):1298-1309[69]. Full paper. McIntyre et al. Safety and tolerability of esketamine nasal spray versus quetiapine extended release in patients with treatment resistant depression. Eur Neuropsychopharmacol. 2024 Aug;85:58-65[15]. Data on file. Unpublished data. Janssen EMEA. 2023. Final clinical study report of esketamine vs. QTP (ESCAPE-TRD)[65]. Data on file. Unpublished data. Janssen EMEA. 2024. Subgroup analyses based on prior treatment failure[66].	ESCAPE-TRD	NCT04338321	Start: 21/08/20 Completion: 15/07/22	ESK NS vs. QTP for patients with TRD that have not responded adequately to three prior treatments.
Full paper. Castro et al. Efficacy and Safety of Esketamine Nasal Spray in Patients with Treatment-Resistant Depression Who Completed a Second Induction Period: Analysis of the Ongoing SUSTAIN-3 Study. CNS Drugs. 2023 Aug;37(8):715-723[72]. Full paper. Zaki et al. Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. Neuropsychopharmacology. 2023 Jul;48(8):1225-1233[44]. Data on file. Unpublished data. Janssen Research & Development. 2023. Final clinical Study Report of esketamine (SUSTAIN-3)[39].	SUSTAIN-3	NCT02782104	Start: 09/06/16 Completion: 30/12/22	SUSTAIN-3 is used to inform the long-term safety of ESK NS.

Abbreviations: ESK, esketamine; TRD, treatment resistant depression.

Notes: * If there are several publications connected to a trial, include all publications used.

Sources: ClinicalTrials.gov, 2020[9]; ClinicalTrials.gov, 2016[77].

5.2 Literature used for the assessment of health-related quality of life

HRQoL data for the estimation of health state utility values was solely obtained from the ESCAPE-TRD head-to-head study. The European Quality of Life (EuroQoL) Group, 5-Dimension, 5-Level (EQ-5D-5L) data from ESCPAE-TRD trial with Danish preference weights was used to calculate the health state utility values. Disutilities for adverse events (AE) were obtained based on literature. The references are presented in Table 10 and the literature search to identify the inputs is described in Appendix I.

Table 10 Relevant literature included for (documentation of) health-related quality of life (See section 0)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Janssen EMEA. ESCAPE-TRD Clinical Study Report. A Long-term Comparison of Esketamine Nasal Spray Versus Quetiapine Extended-Release, Both in Combination With a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor, in Participants With Treatment-Resistant Major Depressive Disorder. [data on file], 2023[65].	The HSUVs for MDE, response, remission, and recovery health states were derived from a mixed effect model.	The application of the data is presented in Section 10.1 and 10.2.
Sullivan PW, Valuck R, Saseen J, MacFall HM. A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions. CNS Drugs. 2004;18(13):911-32. doi: 10.2165/00023210-200418130-00006. PMID: 15521793. [78]	Disutility decrement for: • Dizziness • Fatigue* • Headache • Nausea • Somnolence* • Vertigo* • Vomiting** • Sedation*	Section 10.3.
Revicki DA, Wood M. Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications. J Affect Disord. 1998 Feb;48(1):25-36. doi: 10.1016/s0165-0327(97)00117-1. PMID: 9495599.[79]: differences by depression severity and antidepressant medications. J Affect Disord. 1998 Feb;48(1):25-36. doi: 10.1016/s0165-0327(97)00117-1. PMID: 9495599)[79].	Disutility decrement for: • Dry mouth	Section 10.3.

Abbreviations: HSUV, health-state utility value; MDE, major depressive episode.

Notes: *Assumed to be the same as for dizziness; **Assumed to be the same as nausea; ***Assumed to be the same as for dry mouth.

5.3 Literature used for inputs for the health economic model

Besides data from ESCAPE-TRD, 8 additional references were identified to provide input to the health economic model (excluding cost sources, SmPCs, DRG tariffs etc), which are presented in Table 11. The literature search to identify the inputs is described in Appendix J.

Table 11 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Janssen EMEA. ESCAPE-TRD Clinical Study Report. A Long-term Comparison of Esketamine Nasal Spray Versus Quetiapine Extended-Release, Both in Combination with a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor, in Participants With Treatment-Resistant Major Depressive Disorder. [data on file], 2023[65].	Treatment effect to modify transition probabilities and occurrence of AEs	Main study	Section 8
	Average number of devices used per visit for the ESK arm for each treatment phase		Section 11.1
	Inclusion of the specific SSRI and SNRIs, frequency and dosage		Section 11.2
Daly EJ et. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Re lapse Prevention in Patients with Treatment-Resistant Depression: A Randomized Clinical Trial [SUSTAIN-1/ESKINTRD3003 study]. Jama Psychiatry. 2019 Sep 1;76(9):893-903[74].	Risk of treatment discontinuation upon recovery	Key trial data	Section 8
Janssen. Data on File. Statistical Analysis of Patient Level Data from Esketamine Trials. 2019[80].	Proportion of patients (35.4%) who proactively discontinue ESK upon achieving complete recovery	Key trial data	Section 8
Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17[20].	Loss of response and relapse probabilities in the subsequent treatment arms	Targeted literature review	Section 8 (details reported in Appendix K)
Edwards S HV, Nherera L, Trevor N. Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a	Efficacy for the OADs used as part of the non-specific treatment phase. Reported risks for response discontinue, remission discontinue, relapse from response discontinue, relapse from remission discontinue were used to inform	Targeted literature review	Section 8

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
systematic review and economic evaluation. Health Technol Assess. 2013;17(54)[81].	response, remission, loss of response, and relapse for this model, respectively. Standard methodology was used to convert 2-month risks to 4-week risks.		
Bergfeld IO MM, Figee M, Schuurman PR, Lok A, Denys D. Treatment-resistant depression and suicidality. J Affect Disord. 2018;(235):362-367[24].	Disease-related mortality in the MDE health state (i.e., suicide)	Targeted literature review	Section 8
Ekman M, Granström O, Omérov S, Jacob J, Landén M. The societal cost of depression: evidence from 10,000 Swedish patients in psychiatric care. J Affect Disord. 2013 Sep 25;150(3):790-7. doi: 10.1016/j.jad.2013.03.003. Epub 2013 Apr 21. PMID: 23611536[82].	Direct medical costs associated with the health state remission (calculate from MDE state cost using rate of 7.09)	Targeted literature review	Section 11.4
	Patient cost associated with the health state remission (calculate from MDE state cost using rate of 7.09)		Section 11.7
Petersen J, Gronemann FH, Ankarfeldt MZ, Solem EJ, Jørgensen MB, Osler M. Treatment Resistant Depression in Denmark (TRIDEN): Healthcare resource utilization in relation to treatment resistance in patients with major depression in a nation-wide Danish cohort. 2019 Oct 21. Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospitals; Klinisk Farmakologisk afdeling, Bispebjerg and Frederiksberg Hospital; Psychiatric Center Copenhagen[83].	The average annual number of visits or hospital days for TRD during MDE	Target literature review	Section 11.4 Section 11.7
Starr L. WA, Dale E., . Phase 3 Amendment 4: A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal Esketamine Plus an Oral Antidepressant for relapse prevention in treatment-resistant depression. Psych Congress. 2019[84].	Patient time for administration and post-dosage observation of ESK NS	Target literature review	Section 11.7

Abbreviations: AE, adverse event; ESK, esketamine; MDE, major depressive episode; NS, nasal spray; OAD, oral antidepressants; TRD, treatment resistant depression.

6. Efficacy

6.1 Efficacy of esketamine compared to quetiapine for adults with treatment-resistant Major Depressive Disorder

6.1.1 Relevant studies

The efficacy and safety of ESK NS compared to QTP XR in participants with treatment-resistant MDD with a current moderate to severe depressive episode is assessed in the ESCAPE-TRD study. ESCAPE-TRD is an open-label, single-blind (with raters unaware of group assignments), multicentre, phase 3b, randomized, active-controlled trial. Prior to randomisation the investigator ensured that participants had all necessary information for psychotherapeutic options available to ensure TRD patients are not only offered pharmacological treatment, but also psychotherapy. The study comprised four phases: an up-to-14-day screening phase, an 8-week acute phase, a 24-week maintenance phase, and a 2-week safety follow-up phase. Additionally, in ESCAPE-TRD ESK NS and QTP XR was given in addition to patients' current AD medication (continuing SSRI/SNRI) to which they had non-response, as suggested by the DMC in the previous assessment[70]. Together, the acute and maintenance phase is referred to as the treatment phase. The study is finalised, and thus no early data cut-off has been used in this application. In the ITT population, the median time in the study was 230 days in the group of patients treated with ESK NS + OAD, and 238 days in the group of patients treated with QTP XR + OAD. In the subgroup of patients with 3+ prior treatment failures, the median time in the study was 230.5 days in the ESK NS group and 237 days in the QTP XR group[65,66].

To evaluate the long-term safety of ESK NS, the SUSTAIN-3 study is included in the current submission. However, as long-term efficacy is important within this indication, efficacy data from SUSTAIN-3 is also included as a supplement to ESCAPE-TRD. SUSTAIN-3 is an open-label extension study and includes participants from the studies: TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, SUSTAIN-2 and participants from US study sites in ESKETINTRD3006. In brief, the definition of TRD applied in SUSTAIN-3 is non-response to an adequate trial of at least two ADs in the current episode of depression, one of which was observed prospectively[44]. SUSTAIN-3 had two open-label phases: a 4-week induction phase (if applicable) and a variable duration optimisation/maintenance phase. The study is final, and thus no early data cut-off has been used in this application. The ESCAPE-TRD and SUSTAIN-3 studies are summarised in Table 12. The studies are described in detail in Appendix A. Finally, efficacy and safety data from real-world evidence studies are summarised in section 6.1.5 and in section 9.1, respectively.

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ESCAPE-TRD, NCT04338321 (Janssen EMEA, 2023[65])	Randomised, open-label, rater-blinded, active-controlled, phase 3 study.	The study intervention was 32 weeks. The total duration of the study was approximately 36 weeks.	Participants who have treatment-resistant MDD with a current moderate to severe depressive episode.	ESK NS in combination with a continuing SSRI/SNRI. Participants <65 years: - Weeks 1-4: 56 mg (starting Day 1 dose), hereafter 56 mg or 84 mg twice a week - Weeks 5-8: 56 mg or 84 mg once weekly - From Week 9: 56 mg or 84 mg every two weeks or once weekly Participants 65 to 74 years: - Weeks 1-4: 28 mg (starting Day 1 dose), hereafter 28 mg, 56 mg, or 84 mg twice a week - Weeks 5-8: 28 mg, 56 mg or 84 mg once weekly - From Week 9: 28 mg, 56 mg or 84 mg every two weeks or once weekly	QTP XR in combination with a continuing SSRI/SNRI. Participants 18 to 64 years: - Days 1-2: 50 mg/day - Days 3-4: 150 mg/day - Day 5 or after: 300 mg/day (based on individual participant evaluation) Participants 65 to 74 years: - Days 1-3: 50 mg/day - Days 4-7: 100 mg/day - Day 8: 150 mg/day - Day 22 - not earlier: 300 mg/day (based on individual participant evaluation)	Remission at Week 8 (MADRS total score of ≤10, without discontinuation of any component of study intervention before Week 8), remission at Week 8 and no relapse until Week 32, CFB in MADRS total score (Week 32), CFB in MADRS total score (Day 8), CFB in MADRS individual items (Week 32), CFB in Clinical Global Impression – Severity (CGI-S) (Week 32), Clinical Global Impression – Change (CGI-C) scale score (Week 32), CFB in Patient Health Questionnaire 9-item (PHQ-9) (Week 32), CFB in Sheehan Disability Scale (Week 32), CFB in HRQoL assessed by the 36-Item Short Form Survey (SF-36) (Week 32), CFB in HRQoL assessed by Quality of Life in Depression Scale (Week 32), CFB in HRQoL assessed by EQ-5D-5L (Week 32), CFB in Work Productivity and Activity Impairment: Depression questionnaire score (Week 32), CFB in TEAEs (up to Week 35), CFB in TEAEs of special interest (up to Week 35), and CFB in Columbia-Suicide Severity Rating Scale (C-SSRS) (Week 32). All follow-up periods were predefined.
SUSTAIN-3, NCT02782104 (Janssen Research & Development, 2023[39])	An open-label, long-term extension, phase 3 study.	Two open-label phases: 4-week induction phase (if applicable) and a variable duration	Participants with TRD.	ESK NS Participants <65 years of age (induction): - Day 1: 56 mg - Day 4: 56 mg or 84 mg - Day 8, 11, 15, 18, 22 and 25: 56 mg or 84 mg Participants ≥65 years of age (induction):	N/A	Primary endpoints were CFB in computerised cognitive battery domain score: detection test score; CFB in computerised cognitive battery domain score: identification test score; CFB in computerised cognitive battery domain score: one card learning test score; CFB in computerised cognitive battery domain score: one back test score; CFB in computerised cognitive battery domain score: Groton Maze learning test score; CFB in Hopkins verbal learning

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
		optimisation/ maintenance phase.		- Day 1: 28 mg - Day 4: 28 mg or 56 mg - Day 8, 11, 15, 18, 22 and 25: 28 mg, 56 mg or 84 mg All patients (optimisation/maintenance): - 28 mg, 56 mg or 84 mg once weekly, depending on induction phase dosing and previous study participation		test-revised score; percentage of participants based on C-SSRS score; number of participants with TEAEs; CFB in heart rate; CFB in systolic and diastolic blood pressure; CFB in respiratory rate; and CFB in blood oxygen saturation. Secondary endpoints were CFB in MADRS total score; CFB in PHQ-9 total score; CFB in CGI-S score; CFB in Sheehan Disability Scale total score; CFB in EQ-5D-5L Valuation Index Score; CFB as assessed by EQ 5D-5L: sum score; and CFB in the Quality of Life in Depression Scale. All follow-up periods were predefined, and outcomes from the induction phase was assessed at up to 4 weeks, while the optimisation/maintenance phase was assessed at up to 72 weeks.

Abbreviations: CFB, change from baseline; CGI-C, Clinical Global Impression – Change; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; ESK, esketamine; HRQoL, health-related quality of life; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; N/A, not applicable; NS, nasal spray; PHQ-9, Patient Health Questionnaire 9-item; QTP, quetiapine; SF-36, 36-item Short-Form Health Survey; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TEAE, treatment-emergent adverse events; TRD, treatment resistant depression; XR, extended-release.

Sources: ClinicalTrials.gov, 2020[9]; Janssen EMEA, 2023[65]; ClinicalTrials.gov, 2016[77]; Janssen Research & Development, 2024[39].

6.1.2 Comparability of studies

The comparison of ESK NS and QTP XR is based on the head-to-head trial ESCAPE-TRD. However, as the SUSTAIN-3 study contributes to the evaluation of long-term safety of ESK NS and the efficacy data is presented as a supplement, a comparison of the ESCAPE-TRD and SUSTAIN-3 is provided here. SUSTAIN-3 is an open-label extension study without a comparator arm, specifically aimed at assessing the long-term safety of ESK NS. Therefore, SUSTAIN-3 serves as a valuable supplement to ESCAPE-TRD.

6.1.2.1 Comparability of patients across studies

Baseline characteristics for the full analysis set including all participants who were randomised in ESCAPE-TRD (the ITT population) and baseline characteristics for the subpopulation of patients with 3+ prior treatment failures are presented in Table 13. In addition, Table 13 presents characteristics of all participants in SUSTAIN-3 who were eligible to enter the study and who received at least one dose of study intervention (All Enrolled Analysis Set). Since patients in SUSTAIN-3 come from various parent studies, some baseline characteristics are marked as N/A in Tabel 13. This is because these data are only available in the individual parent clinical study reports and are not compiled in the SUSTAIN-3 clinical study report.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	ESCAPE-TRD (ITT population)		ESCAPE-TRD (3+ prior treatment failures)		SUSTAIN-3
	QTP XR + OAD (N = 340)	ESK NS + OAD (N = 336)	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)	ESK (N = 1,148)
Age in years, mean (SD)	45.7 (13.38)	44.3 (13.60)	[redacted]	[redacted]	49.6 (12.28)
Sex, n (%)					
Male	118 (34.7)	111 (33.0)	[redacted]	[redacted]	384 (33.4)
Female	222 (65.3)	225 (67.0)	[redacted]	[redacted]	764 (66.6)
Race, n (%)					
American Indian or Alaskan Native	N/A‡	N/A‡	[redacted]	[redacted]	1 (0.1)*
Asian	10 (5.9)‡	9 (6.0)‡	[redacted]	[redacted]	45 (3.9)*
Black or African American	7 (4.1)‡	5 (3.3)‡	[redacted]	[redacted]	45 (3.9)*
White	152 (89.4)‡	137 (90.7) ‡	[redacted]	[redacted]	996 (86.8)*
Other	N/A‡	N/A‡	[redacted]	[redacted]	29 (2.5)*
Multiple	N/A‡	N/A‡	[redacted]	[redacted]	10 (0.9)*
Unknown/not reported	1 (0.6)‡	0‡	[redacted]	[redacted]	22 (1.9)*
Body mass index (BMI), mean (SD)	27.46 (5.038), n=290	26.61 (4.920), n=282	[redacted]	[redacted]	28.8 (6.23)*
Hypertension status, n (%)					
Yes	N/A	N/A	[redacted]	[redacted]	271 (23.6)*Ω
No	N/A	N/A	[redacted]	[redacted]	877 (76.4)*Ω

	ESCAPE-TRD (ITT population)		ESCAPE-TRD (3+ prior treatment failures)		SUSTAIN-3
	QTP XR + OAD (N = 340)	ESK NS + OAD (N = 336)	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)	ESK (N = 1,148)
Stratification based on treatment failures (electronic case report form), n (%)					
2	211 (62.1)	204 (60.7)	[redacted]	[redacted]	N/A
≥3	129 (37.9)	132 (39.3)	[redacted]	[redacted]	N/A
Systolic blood pressure in mmHg, mean (SD)	122.1 (10.24)	121.7 (10.92)	[redacted]	[redacted]	N/A
Diastolic blood pressure in mmHg, mean (SD)	77.8 (8.11)	77.4 (7.91)	[redacted]	[redacted]	N/A
Pulse in bpm, mean (SD)	74.1 (10.17)	73.8 (10.30)	[redacted]	[redacted]	N/A
Age at MDD diagnosis, mean (SD)	34.8 (11.72)	33.5 (11.74)	[redacted]	[redacted]	N/A
Baseline MADRS total score, mean (SD)	31.0 (5.83), n=339	31.4 (6.06)	[redacted]	[redacted]	N/A
EQ-5D Health Status Index, mean (SD)	0.5 (0.23), n=336	0.4 (0.22), n=335	[redacted]	[redacted]	N/A
Duration of current episode in weeks, mean (SD)	64.6 (65.66)	68.8 (84.17)	[redacted]	[redacted]	N/A
Total number of depressive episodes, mean (SD)	3.6 (4.10)	3.4 (2.44)	[redacted]	[redacted]	N/A

Abbreviations: BMI, body mass index; EQ-5D, European Quality of Life Group, 5-Dimension; ESK, esketamine; ITT, intention-to-treat; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; N/A, not applicable; NS, nasal spray; OAD, oral antidepressants; QTP, quetiapine; SD, standard deviation ; XR, extended-release.

Notes: If a patient did not have a pre-dose value in SUSTAIN-3, the last record in the parent study was used. ‡ Collected only for participants who provided biomarker samples (n=170 for QTP XR and n=151 for ESK NS in the ITT population, n=73 for QTP XR and n=67 for ESK NS in the subgroup). * Data from parent study. ¤ Hypertension status is classified as Yes if hypertension is recorded in medical history.

Source: Janssen EMEA, 2023, Table 6, Table 7, and attachment TSIDEM05SGC[65]; Janssen EMEA, 2024[66]; Janssen Research & Development, 2023, Table 10[39].

In ESCAPE-TRD, participant demographic and clinical baseline characteristics were similar between the two treatment arms in the ITT population and in the subgroup with 3+ prior treatment failures, respectively. Overall, the ITT population and subgroup were similar, except from the duration of current episode which was longer in the subgroup (mean duration above 90 weeks) compared to in the ITT population (mean duration around 65 weeks). The available baseline characteristics from the SUSTAIN-3 population were similar to those of the ESCAPE-TRD ITT population and the subgroup with 3+ prior treatment failures.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In Table 14, characteristics of patients with TRD in Denmark (defined as two shifts in antidepressant treatment for MDD in the study by Gronemann et al. 2021[26]) as well as values used in the health economic model are presented.

Patient characteristics used in the model were based on ESCAPE-TRD trial[65]. Generally, participants in the ESCAPE-TRD trial are comparable to the Danish patient population for both age and gender distribution, although patients in ESCAPE-TRD were slightly younger than those in the Danish population. However, values used in the model cannot be compared directly to the Danish population due to the difference in indication (at least 3 vs. 2 prior treatment failures).

Table 14 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (Gronemann et al. 2021[26]) N=29,212	Value used in health economic model (ESCAPE-TRD, +3 prior treatment failures)
Age, mean (quartiles)	51.4 (36.2-66.8)	44 (N/A)
Sex, n (%)		
Male	10,366 (35.5 %)	32.9 %
Female	18,846 (64.5 %)	67.1 %

Abbreviations: N/A = not applicable.

Source: Gronemann et al., 2021, Table 1[26].

6.1.4 Efficacy – results per ESCAPE-TRD

In this section, results from the subgroup with 3+ prior treatment failures are presented. Results from the ITT population are presented in Reif et al. 2023[69]. Whilst the relative efficacy for ESK NS improves when focusing on the subgroup of 3+ prior failures, the absolute efficacy for ESK-NS in both subgroups is maintained across both the ≥2 and ≥3 subgroups[66,69].

The number and proportion of patients in the subgroup with 3+ prior treatment failures who discontinued the study in each treatment arm and the reason for discontinuation are presented in Table 15.

Table 15 Discontinuation in ESCAPE-TRD (subgroup with 3+ prior treatment failures)

	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)
Discontinued, n (%)	[redacted]	[redacted]
Primary reason for discontinuation, n (%)		
Adverse event	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Minimal required study drug dose cannot be tolerated	[redacted]	[redacted]
Non-compliance with study drug	[redacted]	[redacted]
Other	[redacted]	[redacted]
Subject refused further study treatment	[redacted]	[redacted]

Abbreviations: ESK, esketamine; NS, nasal spray; OAD, oral antidepressants; QTP, quetiapine; XR, extended-release.

Source: Janssen EMEA, 2024[66].

6.1.4.1 Remission at Week 8 and 32

[redacted] participants in the ESK NS + OAD arm and [redacted] participants in the QTP XR + OAD arm achieved remission at Week 8. The OR was [redacted]. These results statistically significantly favoured the ESK NS arm compared with the QTP XR arm. [redacted] participants in the ESK NS + OAD arm and [redacted] participants in the QTP XR + OAD arm were in remission at Week 32. The OR was [redacted] These results statistically significantly favoured the ESK NS + OAD arm compared with the QTP XR + OAD arm (Table 16 and [redacted]

Table 16 Remission at Week 8 and 32 (subgroup with 3+ prior treatment failures)

	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)
Week 8		
Subjects in remission, n (%)	[redacted]	[redacted]
Difference in percentage (95% CI)	Reference	[redacted]
Unadjusted OR (95% CI), p-value[a]	Reference	[redacted]
Week 32		
Subjects in remission, n (%)	[redacted]	[redacted]
Difference in percentage (95% CI)	Reference	[redacted]
Unadjusted OR (95% CI), p-value[a]	Reference	[redacted]

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ESK, esketamine; NS, nasal spray; OAD, oral antidepressants; OR, odds ratio; QTP, quetiapine; XR, extended-release.

Notes: Analysed using the NRI approach. [a] CMH chi-square tests.

Source: Janssen EMEA, 2024[66].

[redacted]

6.1.4.2 Source: Janssen EMEA, 2024[66].Response rate at Week 8 and 32

[redacted] participants in the ESK NS + OAD arm and [redacted] participants in the QTP XR + OAD arm achieved a response at Week 8. The OR was [redacted] These results statistically significantly favoured the ESK NS arm compared with the QTP XR arm. [redacted] participants in the ESK NS + OAD arm and [redacted] participants in the QTP XR + OAD arm achieved a response at Week 32. The OR was [redacted]. These results statistically significantly favoured the ESK NS + OAD arm compared with the QTP XR + OAD arm (Table 17 and [redacted]

Table 17 Response rate at week 8 and 32 (subgroup with 3+ prior treatment failures)

	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)
Week 8		
Subjects in response, n (%)	[redacted]	[redacted]
Difference in percentage (95% CI)	Reference	[redacted]
Unadjusted OR (95% CI), p-value[a]	Reference	[redacted]
Week 32		
Subjects in response, n (%)	[redacted]	[redacted]
Difference in percentage (95% CI)	Reference	[redacted]
Unadjusted OR (95% CI), p-value[a]	Reference	[redacted]

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ESK, esketamine; NRI, non-responder imputation; NS, nasal spray; OAD, oral antidepressants; OR, odds ratio; QTP, quetiapine; XR, extended-release.

Notes: Analysed using the NRI approach. [a] CMH chi-square tests.

Source: Janssen EMEA, 2024[66].

6.1.4.3 Change from baseline in MADRS score (Week 8 and 32)

The mean CFB in MADRS score was [redacted] in the ESK NS + OAD arm and [redacted] in the QTP XR + OAD arm, with a statistically significant difference of [redacted] at Week 8. The mean change from baseline in MADRS score was [redacted] in the ESK NS + OAD arm and [redacted] in the QTP XR + OAD arm, with a significant difference of [redacted] (Table 18).

Table 18 Change from baseline in MADRS score at week 8 and 32 (subgroup with 3+ prior treatment failures)

	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)
Week 8		
Subjects without BOCF imputation, n (%)	[redacted]	[redacted]
Least squares mean (LSM) for CFB on MADRS total score (95% CI)	[redacted]	[redacted]
Difference in LSM for CFB on MADRS total score (95% CI), p-value	Reference	[redacted]
Hedge's G for difference in LSM for CFB on MADRS total score (95% CI), p-value	Reference	[redacted]
Week 32		
Subjects without BOCF imputation, n (%)	[redacted]	[redacted]
LSM for CFB on MADRS total score (95% CI)	[redacted]	[redacted]
Difference in LSM for CFB on MADRS total score (95% CI), p-value	Reference	[redacted]
Hedge's G for difference in LSM for CFB on MADRS total score (95% CI), p-value	Reference	[redacted]

Abbreviations: ANCOVA, analysis of covariance; BOCF; baseline observation carried forward; CFB, change from baseline; CI, confidence interval; ESK, esketamine; LSM, least squares mean; MADRS, Montgomery-Asberg Depression Rating Scale; NS, nasal spray; OAD, oral antidepressants; QTP, quetiapine; XR, extended-release.

Notes: CFB on MADRS total score was analysed using ANCOVA models with treatment and baseline total MADRS scores. Missing data were imputed using a BOCF approach.

Source: Janssen EMEA, 2024[66]

6.1.4.4 Relapse-free after remission (Week 32)

[redacted] participants in the ESK NS + OAD arm and [redacted] participants in the QTP XR + OAD arm were in remission at Week 8 and relapse-free at Week 32 after remission. The adjusted OR was [redacted] These results statistically significantly favoured the ESK NS + OAD arm compared with the QTP XR + OAD arm (Table 19).

Table 19 Relapse-free after remission at week 32 (subgroup with 3+ prior treatment failures)

	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)
Subjects with relapse, n (%)	[redacted]	[redacted]
Subjects without relapse and discontinued after being in remission at week 8, n (%)	[redacted]	[redacted]
Remission at Week 8 and relapse-free at Week 32, n (%)	[redacted]	[redacted]
Difference in percentage (95% CI)	Reference	[redacted]
Adjusted OR (95% CI), p-value[a]	Reference	[redacted]

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ESK, esketamine; NRI, non-responder imputation; NS, nasal spray; OAD, oral antidepressants; OR, odds ratio; QTP, quetiapine; XR, extended-release.

Notes: Analysed using the NRI approach. [a] p-value for CMH row mean difference, adjusting for age groups (18-64; ≥65).

Source: Janssen EMEA, 2023, attachment TEFMADRLP01SGC[65].

6.1.5 Efficacy – results per SUSTAIN-3

As long-term efficacy is important within this indication, a short summary of the finding of SUSTAIN-3 (N=1,148) is provided here. In total, 458 subjects participated in the induction phase, and 1,110 subjects participated in the optimisation/maintenance phase. 420 (91.7%) of the participants in the induction phase continued to the optimisation/maintenance phase. Of the 1,110 participants who entered the optimisation/maintenance phase, 430 (38.7%) participants withdrew during the optimisation/maintenance phase. The median ESK NS exposure in SUSTAIN-3 was 45.8 months[85]. As SUSTAIN-3 was a safety study with the primary objective to investigate safety related to the long-term use of ESK NS, patients continued treatment in the trial for longer than expected in clinical practice aligned with the SmPC.

The change from induction baseline in MADRS total score to the last postbaseline assessment during induction showed a clinically meaningful reduction in depressive symptoms following 4 weeks of treatment with esketamine. The mean change was -12.8 (SD: 9.73). For the optimisation/maintenance phase, the results indicated that the decrease in depressive symptomatology appeared to be maintained with continued esketamine treatment. The mean change from optimisation/maintenance baseline in MADRS total score to the last post-baseline assessment during optimisation/maintenance was 0.2 (SD: 9.93). Further, the percentage of responders (i.e., participants who had ≥50% reduction in MADRS total score from induction baseline) increased from 15.0% on Day 8 to 50.6% on Day 28 and 49.2% at the last post-baseline assessment during the induction phase. The percentage of participants in remission (defined as MADRS total score ≤12) increased over time during the induction phase: 15.7% at Day 8, 35.9% at Day 28, and 35.6% at the last post-baseline assessment during induction. The percentage of participants in remission during the optimisation/maintenance phase was 48.5% at Week 112, and 49.6% at end the last postbaseline assessment during optimisation/maintenance[39]. These data highlight the long-term efficacy of ESK NS and show that the clinically meaningful reductions in depressive symptoms observed are sustained over time.

6.1.6 Efficacy – results per real-world evidence studies

A summary of European real-world evidence studies (main studies with >100 TRD patients) is included here to demonstrate the efficacy of ESK NS in clinical practice with a more heterogenous patient population covering a broader range of prior treatment trials and psychiatric comorbidities. These studies[86-89] show that the efficacy of ESK NS in a RCT setting is similar to the effectiveness observed in a real-world population with comorbidities.

Table 20 Overview of results from real-world evidence studies

	Patients treated with ESK NS (N)	Timepoint of assessment	ESK NS remission	ESK NS response
ESCAPE-TRD (3+ prior treatment failures)	132	Week 8 Week 32	[redacted]	[redacted]
Samalin et al.[87]	157	Month 1 Month 12	19.7% 28%	40.2% 61%
Martinotti et al. [88]	116	Month 1 Month 3	11.2% 40.6%	28.4% 64.2%
Molero et al.[89]	127*	Month 1 Month 3	20% 28%	40% 61%

Abbreviations: ESK, esketamine; NS, nasal spray.

* With MADRS scores available; Abbreviations: ESK, esketamine; NS, nasal spray.

A French study by Samalin et al. (2024)[97] analysed 157 patients with TRD who had previously received ESK NS during the French early access period and after reimbursement. Seventy-five percent of the patients experienced severe depression, with a mean MADRS total score of 32.1 (SD: 7.7). The median duration of depression was 10.5 years (interquartile range: 4.2; 21.2), and they had an average of 3 episodes in their lifetime. Additionally, 15.5% had a history of substance abuse, 14.9% had post-traumatic stress disorder, and 28.4 had anxiety disorder. The median number of previous lines of treatment was 6, with 45.5% had received neurostimulation in the current episode (ECT, rTMS, transcranial direct current stimulation). Most patients started treatment at 56 mg ESK NS and increased to 84 mg during the study with a median interval of 8.5 days. The median treatment duration was 19.4 weeks (interquartile range: 4.4-40.1); however, 79.6% discontinued treatment within 12 months. Among the 92 patients with an available MADRS score at the time of permanent discontinuation, 46% were responders and 36% were remitters, with only 13.4% discontinuing due to AEs. One month after ESK NS initiation, 40.2% achieved clinical response and 19.7% remission (median time to response was 5.7 weeks; 95% CI: 4.1, 8.4), with values rising to 61% and 28%, respectively, at 12 months.

The Italian REAL-ESK study by Martinotti et al. (2022)[88] included 116 patients with TRD treated with ESK NS. Patients had on average severe depression (MADRS score: 35 (SD: 8.53)); the mean duration of depression was more than 19 years and patients had on average been treated with 3.23 (SD: 1.89) adequate antidepressant trials in lifetime. 37%

had a psychiatric comorbidity and received ESK NS as adjunctive treatment to a vast number of different treatments including SSRIs/SNRIs, other ADs, mood stabilisers and antipsychotics. Clinical response rates improved from 28.4% at one month to 64.2% at three months, while remission rates increased from 11.2% to 40.6% after three months. Notably, 38% of those who were in remission at three months had not responded at one month. There were no significant differences in response rates between patients with and without psychiatric comorbidities.

Long-term effectiveness of ESK NS was assessed by Rosso et al. 2025[90] in the REAL-ESK study among 78 patients after 6 and 12 months, showing that 76.2% and 78.9% were responders/remitters, respectively.[90] A subpopulation analysis of REAL-ESK among 30 elderly patients with TRD (≥ 65 years) by d'Andrea et al. 2023[91] found that 53.3% of the patients experienced clinical response and 33.3% remission at three months 53.3% and 33.3% respectively. Furthermore, Chiappini et al. 2023[86] examined a subsample of 26 patients with a substance use disorder in the REAL-ESK study and noted a decrease in MADRS scores over time, indicating the efficacy of ESK NS, with no reported cases of misuse. Martinotti et al. 2023[92] investigated the effectiveness and tolerability of ESK NS in 70 patients with either bipolar TRD (n=35) or unipolar TRD (n=35). At three months, 57.14% of patients with unipolar TRD and 68.57% of bipolar TRD had a clinical response respectively, while the proportion of patients achieving clinical remission was 28.57% for unipolar TRD and 48.57% for bipolar TRD.

Finally, a recent Spanish study (INTEGRATE) by Molero et al. (2025) included 189 TRD patients who had not responded to at least three different AD strategies of which at least one was a combination or augmentation strategy. Among the patients 22.8% had received neuromodulation, mostly ECT (20.1%), while nearly 30% of patients had additional psychiatric conditions and more than 50% a general medical condition. The study found that 80.4% of participants achieved response or remission during the induction phase, with this increasing to 90% during the maintenance phase. Remission rates were reported at 9.5%, 18.7%, and 38.3% across the induction, optimization and maintenance phases, respectively[89].

Overall, these studies show results similar to patients treated with ESK NS in ESCAPE-TRD in which [redacted]% were in response at week 8 and [redacted]% were in remission at week 8.

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

A summary of results presented in section 6.1.4 is presented here in Table 21.

Table 21 Results from the comparative analysis of ESK NS + OAD vs. QTP XR + OAD (3+ prior treatment failures)

Outcome measure	QTP XR + OAD (N=129)	ESK NS + OAD (N=132)	Result (95% CI), p-value
Remission, Week 8	[redacted]		
Remission, Week 32	[redacted]		
Response rate, Week 8	[redacted]		
Response rate, Week 32	[redacted]		
LSM for CFB in MADRS score (95% CI), Week 8	[redacted]		
LSM for CFB in MADRS score (95% CI), Week 32	[redacted]		
Relapse-free after remission, Week 32	[redacted]		

Abbreviations: CFB, change from baseline; CI, confidence interval; ESK, esketamine; LSM, least squares mean; MADRS, Montgomery-Asberg Depression Rating Scale; NRI, non-responder imputation; NS, nasal spray; OAD, oral antidepressants; OR, odds ratio; QTP, quetiapine; XR, extended-release.Notes: Relevant notes are provided in the respective table in section 6.1.4. * OR adjusted for age groups (18-64; ≥65).

Source: Janssen EMEA, 2023[65]; Janssen EMEA, 2024[66].

7.1.4 Efficacy – results per [outcome measure]

N/A

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

As presented in Section 4, the cost-effectiveness analysis relied on a Markov cohort model. The calculation of the transition probabilities is described in this section.

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 22 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

Abbreviations: N/A = not applicable.

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

Treatment effect estimates used to modify transition probabilities are primarily based on the head-to-head ESCAPE-TRD trial.

An overview of the transition probabilities used in the base case analysis is presented in Appendix K. Transition probabilities utilised to model the re-treatment scenario are reported in Appendix L.

8.1.2.1 Treatment discontinuation

Discontinuation in acute and maintenance phase (weeks 5-8)

The discontinuation rates are treatment- and health state-dependent, and independent of prior lines of treatment. The discontinuation rates are informed by the observed data

in the subgroup (3+ prior treatment failures) obtained from the ESCAPE-TRD trial[65]. Refer to Table 117 in Appendix K for details.

The number of patients who discontinue each cycle was calculated by applying the appropriate risk of discontinuation directly to the number of patients in each health state at each cycle.

Discontinuation in response or remission phase

Patients in ESCAPE-TRD were followed for 32 weeks (8 weeks in the acute phase and 24 weeks in the maintenance phase).

Patients who discontinue treatment after achieving response or remission were assumed to remain in their respective health states. The probability of treatment discontinuation following response or remission was derived from the ESCAPE-TRD post hoc analysis, applied as a 2.13 % discontinuation rate per four-week cycle in the ESK NS arm and 2.04 % in the QTP arm.

ESK NS treatment discontinuation upon reaching recovery

The SmPC for ESK NS states that 'the need for continued treatment should be re-examined periodically'. It is well established that when remission has been achieved and sustained for a sufficient period of time, the risk of relapse falls. In a clinical setting, a declaration of a full functional recovery state raises the possibility that treatment can be discontinued or, if treatment is continued, the aim is prevention of a subsequent episode[93]. Full functional recovery is expected to be achieved after 6-9 months in a remission health state. As such, in the economic model, the definition of recovery is 9 months of relapse-free remission.

To estimate the probability of treatment discontinuation upon recovery, the probability was sourced from the SUSTAIN-1 study[72], where 35.4% of patients discontinued treatment with ESK NS immediately upon achieving recovery.

For the remaining patients, it was assumed that patients discontinue ESK NS over time (applied as 24.9% discontinuing rate per four-week cycle). This means that a proportion of patients continued ESK NS therapy for up to 2 years in remission, depending on the level of risk of relapse/recurrence.

This assumption is based on the natural history of disease as well as national and international guidelines, which recommend continuing treatment with current OADs for at least 6–12 months after remission to reduce the risk of relapse. The required duration of recurrence prevention treatment with the OADs beyond this period remains uncertain, ranging from 3 years to a lifetime[45,55-58].

QTP XR treatment discontinuation upon reaching recovery

As no information to inform long-term discontinuation for QTP was available, the assumptions for discontinuation described above for the ESK NS arm were applied to the QTP XR arm, following a conservative approach.

8.1.2.2 Mortality

Mortality is accounted for using two different sources for risk of death, which are applied concurrently: all-cause mortality risk, specific to age and gender adjusted for the background mortality based on Danish life tables, and suicide-related mortality risk, specific to each health state.

For the all-cause mortality, first, the model derives a weighted mortality risk for each age. This is weighted according to the proportion of males and females in the model's cohort. At the beginning of the model, the mortality risk for the baseline age of the cohort (i.e., 44 years in the 3+ prior treatment failures subgroup) is used.

The additional mortality from suicide attempts is also explicitly modelled, which is calculated by adding the annual probability of a fatal suicide attempt to the background annual age and sex specific probability of death. Given the limited suicide data from ESCAPE-TRD, the meta-analysis by Bergfeld et al. investigating suicidality in patients with TRD was used to estimate the incidence of completed suicides at 0.47 per 100 patient-years[24]. This rate is applied to the MDE state in the model.

While patients in the response state achieve ≥50% improvement from baseline in the MADRS score, they are still affected by the TRD symptoms. Excess mortality due to suicide during response is therefore included and assumed to be half of MDE (i.e., 0.00235). It is assumed that patients in remission and recovery had no excess mortality.

8.1.2.2.1 Initial treatment

Except where indicated, ESCAPE-TRD individual-level patient data was used to derive health state transition probabilities in the initial treatment line with ESK NS + OAD or QTP XR + OAD. The data used to derive transitions from ESCAPE-TRD include MADRS scores, relapse, and treatment discontinuation rates.

a) Transition Probabilities for Response, Remission and treatment discontinuation from MDE

Probability of transition from MDE to response, remission, and MDE on subsequent treatment were calculated using the observed case approach. At the end of cycles 1, 2, 3, 4, and 5, these transition probabilities were estimated by dividing the number of patients in response state, in remission state, and those discontinuing treatment without reaching response or remission. For example, in the ESK cohort (3+ prior treatment failures), there were 130 patients who were in MDE state on day 1 and who were not censored on day 36. Among these, 130 patients, 30 were in response state on day 36. Probability of transitioning from MDE to response in cycle 1 for the ESK cohort was then calculated as 30/130 = 23.08%.

b) Transition probabilities from response to remission, loss of response, relapse and discontinuation in response or remission

For estimation of transition probabilities from response to remission, loss of response and relapse, the number of patients who had the state transition in the trial arm was divided by the number of days for which patients in the same arm were at risk of the transition. This yielded a per patient-day rate of transition. The daily transition rate was multiplied by 28 to get the per-cycle transition rate (*r*). The 28-day rate was then converted to probability (*p*) with the formula: $p_{4-week} = 1 - e^{-r}$.

When calculating the rate of loss of response (i.e. from response to MDE on subsequent treatment), patients who had remitted were censored on the day of going to remission. For example, a patient who had a response, then remission, then a relapse, would be censored at the time of their remission for the purposes of loss of response rate calculation. Relapse after remission is calculated separately from the loss of response rate.

Given the low number of loss of response and relapse events, the transition probabilities for loss of response and relapse in the analysis are populated using the ITT population from the ESCAPE-TRD trial. All other transitions are based on the 3+ prior treatment failures subgroup.

c) Transition probability for Recurrence

Patients that achieve remission and recovery might experience a recurrence of an MDE and initiate subsequent treatment. As there is no sufficient follow-up data in ESCAPE-TRD to derive the probability of recurrence to model differences between treatment arms, a conservative assumption is used by setting the probability of recurrence equal to the relapse probability of ESK in both treatment arms (applied as 0.97% per four-week cycle)[94].

8.1.2.3 Subsequent Treatment

The probabilities of transitioning from MDE to response, from MDE to remission, and from response to remission in the subsequent treatment line were estimated by dividing the number of patients who made the transition by the number of days at risk of the transition, and converting this daily rate to a 28-day cycle probability as described above. Only two loss of response and three relapse events were recorded in this period in ESCAPE-TRD, therefore loss of response and relapse probabilities in the subsequent treatment line were derived from literature[20]. Details of this derivations are described in Appendix K. The model includes three subsequent treatment lines, that patients can initiate if they experience more relapses before transitioning to the non-specific treatment state. The division of subsequent treatment and non-specific treatment is made to capture the difference in probability of achieving response and remission in earlier vs later treatment lines as well as the increased risk of relapse in the later lines.

8.1.2.4 Non-specific Treatment

After exhausting three subsequent treatments, patients are assumed to transition to a best supportive care (a non-specific treatment mix) phase, where they could still achieve response or remission. This phase does not represent a single treatment given the heterogeneity of treatments given to patients at this late stage, who have failed multiple lines of treatment. In the absence of a clear best supportive care treatment the model uses weighted average cost estimates of OADs from two classes: SSRIs (escitalopram, sertraline, paroxetine, fluoxetine, citalopram, or fluvoxamine) and SNRIs (duloxetine or venlafaxine XR). The division of subsequent treatment lines and non-specific treatment (which both contain the same treatments, OADs) is made to capture the difference in probability of achieving response and remission in earlier vs later treatment lines as well as the increased risk of relapse in the later lines. Efficacy for the non-specific treatment phase were sourced from Edwards et al.[81]. Specifically, expert clinical opinion sourced from Edwards et al. provided estimates on the annual probability of remission or response. The 2-month probabilities are converted to a constant rate (r=-LN(1-p)/t), which is then converted to 4-week probabilities (p=1-exp(-r*t).

Only low rates of response (<10-25%) and sustained remission (≤12%) are achieved in current clinical practice for up to 3.5 years (refer to Appendix M). For the minority who achieve benefit, these patients are more likely than patients with treatment-responsive MDD to experience relapse and recurrence and have lower remission rates.

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

Described in Section 8.1.2, above.

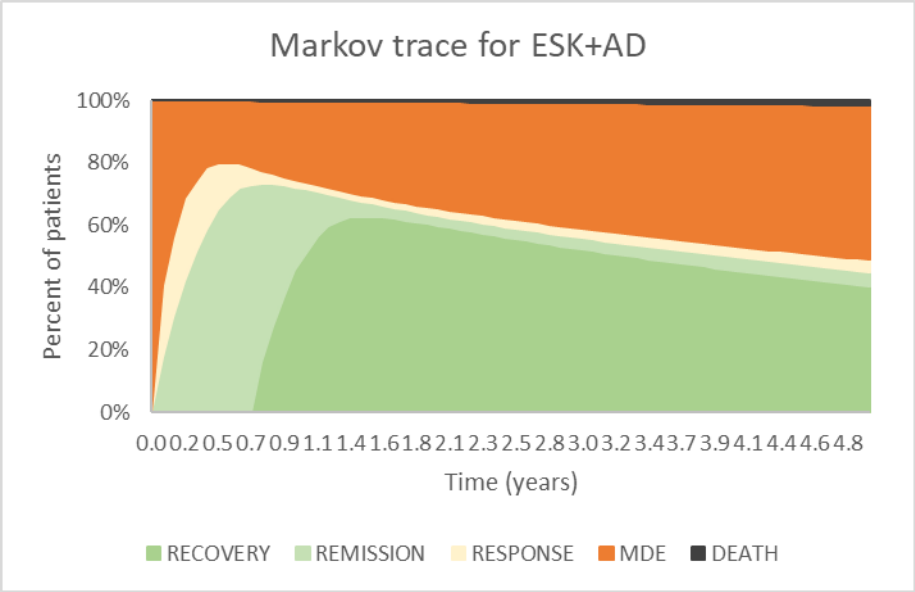
8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

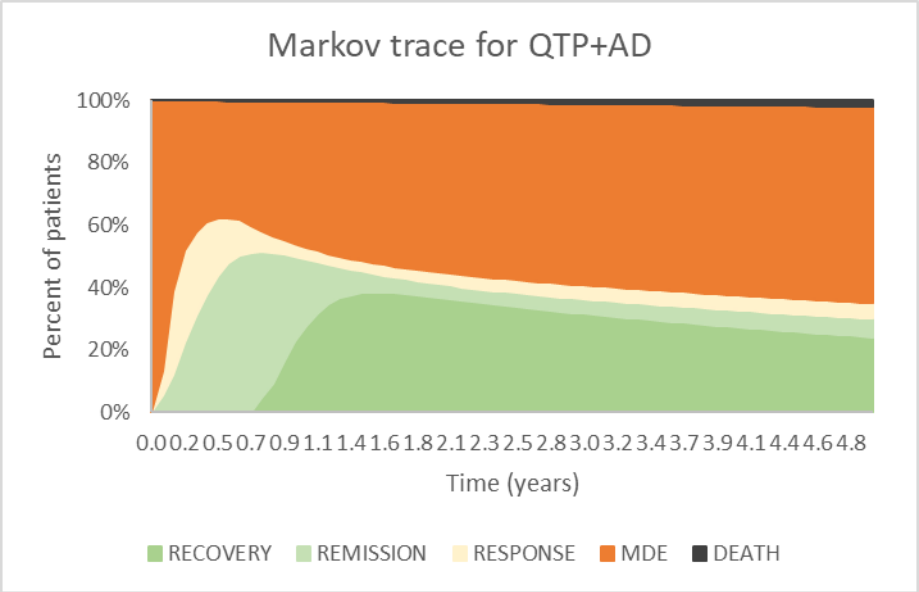
An overview of proportion of patients by health state in the ESK NS + OAD arm and QTP XR + OAD arm are provided in Figure 4 and Figure 5, respectively.

Figure 4 Health states distribution over time in the ESK NS + OAD arm



Abbreviations: AD, antidepressant; ESK, esketamine; MDE, major depressive episode; NS, nasal spray.

Figure 5 Health state distribution over time in the QTP XR + OAD arm



Abbreviations: AD, antidepressant; MDE, major depressive episode; QTP, quetiapine; XR, extended-release.

OS and PFS are not states being modelled in this analysis, hence Table 23is not applicable. An overview of the modelled average treatment length and the mean duration in the TRD health states are provided in Table 24 and Table 25, respectively. Table 25

Table 23 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A

Abbreviations: N/A, not applicable.

Table 24 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	MDE [years]	Response [years]	Remission [years}	Recovery [years)
ESK NS + OAD	0.774	0.134	0.109	0.428	0.102
QTP XR + OAD	0.577	0.148	0.108	0.261	0.060

Abbreviations: ESK, esketamine; MDE, major depressive episode, NS, nasal spray; QTP, quetiapine; XR, extended-relase

Table 25 Overview of modelled average duration in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	MDE [years]	Response [years]	Remission [years}	Recovery [years)
ESK NS + OAD	0.774	1.873	0.246	0.677	2.149
QTP XR + OAD	0.577	2.761	0.313	0.579	1.281

Abbreviations: ESK, esketamine; MDE, major depressive episode, NS, nasal spray; QTP, quetiapine; XR, extended-relase

9. Safety

9.1 Safety data from the clinical documentation

In ESCAPE-TRD, safety data for both the ITT population and the subgroup are provided for the safety analysis set including all randomised participants who received at least one dose of study intervention. AEs were measured as TEAEs. AEs were considered treatment-emergent if they started after administration of the first dose and until 14 days after the last dose of study medication. A serious AE was considered treatment emergent if it started within 30 days of the last dose of study medication. In SUSTAIN-3, safety data is provided for all participants who were eligible to enter the study and who received at least one dose of study intervention (All Enrolled Analysis Set). An AE that started in the induction or optimisation/maintenance phase and resulted in study discontinuation is counted as treatment-emergent.

Table 26 presents safety data from ESCAPE-TRD and from SUSTAIN-3. Dose reductions, discontinuation regardless of reason, and discontinuation due to AEs were more frequent in the QTP XR arm than in the ESK NS arm.

Generally, TEAEs and TEAEs possibly related to study drug were more frequent in the ESK NS + OAD arm than in the QTP XR + OAD arm. Serious TEAEs were similarly distributed across treatment arms and populations in ESCAPE-TRD. However, serious TEAEs were more frequent in SUSTAIN-3 than in ESCAPE-TRD. Although TEAEs and TEAEs possibly related to study drug were more common with ESK NS + OAD than QTP XR + OAD (Table 26), the TEAEs were typically transient in nature and the odds of discontinuation due to a TEAE were significantly lower in the ESK NS group compared to the QTP XR group (OR in subgroup with 3+ prior treatment failures: [redacted]).

In the full analyses set in ESCAPE-TRD, 92.0% of all TEAEs resolved on the same day with ESK NS + OAD vs 12.1 % with QTP XR + OAD. The majority of the most common TEAEs (occurring in ≥5 % of patients in either arm) most frequently resolved within ≤1 hour. For example, for dizziness, the most frequent TEAE reported with ESK NS + OAD, [redacted] of events resolved within 1 hour with ESK NS + OAD vs [redacted] of events with QTP XR + OAD, while [redacted] and [redacted] respectively, lasted 2 days or more. Similarly for somnolence, the most frequent TEAE reported with QTP XR + OAD, [redacted] of events resolved within 1 hour with ESK NS + OAD, vs just [redacted] of events with QTP XR + OAD. Furthermore, the median number of study intervention days with TEAEs was lower with ESK NS + OAD vs QTP XR + OAD: 16.0 vs 18.0 days, respectively, culminating in a significantly lower overall proportion of study intervention days with TEAEs with ESK NS + OAD vs QTP XR + OAD (median: [redacted] vs [redacted] of days, respectively; mean difference [95% CI]: [redacted])[15]. In addition, AEs during treatment with ESK NS + OAD generally become less frequent with ongoing treatment, and most are mild to moderate in severity[95].

In the previous assessment of ESK NS, DMC expressed a concern about dissociation as a TEAE[70]. However, in ESCAPE-TRD, while dissociation occurred in [redacted] of patients, the events were generally mild or moderate and transient in nature[65].

Moreover, relative to patients who received ESK NS + OAD, who generally maintained a stable weight and BMI over 32 weeks of treatment, patients treated with QTP XR + OAD more commonly experienced a TEAE of weight increased: [redacted] patients, respectively[15]. A recent review supports these findings, indicating that antipsychotics are associated with relatively more weight gain than most other psychotropic agents. Specifically, while the risk of weight gain with QTP is considered moderate, it is not deemed clinically relevant for ESK NS[96]. Weight gain can negatively impact quality of life, contribute to morbidity, and is a frequent reason for treatment discontinuation. Additionally, evidence suggests that low-dose QTP is associated with an increased risk of major adverse cardiovascular events[97].

Table 26 Overview of safety events in ESCAPE-TRD (full safety population [treatment phase] and subgroup safety population [treatment phase]) and SUSTAIN-3 (induction and maintenance severity phase)

	QTP XR + OAD (N=128) (subgroup, ESCAPE-TRD)	ESK NS + OAD (N=131) (subgroup, ESCAPE-TRD)	QTP XR + OAD (N=336) (ITT, ESCAPE-TRD)	ESK NS + OAD (N=334) (ITT, ESCAPE-TRD)	ESK NS (N=1,148) (SUSTAIN-3)
Number of AEs, n	[redacted]	[redacted]	825	6,737	N/A
Number and proportion of patients with ≥1 AEs, n (%)	[redacted]	[redacted]	262 (78.0)	307 (91.9)	1,089 (94.9)
Number of serious AEs*, n	[redacted]	[redacted]	19	20	N/A
Number and proportion of patients with ≥ 1 serious AEs*, n (%)	[redacted]	[redacted]	17 (5.1)	19 (5.7)	216 (18.8)
Number of Common Terminology Criteria for Adverse Events (CTCAE)† grade ≥ 3 events, n	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE† grade ≥ 3 events§, n (%)	N/A	N/A	N/A	N/A	N/A
Number of adverse reactions, n	[redacted]	[redacted]	435	6,138	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	208 (61.9)π	283 (84.7)π	858 (74.7)Ω
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	[redacted]	37 (11.0)	21 (6.3)	14 (3.1) of 458 during the induction phase and 202 (18.2) of 1.110 during the optimisation/maintenance phase¥
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	137 (40.3), n=340 (full analysis set)	78 (23.2), n=336 (full analysis set)	468 (40.8)

	QTP XR + OAD (N=128) (subgroup, ESCAPE-TRD)	ESK NS + OAD (N=131) (subgroup, ESCAPE-TRD)	QTP XR + OAD (N=336) (ITT, ESCAPE-TRD)	ESK NS + OAD (N=334) (ITT, ESCAPE-TRD)	ESK NS (N=1,148) (SUSTAIN-3)
Number and proportion of patients who discontinue treatment due to AEs, n (%)	[redacted]	[redacted]	37 (11.0)	14 (4.2)	72 (6.3)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ESK, esketamine; ITT, intention-to-treat; NS, nasal spray; OAD, oral antidepressants; QTP, quetiapine; TEAE, treatment-emergent adverse events; XR, extended-release.

Notes: * A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available. † CTCAE is not commonly addressed in this indication; therefore, the questionnaire necessary to assess it was not administered in the studies. ᵡ Defined as TEAE possibly related to study drug. ᵅ Defined as TEAE possibly related to intranasal drug including study drug relationships classified as possible, probable, and very likely. ᵻ The incidence of one or more TEAEs leading to dose reduction or interruption of treatment with ESK.

Sources: Janssen EMEA, 2024[66]; Janssen EMEA, 2023, Table 19 and Table 3[65]; McIntyre et al., 2024Sources: Janssen EMEA, 2024[66]; Janssen EMEA, 2023, Table 19 and Table 3[65]; McIntyre et al., 2024[15]; Janssen Research & Development, 2023, Table 9 and Table 36[39]2024[15]; Janssen Research & Development, 2023, Table 9 and Table 36[39].
Sources: Janssen EMEA, 2024[66]; Janssen EMEA, 2023, Table 19 and Table 3[65]; McIntyre et al., 2024[15]; Janssen Research & Development, 2023, Table 9 and Table 36[39]2024[15]; Janssen Research & Development, 2023, Table 9 and Table 36[39].
; Janssen Research & Development, 2023, Table 9 and Table 36[39].
Sources: Janssen EMEA, 2024[66]; Janssen EMEA, 2023, Table 19 and Table 3[65]; McIntyre et al., 2024[15]; Janssen Research & Development, 2023, Table 9 and Table 36[39].

In Table 27, the frequency of all serious TEAEs with a frequency of ≥ 5% recorded in the ESCAPE-TRD and SUSTAIN-3 are presented. In ESCAPE-TRD (ITT population and subgroup 3+ prior treatment failures) and in SUSTAIN-3, no serious TEAEs were recorded in ≥ 5% of study subjects.

Table 27 Serious adverse events in ESCAPE-TRD (full safety population [treatment phase] and subgroup [treatment phase]) and SUSTAIN-3 (induction and maintenance phase)

Adverse events	QTP XR + OAD (N=129) (subgroup, ESCAPE-TRD)		ESK NS + OAD (N=132) (subgroup, ESCAPE-TRD)		QTP XR + OAD (N=336) (ITT, ESCAPE-TRD)		ESK NS + OAD (N=334) (ITT, ESCAPE-TRD)		ESK NS N=1,148 (SUSTAIN-3)	
	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs
Adverse event, n (%)	0	0	0	0	0	0	0	0	0	0
...	0	0	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; ESK, esketamine; ITT, intention-to-treat; NS, nasal spray; QTP, quetiapine; XR, extended-release.

Notes: * A serious AE is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Source: Janssen EMEA, 2024[66]; Janssen EMEA, 2023, Table 21[65]; Janssen Research & Development, 2023[39].

9.1.1 Real-world evidence on substance abuse/misuse

In the subgroup analysis of patients with a substance use disorder from REAL-ESK, no cases of abuse or misuse of ESK NS were reported[86]. This is important as the DMC has previously expressed a concern about the potential for misuse of ESK NS[70]. Since the DMC published the existing ESK NS recommendation, a paper examining the association between ESK, and alcohol and substance misuse has been published[98]. The study used the United States Food and Drug Administration Adverse Event Reporting System to identify reported post-marketing AEs associated with ESK NS use. Although it remains inconclusive whether there is a direct link between new-onset alcohol and substance misuse and ESK NS due to limitations in the data, it was observed that the reporting ORs (ESK NS vs. acetaminophen) were significantly reduced for substance abuse, drug dependence, and drug abuse. Acetaminophen was chosen as comparator, as it is not known to be associated with alcohol and substance misuse. In a similar study based on the World Health Organization pharmacovigilance database, the authors found that ESK NS was not associated with an increased reporting odds ratios for any parameter of alcohol and/or substance use disorder[98].

9.1.2 Safety data used in the health economic model

Safety data used in the health economic model was sourced from the ESCAPE-TRD trial to align with the source of the efficacy data.

The model includes all AEs experienced by ≥5% of subjects in any of the treatment groups of the ESCAPE-TRD. The AE incidence in each treatment arm was calculated as the number of events that occurred during the acute phase of treatment (first 4 weeks) divided by the number of patients in each arm.

Table 28 Adverse events used in the health economic model

AE	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Blood pressure increased	[redacted]		ESCAPE-TRD[65]	All AEs that were experienced by ≥5% of subjects in any of the treatment groups (3+ prior treatment failures subgroup)
Dissociation			ESCAPE-TRD[65]	Same as above.
Dizziness			ESCAPE-TRD[65]	Same as above.
Dry mouth			ESCAPE-TRD[65]	Same as above.
Dysgeusia			ESCAPE-TRD[65]	Same as above.
Fatigue			ESCAPE-TRD[65]	Same as above.

Headache	[redacted]	ESCAPE-TRD[65]	Same as above.
Hypoaesthesia		ESCAPE-TRD[65]	Same as above.
Nausea		ESCAPE-TRD[65]	Same as above.
Paraesthesia		ESCAPE-TRD[65]	Same as above.
Somnolence		ESCAPE-TRD[65]	Same as above.
Vertigo		ESCAPE-TRD[65]	Same as above.
Vomiting		ESCAPE-TRD[65]	Same as above.
Sedation		ESCAPE-TRD[65]	Same as above.

Abbreviation: AE, a

9.2 Safety data from external literature applied in the health economic model

Not applicable.

Table 29 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A, not applicable.

10. Documentation of health-related quality of life (HRQoL)

Table 30 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	ESCAPE-TRD	HRQoL data was collected to estimate HSUVs for MDE, response, remission, and recovery.

Abbreviations: EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; HRQoL, health-related quality of life; HSUV, health-state utility value; MDE, major depressive episode.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The HRQoL of ESK NS was assessed in the ESCAPE-TRD trial among the patient population with 3+ prior treatment failures using the EQ-5D-5L and EQ-VAS instrument. In this section the results are presented.

10.1.2 Data collection

Patient-reported outcomes (PRO) were completed by the participants every four weeks. All PROs assessments were conducted/completed prior to clinical-rated assessment, any tests, other consultations or administration of ESK NS. The pattern of missing data and completion are reported in Table 31. The presented numbers were computed using the time windows around each visit that were pre-specified for the study.

Table 31 Pattern of missing data and completions

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	261	1 (0.38)	261	260 (99.6%)
Week 4	261	17 (6.51)	258	241 (93.4%)
Week 8	261	16 (6.13)	225	209 (92.9%)
Week 12	261	6 (2.30)	202	196 (97%)
Week 16	261	8 (3.07)	193	185 (95.9%)
Week 20	261	6 (2.30)	185	179 (96.8%)
Week 24	261	7 (2.68)	179	172 (96.1%)
Week 28	261	6 (2.30)	174	168 (96.6%)
Week 32	261	4 (1.53)	173	169 (97.7%)

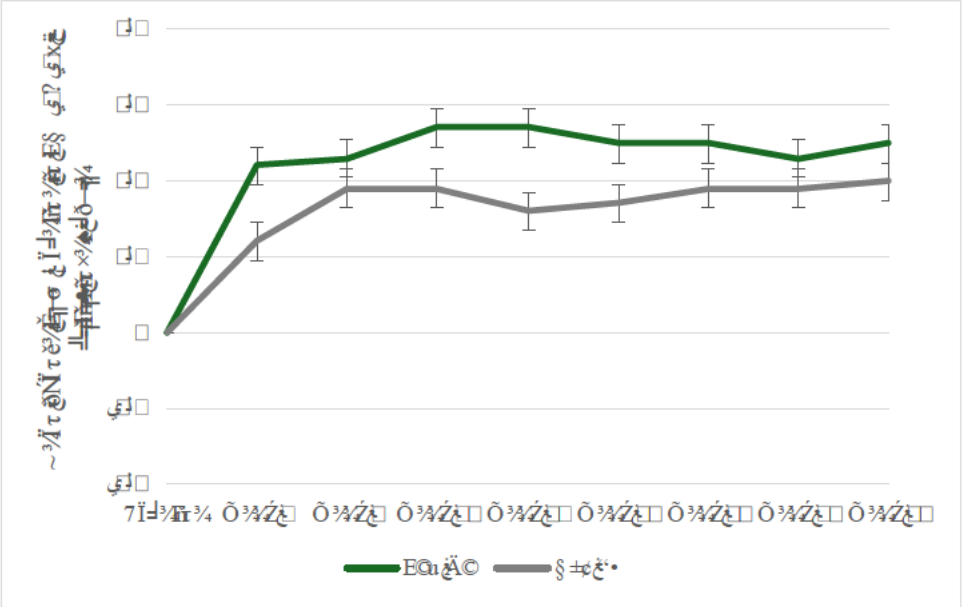
Abbreviations: HRQoL, health-related quality of life.

10.1.3 HRQoL results

The mean change from baseline for the EQ-5D-5L is presented in Figure 6 for index values and in Figure 7 for VAS scores. The analysis set includes all randomized subjects with 3+ prior treatment failures who received any amount of study treatment and completed at least one assessment at baseline. The analyses were conducted using on-treatment visits, and imputing missing data using a Baseline Observation Carried Forward (BOCF) approach. Least-Square (LS) means and difference between treatments were then estimated using ANCOVA models at each visit, including only baseline value as an

adjustment variable. Results at baseline and relevant timepoints are presented in Figure 6 for the utility index values and in Table 33 for VAS scores.

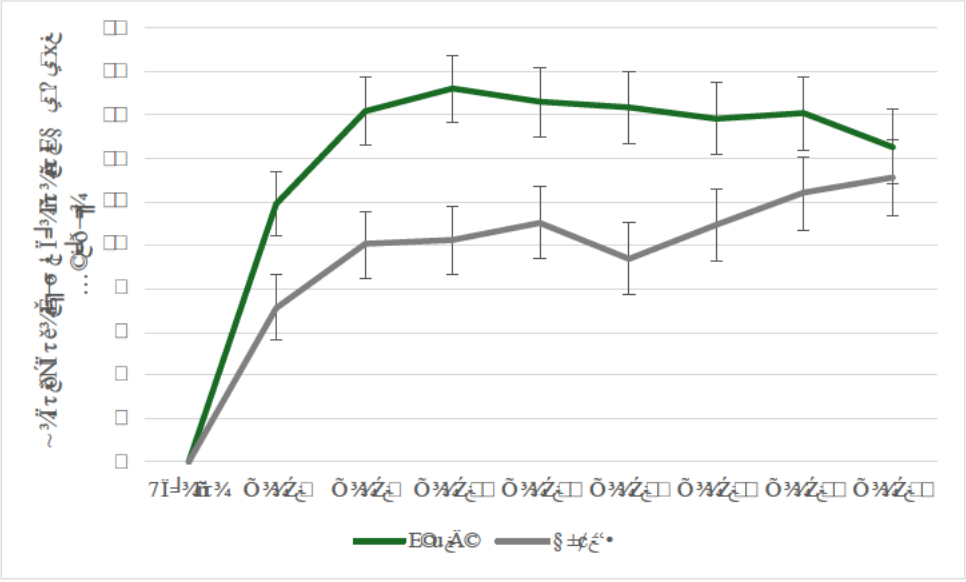
Figure 6 Mean change from baseline through the different data collection time points for both the ESK NS and QTP XR, EQ-5D-5L with utility index values



Abbreviations: EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; ESK, esketamine; NS, nasal spray; QTP, quetiapine; XR, extended-release.

Note: Standard deviation represents the measure of uncertainty.

Figure 7 Mean change from baseline through the different data collection time points for both the ESK NS and QTP XR, VAS scores



Abbreviations: ESK, esketamine; NS, nasal spray; QTP, quetiapine; VAS, visual analogue scale; XR, extended-release.

Note: Standard deviation represents the measure of uncertainty.

Table 32 HRQoL EQ-5D-5L summary statistic, utility index scores

	Intervention		Comparator		Intervention vs. comparator*
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
Baseline	132	0.44 (0.27)	128	0.41 (0.28)	N/A
Week 4	128	0.65 (0.02)	115	0.54 (0.02)	0.11 (0.04,0.17), 0.0011
Week 8	119	0.65 (0.02)	91	0.62 (0.02)	0.03 (-0.04,0.10), 0.3684
Week 12	113	0.69 (0.02)	83	0.62 (0.02)	0.07 (0.01,0.13), 0.0186
Week 16	110	0.70 (0.02)	76	0.59 (0.02)	0.11 (0.05,0.17), 0.0008
Week 20	106	0.68 (0.02)	74	0.59 (0.02)	0.08 (0.02,0.15), 0.0127
Week 24	101	0.67 (0.02)	73	0.61 (0.02)	0.06 (-0.01,0.12), 0.0943
Week 28	94	0.65 (0.02)	73	0.62 (0.02)	0.04 (-0.03,0.11), 0.2571
Week 32	97	0.67 (0.02)	72	0.62 (0.02)	0.04 (-0.02,0.11), 0.1976

Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; HRQoL, health-related quality of life; N/A, not applicable; SD, standard deviation.
*Least square means differences

Table 33 HRQoL EQ-5D-5L summary statistic, VAS scores

	Intervention		Comparator		Intervention vs. comparator*
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p-value
Baseline	131	46.7 (18.4)	129	45.1 (17.5)	N/A
Week 4	127	57.84 (1.48)	127	53.04 (1.50)	4.80 (0.65,8.95), 0.0237
Week 8	119	62.11 (1.54)	119	55.93 (1.55)	6.18 (1.88,10.48), 0.0050
Week 12	114	63.12 (1.54)	114	56.16 (1.55)	6.96 (2.65,11.27), 0.0017
Week 16	110	62.51 (1.63)	110	56.92 (1.64)	5.58 (1.04,10.13), 0.0162
Week 20	106	62.29 (1.63)	106	55.27 (1.64)	7.02 (2.47,11.57), 0.0026
Week 24	101	61.78 (1.67)	101	56.85 (1.69)	4.93 (2.0.25,9.61), 0.0389
Week 28	96	61.98 (1.71)	96	58.30 (1.72)	3.68 (-1.11,8.46), 0.1315
Week 32	97	60.48 (1.74)	97	59.02 (1.75)	1.46 (-3.40,6.32), 0.5543

Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; HRQoL, health-related quality of life; N/A, not applicable; SD, standard deviation; VAS, visual analogue scale.

*Least square means differences

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The health economic model uses EQ-5D-5L data from ESCAPE-TRD to inform the health state utility values. Responses to the EQ-5D-5L are converted to a utility score, a weighted heath state index using the value set reported by Jensen et al., 2021[99]. Age-

adjustment was conducted following the DMC method guide[100]; however, as the base case time-horizon of the model is 5 years age-adjustments were only activated in the 7-year time-horizon scenario.

The utilities are stratified by health states (MDE, response, remission, recovery). For both MDE and remission a time dependent approach is used, where a different utility value is assigned based on the time spent in the health state. For each health state listed in the first column of Table 34, the mean of utility values from patients regardless of randomization to ESK NS or QTP XR who were in the health state on the day of the EQ-5D-5L administration was used in the model as the health state utility. For each remission tunnel state, only utility values obtained during the cycle were included in the estimation. For example, utility in remission cycle 3 state was calculated as the mean utility score from patients who were in remission at the day of the EQ-5D-5L administration and who have been in remission for at least 56 days but no more than 84 days. There were only two EQ-5D-5L responses obtained from patients who have been in remission for at least eight cycles (i.e. at least 224 days). For this reason, remission cycle 9 and recovery utility values were assumed to be equal to the utility value of remission cycle 8.

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A. The disutility calculations are based on external literature described in 10.3.4.

10.2.3 HSUV results

Danish HSUV used in the base case analysis are summarised in Table 34.

Table 34 Overview of health state utility values [and disutilities]

	N	Results (standard error [95% CI])*	SE	Instrument	Tariff (value set) used	Comments
HSUVs						
MDE, cycle 1	288	0.423 (0.401 to 0.464)	0.016	EQ-5D-5L	DK	Estimate is based on mean of both trial arms for the sub-group, patients with +3 prior treatment failures.
MDE, cycle 2	151	0.560 (0.512 to 0.607)	0.024	EQ-5D-5L	DK	
MDE, cycle 3	77	0.605 (0.542 to 0.669)	0.032	EQ-5D-5L	DK	
MDE, cycle 4	49	0.555 (0.472 to 0.639)	0.043	EQ-5D-5L	DK	
MDE, cycle 5	35	0.574 (0.467 to 0.681)	0.055	EQ-5D-5L	DK	
Response	314	0.733 (0.71 to 0.756)	0.012	EQ-5D-5L	DK	
Remission, cycle 1	147	0.805 (0.776 to 0.834)	0.015	EQ-5D-5L	DK	
Remission, cycle 2	122	0.818 (0.784 to 0.852)	0.017	EQ-5D-5L	DK	

	N	Results (standard error [95% CI])*	SE	Instrument	Tariff (value set) used	Comments
Remission, cycle 3	111	0.831 (0.801 to 0.861)	0.015	EQ-5D-5L	DK	
Remission, cycle 4	98	0.857 (0.827 to 0.886)	0.015	EQ-5D-5L	DK	
Remission, cycle 5	81	0.868 (0.836 to 0.9)	0.016	EQ-5D-5L	DK	
Remission, cycle 6	64	0.860 (0.821 to 0.898)	0.020	EQ-5D-5L	DK	
Remission, cycle 7	45	0.883 (0.842 to 0.923)	0.021	EQ-5D-5L	DK	
Remission, cycle 8	15	0.884 (0.832 to 0.936)	0.026	EQ-5D-5L	DK	
Remission, cycle 9	NA	0.884 (0.832 to 0.936)	0.026	EQ-5D-5L	DK	Assumed equal to remission cycle 8 utility
Recovery	NA	0.884 (0.832 to 0.936)	0.026	EQ-5D-5L	DK	
Disutilities are based on external literature. Refer to Table 36.						

Abbreviations: DK, Denmark; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; MDE, Major depressive episode; SE, standard error.
*Patients could have contributed more than one utility score for a health state

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

N/A. Only used for disutilities.

10.3.2 Data collection

N/A. Only used for disutilities.

10.3.3 HRQoL Results

N/A. Only used for disutilities.

10.3.4 HSUV and disutility results

To account for disutilities associated with AEs, existing literature was used to inform decrements in the CEM. Mean AE duration was based on AE events from both ESK NS + OAD and QTP XR + OAD arms from the ESCAPE-TRD[9] and was calculated by summing the number of days with each AE during the first four weeks and dividing the sum by the number

of patients who had at least one record of the AE during the first four weeks. The mean duration in days was then converted to weeks. This decrement is added to the utility only for patients on treatment; it is assumed that patients who are not on treatment do not experience any AEs. AEs associated with treatment are assessed only in the induction treatment phase and not in the maintenance phases as it is assumed that patients are likely to have adapted well to the treatment by this time.

An overview of the literature health state utility values is presented in Table 35.

Table 35 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	All HSUV are measured in the ESCAPE-TRD trial. Disutilities are based on external literature. Refer to Table 36.			

Abbreviations: CI, confidence interval; HSUV, health state utiliy values.

Table 36 Overview of literature-based health state utility values

	Decrement (SE)	Instrument	Tariffs (value set) used	Percent of AEs resolved in one day in ESCAPE-TRD[65]	Comments
Dizziness	-0.085 (0.021)	EQ-5D	UK	[redacted]	Source: Sullivan et al.[78]
Dry mouth	-0.010 (0.003)	36-Item Short Form Survey (SF-36)	US		Revicki et al.[79]
Fatigue	-0.085 (0.021)	EQ-5D	UK		Assumed to be the same as for dizziness
Headache	-0.115 (0.029)	EQ-5D	UK		Source: Sullivan et al.[78]
Nausea	-0.065 (0.061)	EQ-5D	UK		Source: Sullivan et al.[78]
Somnolence	-0.085 (0.021)	EQ-5D	UK		Assumed to be the same as for dizziness
Vertigo	-0.085 (0.021)	EQ-5D	UK		Assumed to be the same as for dizziness
Vomiting	-0.065 (0.016)	EQ-5D	UK		Assumed to be the same as nausea

	Decrement (SE)	Instrument	Tariffs (value set) used	Percent of AEs resolved in one day in ESCAPE-TRD[65]	Comments
Sedation	-0.085 (0.021)	EQ-5D	UK	[redacted]	Assumed to be the same as for dizziness

Abbreviations: EQ-5D, European Quality of Life Group, 5-Dimension; N/A, not applicable; SE, standard error; SF-36, 36-Item Short Form Survey. Note: The following adverse events are included in the model; however, no disutilities were reported to be associated with them: Blood pressure increased, dissociation, hypoaesthesia, paraesthesia, dysgeusia

Table 37 Duration of adverse events in ESCAPE-TRD (3+ prior treatment failures)

	Mean duration of adverse event (weeks)		Average duration in the health economic model (weeks)
	ESK NS	QTP XR	
Dizziness	[redacted]		0.69
Dry mouth			1.43
Fatigue			1.21
Headache			0.87
Nausea			0.40
Somnolence			1.29
Vertigo			0.39
Vomiting			0.16
Sedation			0.73

11. Resource use and associated costs

The model considers the following two cost categories: pharmaceutical costs, administration costs, disease management cost and AE-related costs and patient costs, consistent with the restricted societal perspective as described in the DMC guidelines[68]. All costs are valued in 2025 Danish Krone (DKK).

11.1 Medicines - intervention and comparator

The dosage for the pharmaceuticals (intervention and comparator) applied in the model are summarized in Table 38.

In the base case analysis, the average number of devices used per visit for the ESK NS arm were obtained from the ≥ 3 prior treatment failures subgroup from the ESCAPE-TRD trial for each treatment phase: induction phase (week 0-4), maintenance phase (week 5-8), maintenance phase (week 9-40).

The average dose for ESK NS in recovery (i.e., maintenance treatment after 9 uninterrupted cycles in the remission state) was derived from SUSTAIN-1[94]. The estimate was informed by data from 49 patients. The average dose per administration and the number of administrations for the QTP arm were obtained from the ≥ 3 prior treatment failures subgroup from the ESCAPE-TRD data.

ESK NS is available in a fixed 28 mg dosage per each device. However, since ESK NS comes in packs of either 2 or 3 units of 28 mg, it is assumed that the packs can be split. Hence, vial sharing is considered in the current model. Cost of wastage per each pack of 3 devices is therefore not considered in the base case.

Medicine costs included in the health economic analysis are provided in the model's tab [*Medicine*]. If multiple packages of the medicine (including co-medication) were available, the lowest price per mg was used in the model.

Table 38 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
ESK NS, acute phase (week 0-4	63 mg*	100%	Approximately every 4 days	Yes
ESK NS, maintenance (week 5-8)	72 mg**	100%	Approximately every 7 days	Yes
ESK NS, maintenance (week 9-40)	75 mg***	100%	Approximately every 8 days	Yes
ESK NS, maintenance in recovery (week 40+)	72 mg****	100%	Approximately every 10 days	Yes
QTP XR	193 mg	100%	Every day	Yes

Abbreviations: ESK, esketamine; NS, nasal spray; QTP, quetiapine; XR, extended-release.

Note: A total of 35.4% of patients were assumed to discontinue ESK NS immediately upon achieving recovery. The rest is assumed to discontinue ESK NS after a maximum period of two years (applied as 24.9% per four-week cycle) after the acute treatment period (i.e., two years after first achieving remission). The same assumptions were adaopted in the QTP arm, following a conservative approach.
*Average number of devices per session = 2.261
**Average number of devices per session 2.591
*** Average number of devices per session = 2.667
**** Average number of devices per session = 2.571

11.2 Medicines– co-administration

In the model, ESK NS and QTP XR are administrated in combination with either SSRI or SNRI. A mix of SSRI and SNRIs used in clinical practice and in line with the Danish treatment recommendation[101] for adult patients with unipolar depression is displayed in

Table 39. The frequency of administration and dosage the SSRI and SNRIs are based on the ESCAPE-TRD trial and were assumed to remain constant across all treatment phases.

All patients were initiated, on 1 of 4 OADs from two classes: a SSRI (escitalopram, sertraline, paroxetine, fluoxetine, citalopram, or fluvoxamine), or a SNRI (duloxetine or venlafaxine XR). Treatment with SSRI and SNRI is continuous and patients in long-term treatment with OADs (> 2 years) should be considered min. one time during the year with respect to whether treatment indication remains[101].

The medication cost for co-administration was calculated as the weighted acquisition cost per dose for a 4-week cycle. As there are no specific recommendations or a defined standard of care within the SSRI/SNRI drug classes, an even market share distribution (12.5% per treatment) was applied. This assumption only impacts the drug acquisition costs, but as they are similar for all OADs the distribution in market share does not have a big impact on the results.

Co-medications used in the model are reported in Table 39.

Table 39 Co-medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Duloxetine	120 mg	100 %	Every day	No
Escitalopram	20 mg	100 %	Every day	No
Sertraline	200 mg	100 %	Every day	No
Venlafaxine	225 mg	100 %	Every day	No
Paroxetine	50 mg	100 %	Every day	No
Fluoxetine	80 mg	100 %	Every day	No
Citalopram	60 mg	100 %	Every day	No
Fluvoxamine	50 mg	100 %	Every day	No

11.3 Administration costs

ESK NS is intended to be self-administered by the patient under the direct supervision of an HCP[56]. A treatment session consists of nasal administration of ESK NS and a post-administration observation period. Both administration and post-administration observation of ESK NS are assumed to be carried out in an appropriate clinical setting (i.e., outpatient clinics).

Based on the previous DMC analysis[35], the following assumptions were made: an HCP will assist the patient during self-administration of ESK NS and supervise the subsequent post-dose observation period. It is assumed that one HCP can supervise three patients simultaneously during post-dose observation. Observation time for ESK NS is estimated at approximately 90 minutes, while it is assumed that an HCP spends 60 minutes managing the drug administration. Additionally, it is assumed that patients will have a 30-

minute individual consultation with a resident doctor each month to monitor treatment effectiveness. This was assumed to occur simultaneously with the administration of ESK NS. An outpatient DRG tariff was assumed to cover the costs associated with a resident doctor.

Post-administration observation periods and regular clinical visits are common practices in Danish psychiatry. Danish clinicians have extensive experience with observation periods, as seen with treatments like long-acting antipsychotic olanzapine pamoate and ECT[102,103]. Regular visits, such as biweekly or monthly, are also standard for maintenance treatment with long-acting antipsychotics[104,105]. In line with the product characteristics of ESK NS[56], the availability of blood pressure monitoring equipment is generally required in addition to a chair or bed during administration. These resources are already standard in Danish healthcare facilities and do not necessitate major infrastructure changes. Costs for outpatient clinic facilities are excluded as they are generally covered under standard clinic operations.

As for the QTP XR arm, no costs associated with the mode of administration were assumed as this is intended for oral use. The same assumption applies to all co-medicines. Assumptions concerning resource use, frequency, and unit costs are presented in Table 40.

Table 40 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Administration – ESK NS	Approximately every 4 days (week 0-4), 7 days (week 5-8), 8 days (week 9-40), 10 days (week 41+)	2,168	SENGEDAGE. DRG outpatient visit ("psykiatritakster")	DRG 2025[106]
Post-administration observation – ESK NS	Approximately every 4 days (week 0-4), 7 days (week 5-8), 8 days (week 9-40), 10 days (week 41+)	464	Nurse, hourly rate	DMC catalogue for unit costs (2024)[73]

Abbreviations: DMC, Danish Medicines Council; DRG, diagnosis-related group; ESK, esketamine.

11.4 Disease management costs

Calculation of disease management costs associated with MDE

To estimate the direct medical care costs associated with the different health states of the model i.e. MDE, response, remission and recovery, real-world data on the healthcare utilization of SSRI and SNRI used to treat TRD patients in Denmark was used. The source used is the Danish study TRIDEN: Treatment Resistant Depression in Denmark[83]. The study, sponsored by Johnson and Johnson, was conducted by an external research group at Bispebjerg and Frederiksberg Hospital. The purpose of the study was to describe treatment patterns and analyse healthcare utilisation of TRD patients, using nationwide Danish registry data.

TRIDEN reported average healthcare utilization in the first year after TRD, given for patients treated with SSRI or SNRI as first line treatment. The reported utilization was used to calculate the disease management cost associated with the different health states of the model. The reported utilization is the best available data to estimate the yearly costs associated a depressive episode amongst TRD patients.

The average healthcare utilization by TRD patients treated with SSRI or SNRI in the first year after TRD reported in the TRIDEN study was applied for the costs associated with MDE. The costs are presented in Table 41.

The healthcare utilisation used to calculate the cost associated with a health state MDE was acute hospitalisation days, elective hospitalisation days and emergency department visits within psychiatry. Furthermore, inclusion of the reported outpatient and home visits in the calculation of the cost for the health states would create a double counting for the ESK NS patients as the outpatient visits are accounted for in the administration cost. On the other hand, the exclusion of the outpatient and home visits from the MDE cost estimations could potentially underestimate the costs for patients in MDE treated with QTP, as these activities are not included in the administration costs due to the oral administration of QTP.

Somatic healthcare utilisation was also used to calculate the cost associated with the MDE health state. Lastly, general practitioner (GP) visits were also included in the calculation of the cost associated with the MDE health state.

Note that the reported healthcare utilization, deriving from TRIDEN, covers a TRD population consisting of both mild, moderate and severe patients. Additionally, the reported utilization was not limited to patients experiencing MDE, as the registry did not differentiate between patients in MDE, response and remission in the registry. Consequently, the costs associated with the MDE health state is most likely underestimated. As patients treated with ESK NS + OAD spend less time in the MDE health state compared to patients treated with QTP XR + OAD, this is expected to be a conservative approach.

The reported healthcare utilisation was multiplied with associated DRG 2025 tariffs[106] and unit costs from the DMC catalogue for 2024[73], which have been adjusted to 2025 prices. The exact frequency of healthcare utilisation is detailed in Appendix N.

Table 41 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Psychiatric contacts				
Acute hospitalisation, days	Approximately every 3rd month	4,333	SENGEDAGE. DRG outpatient visit ("psykiatritakster")	DRG 2025[106]
Elective hospitalisation, days	Approximately once every year	4,333	SENGEDAGE. DRG outpatient visit ("psykiatritakster")	DRG 2025[106]

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
ED visits	Approximately once a month every 5th year	2,168	N/A	DRG 2025[106]
Outpatient visits	Approximately every 2nd month	2,168	N/A	DRG 2025[106]
Home visits	Approximately every 6th month	2,168	N/A	DRG 2025[106]
Somatic contacts*				
Acute hospitalisation, days	Approximately every 6th month	24,384	19MA02: Depressive neuroser	DRG 2025[106]
Elective hospitalisation, days	Approximately once every year	24,384	19MA02: De-pressive neuroser	DRG 2025[106]
ED visits	Approximately once every 2nd year	2,571	19MA98: MDC19 1-dagsgruppe, pat. mindst 7 år	DRG 2025[106]
Outpatient visits	Approximately every 4th month	2,571	19MA98: MDC19 1-dagsgruppe, pat. mindst 7 år	DRG 2025[106]
Doctor visit (GP)	Approximately every month	157	Konsultation	DMC 2024[73]

Abbreviations: DMC, Danish Medicines Council; DRG, diagnosis-related group; ED, Emergency Department; GP, general practitioner.*Note: cost applied for somatic acute hospitalization equals the DRG-2025 tariff 24,384 as the number of hospitalisation days is less than four and consequently the "langliggertakst" is not applied. The exact frequency of psychiatric and somatic contacts is reported in Appendix N.

Calculation of disease management cost for the remission, response and recovery health states

The cost of disease management of patients that have failed 3+ prior treatments who are in a response and remission health state is assumed to be significantly lower as patients are expected to reduce the number of acute hospitalisations, outpatient resources etc. Due to lack of Danish data that can be used to estimate the costs of disease management for patients in response, remission and recovery, data from a Swedish study by Ekman et al. 2023[82] is used to estimate the costs. The study reports cost rates of €7,042 per month during a depressive episode and €993 per month during remission. The cost of disease management in the remission health state was estimated by dividing 7.042 with 993 resulting in a rate of 7.09. This rate was then used to calculate the cost associated with the remission health state by dividing the MDE health state cost per 4-week cycle (9,972 DKK) by 7.09. Cost associated with the response health state was assumed to be an average of MDE and remission, and costs associated with recovery were assumed to be the same as remission (Table 42).

Table 42 Average cost per cycle associated the MDE, remission, response and recovery health states applied in the model

Health states	Unit cost [DKK]	Reference
MDE	9,971	Average based disease management costs associated with MDE. Refer to Table 41.
Response	5,689	Assumed the average of MDE and Remission state
Remission	1,406	Calculated from MDE state cost using a rate of 7.09 derived from Ekman et al. 2013
Recovery	1,406	Assumed equal to remission state

Abbreviations: MDE, major depressive episode.

11.5 Costs associated with management of adverse events

The costs associated with the management of AEs were estimated using InteraktivDRG[107]. AEs associated with treatments are assumed to occur during the acute phase of treatment (i.e., first model cycle), aligning with the application of AE utility decrements, as treatment-related AEs were assumed to be associated with treatment initiation instead of occurring on an ongoing basis throughout the entire treatment course. They are not considered in the continuation and maintenance phases as it is assumed that patients will have adjusted well to treatment by this time. The associated costs with the management of each AE were multiplied by the frequency reported in Table 28.

HCP supervision and post-administration observation are required to monitor AEs and confirm that the patient is clinically stable before they leave the clinic where ESK NS is administered. Thus, as a cost is assigned to the observation of patients in the model, the cost associated with management of AEs in the ESK NS arm may be overestimated.

Costs associated with management of AEs are reported in Table 43.

Table 43 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Blood pressure increased	DRG: 05MA08 Action diagnosis: DR030 Secondary diagnosis: DF332	2,240
Dissociation	DRG: 19MA01 Action diagnosis: DF4488 Secondary diagnosis: DF332	4,234
Dizziness	DRG: 19MA98 Action diagnosis: DF332 Secondary diagnosis: BRHE5	2,571
Dry mouth	DRG: 03MA09 Action diagnosis: DR682 Secondary diagnosis: DF332	1,286
Dysgeusia	DRG: 19MA98 Action diagnosis: DR438B Secondary diagnosis: DF332	2,012

	DRG code	Unit cost/DRG tariff
Fatigue	DRG: 19MA98 Action diagnosis: DR688A9B1 Secondary diagnosis: DF332	1,957
Headache	DRG: 23MA03 Action diagnosis: DR519 Secondary diagnosis: DF332	5,271
Hypoaesthesia	DRG: 19MA98 Action diagnosis: DR201 Secondary diagnosis: DF332	2,012
Nausea	DRG: 06MA11 Action diagnosis: DR119B Secondary diagnosis: DF332	4,977
Paraesthesia	DRG: 19MA98 Action diagnosis: DR208 Secondary diagnosis: DF332	2,012
Somnolence	DRG: 19MA98 Action diagnosis: DR400 Secondary diagnosis: DF332	2,012
Vertigo	DRG: 03MA02 Action diagnosis: DR429 Secondary diagnosis: DF332	8,274
Vomiting	DRG: 06MA11 Action diagnosis: DR119C Secondary diagnosis: DF332	4,977
Sedation	DRG: 23MA98 Action diagnosis: DR464 Secondary diagnosis: DF332	1,957
Confusional state	DRG: 19MA98 Action diagnosis: DR410 Secondary diagnosis: DF332	2,012

Abbreviations: DRG, diagnosis-related group.

11.6 Subsequent treatment costs

Pre-defined subsequent treatment consisted of OADs (i.e., SSRI or SNRI). Efficacy for the OADs used as subsequent treatment were sourced from Edwards et al 2021[81]. For details refer to Section 8.1.2.

As there is no standardized treatment pathway for patients who do not achieve a sufficient response with standard OAD treatment (SSRI or SNRI) it is assumed that all patients will move to the same mix of treatments (refer to Table 39). The model included three sequential courses of subsequent treatment, followed by a non-specific treatment mix (which contains the same treatments but has different transition probabilities).

Table 44 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Non-specific treatment mix	Refer to Table 39	Refer to Table 39	Refer to Table 39	Refer to Table 39
Weighted acquisition cost per dosage per 4-week cycle for all subsequent treatment scenarios: 51.49 DKK.				

11.7 Patient costs

Patient and transportation costs sourced from DMC's catalogue of unit costs 2024[73] were applied in the model. A patient hour was valued at 188.64 DKK, and travel expenses were assumed to be 140.48 DKK per roundtrip. Both costs have been adjusted to 2025 prices using the net price index.

Patient costs – ESK NS

Patient cost for ESK NS was calculated based on the average number of treatment sessions per week (refer to Table 40) and time used at each treatment session. In line with the assumptions for the administration cost it was assumed that a patient would use 20 minutes on the nasal spray administration with a subsequent use of 90 minutes on post-administration observation. Consequently, a patient was assumed to use 110 minutes on each treatment session[94].

Duration of treatment administration (chair time) per hospital visit is listed in Table 45.

Table 45 Patient costs used in the model

Activity	Time spent [minutes]
Administration and post-observation, ESK NS	120 minutes

Abbreviations: ESK, esketamine; NS, nasal spray.

Patient costs – disease management

Patient cost associated with disease management was based on the reported use of healthcare utilization from the TRIDEN study[83]. The average annual number of visits or hospital days during MDE, reported in Table 41, were used to calculate the patient cost associated with the respective health states: MDE, response, remission, and recovery. Patient time associated with disease management are summarised in Table 46.

Table 46 Patient costs used in the model [per unit]

Activity	Time spent [hours]
Psychiatric contracts	
Acute hospitalisation	24
Elective hospitalisation	24
ED visits	0.5
Outpatient visits	0.5

Activity	Time spent [hours]
Home visits	0.5
Somatic contracts	
Acute hospitalisation	24
Elective hospitalisation	24
ED visits	0.5
Outpatient visits	0.5
Doctor visit (GP)	0.5

Abbreviations: ED, emergency department; GP, general practitioner.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

12.1 Base case overview

The base case overview is presented in Table 47 with the results of the base case presented in Table 48.

Table 47 Base case overview

Feature	Description
Comparator	QTP XR + OAD
Type of model	Markov model
Time horizon	5 years
Treatment line	4th+ line. Subsequent treatment lines are included.
Measurement and valuation of health effects	HRQoL measures were estimated using EQ-5D-5L data from ESCAPE-TRD (+3 prior treatment failures). Danish population weights were used to estimate HSUVs[108].
Costs included	Medicine costs (including co-administration), hospital costs, costs of AEs, and patient costs
Dosage of medicine	ESK NS: Average dosage obtained from the ESCAPE-TRD[9] (≥ 3 prior treatment failures subgroup) and the SUSTAIN-1 data[94]. QTP XR: Average dosage (193 mg) obtained from ESCAPE-TRD[9] (≥ 3 prior treatment failures subgroup).
Average time on treatment (years)	Intervention: 0.774 Comparator: 0.577
Parametric function for PFS	N/A
Parametric function for OS	N/A

Feature	Description
Inclusion of waste	No.
Average time in model health state (years)	
MDE	ESK NS: 1.873, QTP XR: 2.761
Response	ESK NS: 0.246, QTP XR: 0.313
Remission	ESK NS: 0.677, QTP XR: 0.579
Recovery	ESK NS: 2.149, QTP XR: 1.281

Abbreviations: AE, adverse event; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; ESK, esketamine; HRQoL, health-related quality of life; HSUV, health-state utility value; MDE, major depressive episode; NS, nasal spray; QTP, quetiapine; XR, extended-release.
*Defined as a mix of QADs two classes: a SSRI (escitalopram, sertraline, paroxetine, fluoxetine, citalopram, or fluvoxamine), or a SNRI (duloxetine or venlafaxine XR).

12.1.1 Base case results

Table 48 presents the discounted base-case results for treatment TRD, with ESK NS + OAD versus QTP XR + OAD. The comparison indicates a QALY gain of 0.39 at an incremental cost of 113,114 DKK. Results indicates that ESK NS + OAD is more effective but also more costly than QTP XR + OAD, with an ICER of 293,491 DKK per QALY gained.

Table 48 Base case results, discounted estimates

	ESK NS	QTP XR	Difference
Medicine costs	130,282	578	129,704
Medicine costs – co-administration*	N/A	N/A	N/A
Administration	91,951	0	91,951
Disease management costs	286,674	381,395	-94,720
Costs associated with management of AEs	5,167	1,225	3,942
Subsequent treatment costs	1,411	2,108	-697
Patient costs	118,735	135,801	-17,066
Palliative care costs	N/A	N/A	N/A
Total costs	**634,221**	**521,106**	**113,114**
Life years gained MDE	1.70	2.52	-0.82
Life years gained response	0.23	0.29	-0.06
Life years gained remission	0.65	0.55	0.10
Life years gained recovery	1.95	1.16	0.79
Total life years	**4.54**	**4.53**	**0.01**
QALYs MDE	0.75	1.11	-0.36
QALYs response	0.17	0.21	-0.04
QALYs remission	0.55	0.46	0.09
QALYs recovery	1.73	1.03	0.70

	ESK NS	QTP XR	Difference
QALYs (adverse reactions)	0.00	0.00	0.00
Total QALYs	**3.19**	**2.81**	**0.39**
Incremental costs per life year gained		**11,336,540 DKK**	
Incremental cost per QALY gained (ICER)		**293,491 DKK**	

Abbreviations: AE, adverse event; ESK, esketamine; MDE, major depressive episode; N/A, not applicable; NS, nasal spray; QTP, quetiapine; XR, extended-release.

* Included in medicine cost

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications (for the probabilistic sensitivity analysis [PSA]), including details of how they varied in the model can be found in Appendix G.

12.2.1 Deterministic sensitivity analyses

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using SEs when available or using SEs estimated based on ±10% variation around the mean where measures of variance around the base case values were not available. Pairwise one-way sensitivity analyses were performed separately for each arm and are reported for the 9 most influential parameters on the ICER. OWSA results for ESK NS + OAD and QTP XR + OAD are presented in Figure 8 and Table 49. The OWSA showed that the parameters with the greatest influence on the ICER were the time horizon.

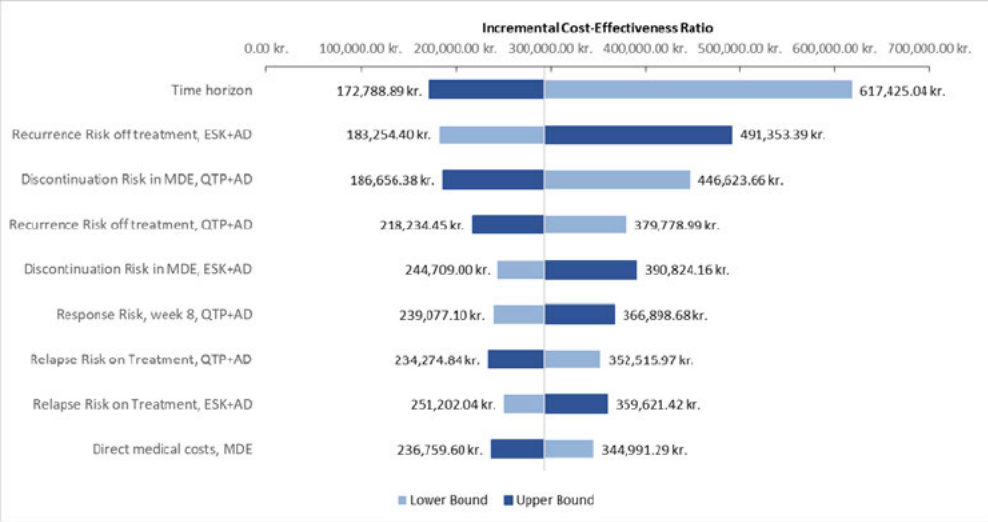
Table 49 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/ QALY)
Base case			113,114	0.39	293,491
Lower bound					
Time horizon (3 years)	3.00	Parameter uncertainty	156,021	0.25	617,425
Recurrence Risk off treatment, ESK NS + OAD	0.00	Parameter uncertainty	85,718	0.47	183,254
Discontinuation Risk in MDE, QTP XR + OAD	Multiple inputs	Parameter uncertainty	137,664	0.31	446,624
Recurrence Risk off treatment, QTP XR + OAD	0.00	Parameter uncertainty	128,645	0.34	379,779
Discontinuation Risk in MDE, ESK NS + OAD	Multiple inputs	Parameter uncertainty	108,729	0.44	244,709

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/ QALY)
Response Risk, week 8, QTP XR + OAD	0.19	Parameter uncertainty	100,758	0.42	239,077
Relapse Risk on Treatment, QTP XR + OAD	0.01	Parameter uncertainty	124,165	0.35	352,516
Relapse Risk on Treatment, ESK NS + OAD	0.00	Parameter uncertainty	105,235	0.42	251,202
Direct medical costs, MDE	Multiple inputs	Parameter uncertainty	132,963	0.39	344,991
Upper bound					
Time horizon (7 years)	7.00	Parameter uncertainty	88,095	0.48	172,789
Recurrence Risk off treatment, ESK NS + OAD	0.02	Parameter uncertainty	143,898	0.29	491,353
Discontinuation Risk in MDE, QTP XR + OAD	Multiple inputs	Parameter uncertainty	87,159	0.47	186,656
Recurrence Risk off treatment, QTP XR + OAD	0.02	Parameter uncertainty	95,599	0.44	218,234
Discontinuation Risk in MDE, ESK NS + OAD	Multiple inputs	Parameter uncertainty	119,124	0.30	390,824
Response Risk, week 8, QTP XR + OAD	0.38	Parameter uncertainty	126,781	0.35	366,899
Relapse Risk on Treatment, QTP XR + OAD	0.03	Parameter uncertainty	99,715	0.43	234,275
Relapse Risk on Treatment, ESK NS + OAD	0.02	Parameter uncertainty	123,164	0.34	359,621
Direct medical costs, MDE	Multiple inputs	Parameter uncertainty	91,249	0.39	236,760

Abbreviations: OAD, oral antidepressant; ESK, esketamine; ICER, incremental cost-effectiveness ratio; MDE, major depressive episode; NS, nasal spray; XR, extended release; QTP, quetiapine; XR

Figure 8 One way sensitivity analysis – tornado graph



Abbreviations: AD, antidepressant; ESK, esketamine; QTP, quetiapine.

12.2.1.1 Scenario analysis

Scenario analyses were performed to test the impact of change in key inputs and assumptions on the cost-effectiveness estimates. Table 50 presents the scenarios evaluated relative to the base case. These scenarios include modifications to the time horizon, treatment discontinuation rates, resource use assumptions and frequency of administration.

Table 50 Scenario analyses for the health economic model

Scenario	Incremental cost	Incremental benefit (QALYs)	ICER
Base Case	113,114	0.385	293,491
Allow retreatment	127,766	0.518	246,666
Time horizon (3 years)	155,542	0.253	615,530
Time horizon (7 years)	82,029	0.481	170,571
Percentage of patients upon achieving recovery with treatment discontinuation after 36 weeks (0%)	124,413	0.385	322,808
Percentage of patients upon achieving recovery with treatment discontinuation after 36 weeks (50%)	107,297	0.385	278,396
Percentage of patients upon achieving recovery with treatment discontinuation after 36 weeks (100%)	90,180	0.385	233,984
Percentage of patients still receiving treatment after 9 months + 2 years in the recovery health state (50%)	190,144	0.385	493,356

Scenario	Incremental cost	Incremental benefit (QALYs)	ICER
Percentage of patients still receiving treatment after 9 months + 2 years in the recovery health state (100%)	103,075	0.385	267,443
Percentage of patients upon achieving recovery with treatment discontinuation after 36 weeks (50%) and percentage of patients still receiving treatment after 9 months + 2 years in the recovery health state (50%)	167,552	0.385	434,736
Average number of device (28 mg) per ESK NS session (1 device)	33,004	0.385	85,633
Average number of device (28 mg) per ESK NS session (3 devices)	133,964	0.385	347,587
Frequency of administration per week (induction: every week; subsequent stages: biweekly)	12,214	0.385	31,690
Frequency of administration per week (induction: twice every week; subsequent stages: every week)	151,914	0.385	394,163
Number of patients a nurse can observe (1)	133,492	0.385	346,364
Number of patients a nurse can observe (5)	108,055	0.385	280,364
HSUV derived from the ITT analysis set	112,286	0.386	290,573

Abbreviations: HSUV, health-state utility value; ITT, intention-to-treat; QALY, quality-adjusted life years.

12.2.2 Probabilistic sensitivity analyses

A PSA was conducted to account for the joint uncertainty of the underlying parameter estimates. The choice of distribution (beta, gamma and normal) applied to parameters was selected based on recommendations outlined in Briggs et al. 2008[109]. SEs were taken directly from source data if reported or calculated from published standard deviations (SD) sample size and/or 95% confidence interval data. If not provided, SEs were estimated at 10% of the default value. The probabilistic base case was run with 1000 iterations.

The probabilistic results (ICER: 299,825 kr. /QALY gained) align well with the deterministic results (ICER: 293,491 kr./QALY gained). The scatterplot of all the PSA iterations is presented in Figure 9, while Figure 10presents the cost-effectiveness acceptability curves (CEAC). A convergence plot is presented in Figure 11. The scatter plot confirms that ESK NS + OAD is associated with higher QALYs but also incurs greater total costs compared to QTP XR + OAD. The CEAC indicates approximately 50% change of ESK NS being cost-effective at a willingness-to-pay threshold of 290,000 DKK per QALY.

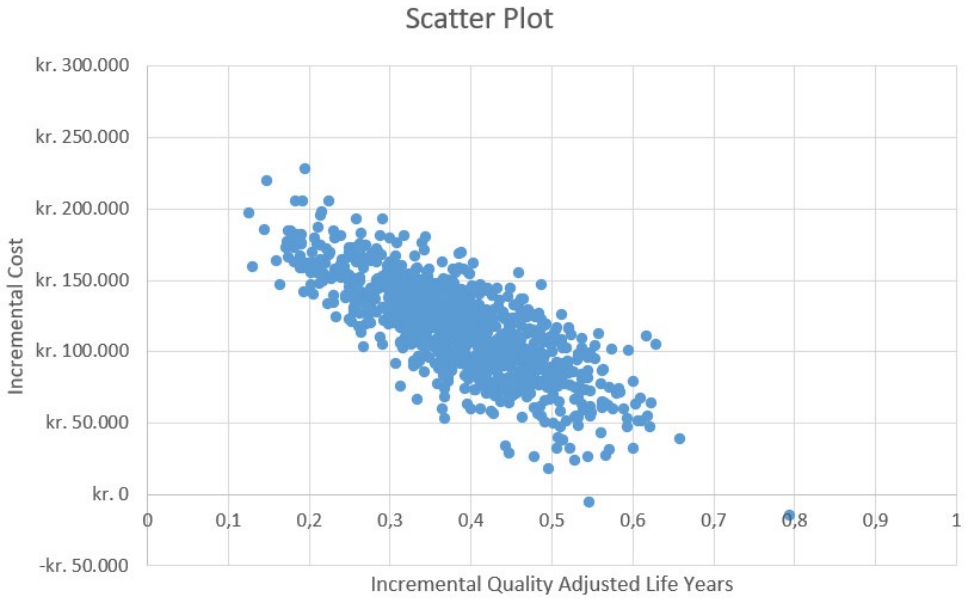


Figure 9 Cost-effectiveness scatterplot

Abbreviations: AD, antidepressant; ESK, esketamine; QALY, quality-adjusted life years; QTP, quetiapine.

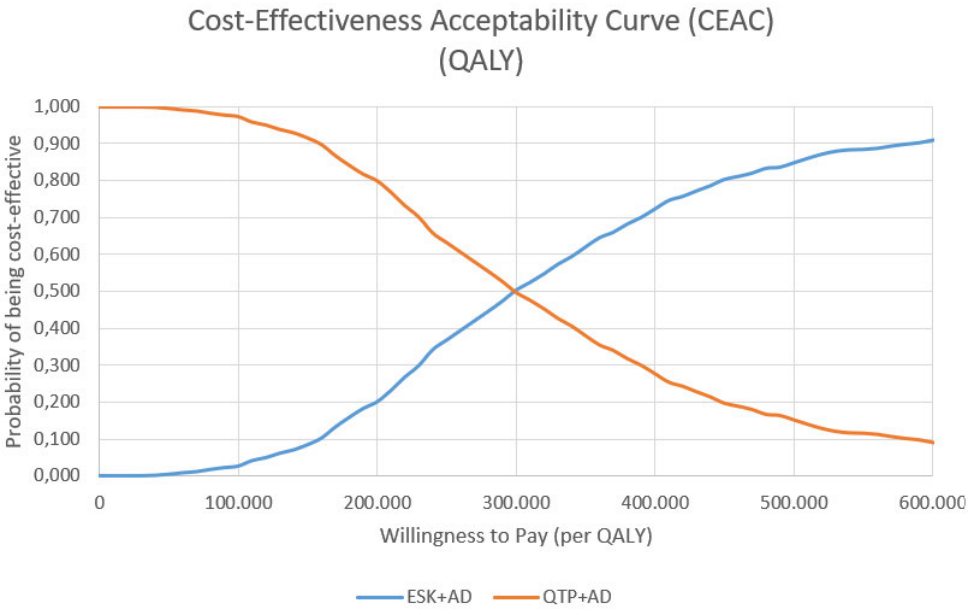


Figure 10 Cost-effectiveness acceptability curves for ESK+AD and QTP+AD

Abbreviations: AD, antidepressant; CEAC, cost-effectiveness acceptability curve; ESK, esketamine; QALY, quality-adjusted life years.

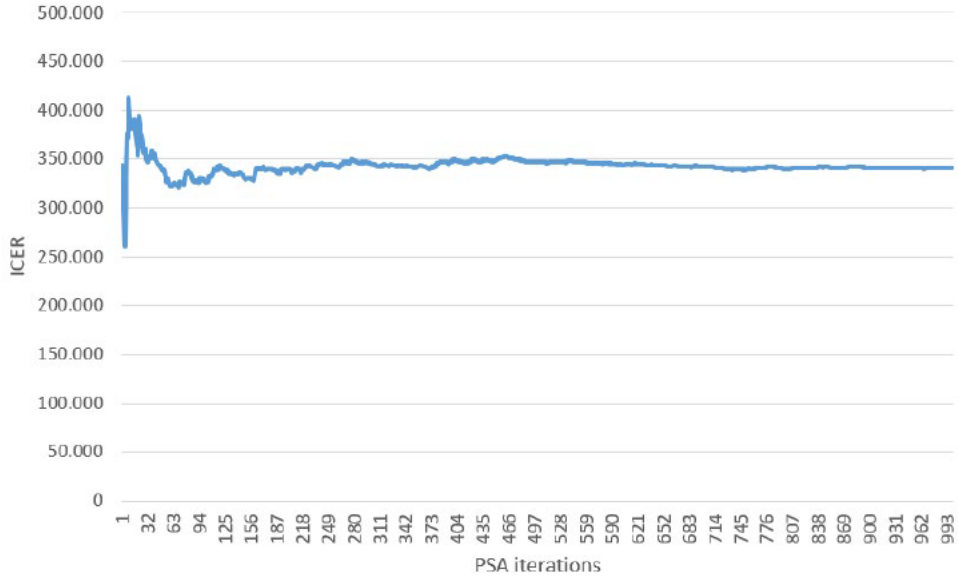


Figure 11 Convergence plot

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, Probabilistic sensitivity analysis

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending ESK NS. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the DMC guidelines.

An additional scenario was analysed to assess the expected budget impact of recommending ESK NS, when allowing retreatment with ESK NS.

Number of patients (including assumptions of market share)

As stated in Section 3.2, the future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Johnson & Johnson estimate that ESK NS will replace the current treatment for approximately 5% of eligible patients within the first year. The share is assumed to grow up to approximately 27% in years 2 to 5[47].

Table 51 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
ESK NS	38	85	128	172	233
QTP XR	721	763	728	688	631
			Non-recommendation		
ESK NS	0	0	0	0	0

	Year 1	Year 2	Year 3	Year 4	Year 5
QTP XR	759	848	856	860	864

Abbreviations: ESK, esketamine; NS, nasal spray; QTP, quetiapine; XR, extended-release.

Budget impact, base case

Table 52 Expected budget impact of recommending the medicine for the indication [DKK]

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	73,875,578	75,912,123	78,722,340	79,900,125	83,946,057
The medicine under consideration is NOT recommended	66,721,824	66,945,696	71,710,527	74,019,381	75,584,039
Budget impact of the recommendation	7,153,754	8,966,427	7,011,813	5,880,744	8,362,018

Budget impact, retreatment scenario

Table 53 Expected budget impact of recommending the medicine for the indication, retreatment scenario analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	73,882,908	75,375,938	76,833,781	76,908,500	80,321,600
The medicine under consideration is NOT recommended	66,715,648	65,999,580	68,640,555	69,153,598	69,472,282
Budget impact of the recommendation	7,167,259	9,376,358	8,193,227	7,754,902	10,849,319

14. List of experts

N/A

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Appendix A. Main characteristics of studies included

Table 54 Main characteristics of ESCAPE-TRD

Trial name: ESCAPE-TRD	NCT number: NCT04338321
Objective	The primary purpose of this study is to evaluate the efficacy of flexibly dosed ESK NS compared with QTP XR, both in combination with a continuing SSRI/SNRI, in achieving remission in participants who have treatment-resistant MDD with a current moderate to severe depressive episode.
Publications – title, author, journal, year	ESK Nasal Spray versus Quetiapine for Treatment-Resistant Depression. Reif A, Bitter I, Buyze J, Cebulla K, Frey R, Fu DJ, Ito T, Kambarov Y, Llorca PM, Oliveira-Maia AJ, Messer T, Mulhern-Haughey S, Rive B, von Holt C, Young AH, Godinov Y; ESCAPE-TRD Investigators. N Engl J Med. 2023[69] Safety and tolerability of ESK nasal spray versus quetiapine extended release in patients with treatment resistant depression. McIntyre RS, Bitter I, Buyze J, Fagiolini A, Godinov Y, Gorwood P, Ito T, Oliveira-Maia AJ, Vieta E, Werner-Kiechle T, Young AH, Reif A. Eur Neuropsychopharmacol. 2024[15] Efficacy of esketamine nasal spray over quetiapine extended release over the short and long term: sensitivity analyses of ESCAPE-TRD, a randomised phase IIIb clinical trial. Young AH, Llorca PM, Fagiolini A, Falkai P, Cardoner N, Nielsen RE, Blomqvist O, Godinov Y, Rive B, Diels J, Mulhern-Haughey S, Reif A. Br J Psychiatry. 2024[94] Improvements in functioning and workplace productivity with esketamine nasal spray versus quetiapine extended release in patients with treatment resistant depression: Findings from a 32-week randomised, open-label, rater-blinded phase IIIb study. Vieta E, Ahmed N, Arango C, Cleare AJ, Demyttenaere K, Dold M, Ito T, Kambarov Y, Krüger S, Llorca PM, McIntyre RS, Sani G, von Holt C, Rive B. Eur Neuropsychopharmacol. 2025[110] Esketamine nasal spray versus quetiapine XR in adults with treatment-resistant depression: a secondary analysis of the ESCAPE-TRD randomized clinical trial. McIntyre RS, Mattingly G, Godinov Y, Buyze J, Turkoz I, Cabrera P, Patel M, Martinez L, Himedan M, Lopena O. CNS Spectr. 2025[111] Adverse Event Duration with Esketamine Versus Quetiapine XR in Adults With Treatment-Resistant Depression: A Subgroup Analysis of ESCAPE-TRD. Mattingly, G., Godinov, Y., Buyze, J., Turkoz, I., Cabrera, P., Lopena, O., ... & Brown, B. CNS Spectrums. 2025[112]
Study type and design	A randomised, open-label, rater-blinded, active-controlled, phase 3 study. Participants were randomly assigned to one of two study intervention groups in a 1:1 ratio based on a computer-generated

Trial name: ESCAPE-TRD	NCT number: NCT04338321
	randomisation schedule prepared before the study by or under the supervision of the sponsor. The randomisation was balanced by using randomly permuted blocks and were stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more [inclusive of current antidepressive treatment at screening used to determine eligibility]). No crossover was allowed. The study has been completed.
Sample size (n)	A total of 676 participants were randomised in this study.
Main inclusion criteria	• At screening, each participant must meet Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnostic criteria for single-episode MDD or recurrent MDD, without psychotic features, based on clinical assessment and confirmed by the Mini International Neuropsychiatric Interview. • At screening and baseline, each participant must have an Inventory of Depressive Symptomatology - Clinician-rated, 30 item total score of greater than or equal to 34. • Must be on a current antidepressive treatment that includes an SSRI/SNRI at screening that resulted in nonresponse (less than 25% improvement of symptoms) after having been given at an adequate dosage (based on antidepressive dosages from summary of products characteristic [or local equivalent, if applicable]) for an adequate duration of at least 6 weeks and having been uptitrated to the maximum tolerated dose; however, at screening the participant must show signs of minimal clinical improvement to be eligible for the study. Clinical improvement of a participant on their current AD treatment will be retrospectively evaluated in a qualified psychiatric interview performed by an experienced clinician. At baseline (Day 1) prior to randomisation, the investigator will evaluate any changes in the participant's signs/symptoms of depression since the screening assessment and confirm that the inclusion criteria for the current AD treatment are still met (that is nonresponse and minimal clinical improvement). • The current antidepressive treatment, was immediately preceded by nonresponse to at least one but not more than five different, consecutive treatments (all within the current moderate to severe antidepressive episode) with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks and must be documented. • Must have been treated with at least two different antidepressive substance classes among the treatments taken at an adequate dosage for an adequate duration of at least 6 weeks resulting in nonresponse in the current moderate to severe depressive episode (including the current treatment with an SSRI/SNRI).

Trial name: ESCAPE-TRD		NCT number: NCT04338321
	• Must be on a single oral SSRI/SNRI on Day 1 prior to randomization.	
Main exclusion criteria	• Received treatment with ESK or ketamine in the current moderate to severe depressive episode. • Received treatment with QTP extended- or immediate-release in the current moderate to severe depressive episode of a dose higher than 50 mg/day. • Had depressive symptoms in the current moderate to severe depressive episode that previously did not respond to an adequate course of treatment with ECT, defined as at least seven treatments with unilateral/bilateral ECT. • Has no signs of clinical improvement at all or with a significant improvement on their current AD treatment that includes an SSRI/SNRI as determined at screening by an experienced clinician during the qualified psychiatric interview. • Received vagal nerve stimulation or has received deep brain stimulation in the current episode of depression. • Has a current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychotic features, bipolar, or related disorders (confirmed by the Mini International Neuropsychiatric Interview), obsessive compulsive disorder (current only), intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319), autism spectrum disorder, borderline personality disorder, or antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder. • Age at onset of first episode of MDD was more than or equal to 55 years. • Has homicidal ideation or intent, per the investigator's clinical judgment; or has suicidal ideation with some intent to act within one month prior to screening, per the investigator's clinical judgment; or based on the C-SSRS, corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent) for suicidal ideation, or a history of suicidal behaviour within the past year prior to screening. Participants reporting suicidal ideation with intent to act or suicidal behaviour prior to the start of the acute phase should also be excluded.	
Intervention	336 patients were included in the ESK NS arm. ESK NS was provided as a NS solution (eq. 140mg/mL NS) in a disposable NS device delivering a total volume of 0.2mL (equivalent to 28mg of ESK). For ESK NS in combination with a continuing SSRI/SNRI, the following recommended dosing regimens are recommended:	

Trial name: ESCAPE-TRD	NCT number: NCT04338321
	Participants <65 years of age (acute phase) Weeks 1-4: Starting Day 1 dose is 56 mg ESK. Subsequent doses are 56 mg or 84 mg twice a week. Weeks 5-8: 56 mg or 84 mg once weekly. Participants <65 years of age (maintenance phase) From Week 9: 56 mg or 84 mg every two weeks or once weekly. Participants 65-74 years of age, inclusive, and adults of Japanese ancestry (acute phase) Weeks 1-4: Starting Day 1 dose is 28 mg ESK. Subsequent doses are 28 mg, 56 mg, or 84 mg twice a week, all dose changes were to be in 28 mg increments. Weeks 5-8: 28 mg, 56 mg, or 84 mg once weekly, all dose changes were to be in 28 mg increments. Participants 65-74 years of age, inclusive, and adults of Japanese ancestry (maintenance phase) From Week 9: 28 mg, 56 mg, or 84 mg every two weeks or once weekly, all dose changes were to be in 28 mg increments.
Comparator(s)	340 patients were included in the QTP XR arm. For QTP XR in combination with a continuing SSRI/SNRI, the following two dosing regimens are recommended: Participants 18 to 64 years of age, inclusive Days 1-2: 50 mg/day Days 3-4: 150 mg/day Day 5 or after: 300 mg/day (based on individual participant evaluation) For participants 65-74 years of age: Days 1-3: 50 mg/day Days 4-7: 100 mg/day Day 8: 150 mg/day Day 22 - not earlier: 300 mg/day (based on individual participant evaluation)
Follow-up time	In the ITT population, the median time in the study was 230 days in the ESK NS group, and 238 days in the QTP XR group. In the subgroup of patients with at least three treatment failures, the median time in the study was 230.5 days in the ESK NS group and 237 days in the QTP XR group[65].

Trial name: ESCAPE-TRD	NCT number: NCT04338321
Is the study used in the health economic model?	Yes

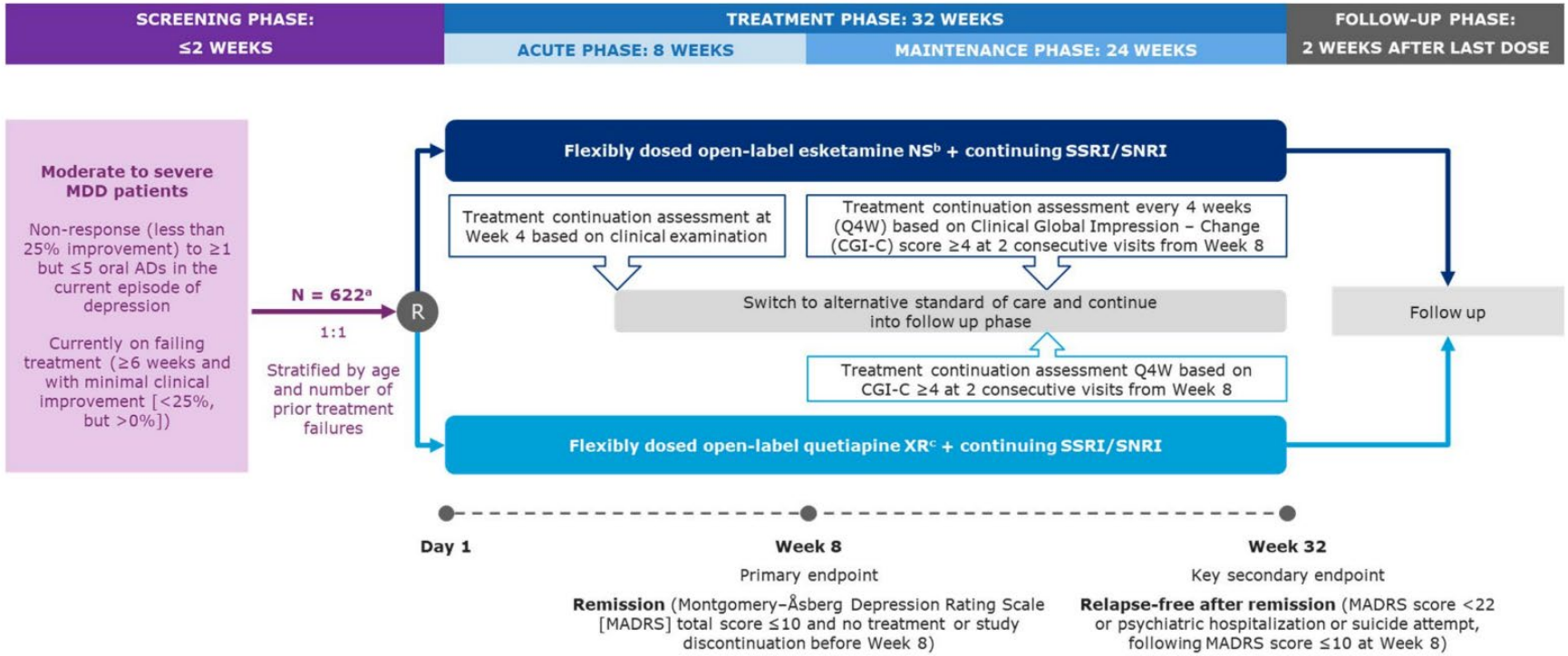
Primary, secondary and exploratory endpoints	**Endpoints included in this application**
	
	The primary endpoint was remission at Week 8.
	
	The key secondary endpoint was remission at Week 8 and no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit.
	
	Other secondary endpoints include CFB at all visits for the following scale scores:
	
	• Clinician-rated MADRS:
	  ○ Overall severity of depressive illness (total score)
	  ○ Response rate at Week 8
	• Participant-reported EQ-5D-5L questionnaire
	• TEAEs
	
	Other endpoints
	
	Other secondary endpoints not included in this application include CFB at all visits for the following scale scores:
	
	• Clinician-rated MADRS:
	  ○ Early onset of action (change in total score from baseline at Day 8 visit)
	  ○ Depressive symptoms (individual items)
	• Clinician-rated overall severity of depressive illness:
	  ○ CGI-S
	  ○ Clinical Global Impression – Change is a measure of change and is analysed as a score not as CFB
	• Participant-reported depressive symptoms: PHQ-9
	• Participant-reported functional impairment and associated disability: Sheehan Disability Scale
	• Participant-reported HRQoL and health status: 36-item Short-Form Health Survey
	• Participant-reported Quality of Life in Depression Scale
	• Participant-reported work productivity: Work Productivity and Activity Impairment: Depression questionnaire
	• TEAEs of special interest

Trial name: ESCAPE-TRD	NCT number: NCT04338321
	• Suicidal ideation and behaviour: C-SSRS
Method of analysis	All efficacy analyses are based on a subgroup of patients with at least three prior treatment failures form the full analysis set (all participants who were randomised in the study, i.e., the ITT population).
Subgroup analyses	Pre-specified subgroup analyses by age (18-64 years, ≥65 years), number of previous treatment failures (2, ≥3), sex (male, female), class of continued OAD (SSRI, SNRI), and median baseline MADRS categories (≥median, <median) were conducted for the primary endpoint, the key secondary endpoint, and other secondary endpoints. Pre-specified subgroup analyses by race (white, black, other) and region (Africa, Asia, Europe, South America) were conducted for the primary and the key secondary endpoint.
Other relevant information	N/A

Abbreviations: AD, antidepressant; AE, adverse event; CFB, change from baseline; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ECT, electroconvulsive therapy; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; ESK, esketamine; ITT, intention-to-treat; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; NS, nasal spray; N/A, not applicable; OAD, oral antidepressant; PHQ-9, Patient Health Questionnaire 9-item; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; QTP, quetiapine; TEAE, treatment-emergent adverse events; XR, extended-release.

Sources: ClinitcalTrials.gov, 2020[9]; Janssen EMEA, 2023[65].

Figure 12 ESCAPE-TRD trial design



Abbreviations: AD. antidepressant; CGI-C, Clinical Global Impression – Change; MADRS, Montgomery–Asberg Depression Rating Scale; MDD, major depressive disorder; NS, nasal spray; Q4W, every 4 weeks; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TRD, treatment resistant depression; XR, extended-release.

Source: Janssen EMEA, 2023, Figure 1[65].Source: Janssen EMEA, 2023, Figure 1[65].

Table 55 Main characteristics of SUSTAIN-3

Trial name: SUSTAIN-3	NCT number: NCT02782104
Objective	The purpose of this studs is to assess the safety and tolerability of ESK NS in participants with treatment-resistant depression.
Publications – title, author, journal, year	Efficacy and Safety of ESK Nasal Spray in Patients with Treatment-Resistant Depression Who Completed a Second Induction Period: Analysis of the Ongoing SUSTAIN-3 Study. Castro M, Wilkinson ST, Al Jurdi RK, Petrillo MP, Zaki N, Borentain S, Fu DJ, Turkoz I, Sun L, Brown B, Cabrera P. CNS Drugs. 2023[72] Long-term safety and maintenance of response with ESK nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. Zaki N, Chen LN, Lane R, Doherty T, Drevets WC, Morrison RL, Sanacora G, Wilkinson ST, Popova V, Fu DJ. Neuropsychopharmacology. 2023[44]
Study type and design	Open-label, long-term extension, phase 3 study. The study is completed.
Sample size (n)	1,148
Main inclusion criteria	• Based on the prior study the participant is entering SUSTAIN-3 from: a) From TRANSFORM-1 (NCT02417064) or TRANSFORM-2 (NCT02418585) study: Participant has completed the induction phase and the 2-weeks follow up phase visit; or Participants completed the induction phase and was a responder and study SUSTAIN-1 is terminated.; b) From SUSTAIN-1 (NCT02493868) study: (1) Participant relapsed during the maintenance phase; or (2) Participant was in the induction phase of the SUSTAIN-1 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or (3) Participant was in the optimisation or maintenance phases at the time the study was terminated; or (4) or (5) Participants was in the induction phase and after completion of induction phase was determined to not meet response criteria, c) (1) Participant completed SUSTAIN-2 study (optimisation/maintenance phase); or (2) Participant was in the induction phase of the SUSTAIN-2 study when the study was terminated and, after completion of the induction phase, was determined to be a responder; or (3) Participant was in the optimisation/maintenance phase at the time the study was terminated; (4) Participant was in the induction phase and did not meet criteria for response may be eligible for to be rolled over into SUSTAIN-3. d) From TRANSFORM-3 (NCT02422186) study: Participant was in the induction phase of the TRANSFORM-3 study at the time enrolment into the SUSTAIN-2 study was closed and, after completion of the induction phase, was determined to be a responder or did not meet the criteria for response. e) From ESKETINTRD3006 study (US Study sites only)

Trial name: SUSTAIN-3	NCT number: NCT02782104
	(1) Participant completed the induction phase and was a responder. • Participant must be medically stable on the basis of physical examination, vital signs, pulse oximetry, and 12-lead Electrocardiogram performed pre-dose on the day of the first intranasal treatment session. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their clinical significance must be determined by the investigator and recorded in the participant's source documents and initialled by the investigator. • Participant must be medically stable according to the investigator's judgment and knowledge of the subject's medical stability in the parent study. This determination must be documented. • A woman of childbearing potential must have a negative serum (beta-human chorionic gonadotropin) pre-dose on the day of the first intranasal treatment session. • During the study (that is, from the first intranasal treatment session) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of intranasal study medication, a man who is sexually active with a woman of childbearing potential must be practicing a highly effective method of contraception with his female partner and must agree not to donate sperm.
Main exclusion criteria	• The evaluation of the benefit versus risk of continued ESK NS treatment is not favourable for the participant in the opinion of the investigator. • Since the last study visit in the participant's prior study, participant has suicidal ideation with intent to act per the investigator's clinical judgment or based on the C-SSRS (corresponding to a response of "Yes" on Item 4 [active suicidal ideation with some intent to act, without specific plan] or Item 5 [active suicidal ideation with specific plan and intent] in the suicidal ideation module of the C-SSRS) or suicidal behaviour per the investigator's clinical judgment or based on the C-SSRS (corresponding to any score higher than 0 in the suicidal behaviour module of the C-SSRS). • Participant has positive test result(s) for drugs of abuse (including barbiturates, methadone, opiates, cocaine, phencyclidine, and amphetamine/methamphetamine) pre-dose on the day of the first intranasal treatment session. • Participant has any anatomical or medical condition that, per the investigator's clinical judgment based on assessment, may impede delivery or absorption of intranasal study drug. • Participant has taken any prohibited therapies that would not permit administration of the first intranasal treatment session.

Trial name: SUSTAIN-3	NCT number: NCT02782104
Intervention	1,148 participants were enrolled to receive ESK NS. Participants <65 years of age (induction phase dose titration of ESK) 56 mg ESK on Day 1. 56 or 84 mg on Day 4. The dose could remain at 56 mg or be increased to 84 mg, as determined by the investigator based on efficacy and tolerability. 56 or 84 mg on Day 8, 11, 15, 18, 22, and 25. The dose could be increased to 84 mg (if previous dose was 56 mg), remain the same, or be reduced to 56 mg (if previous dose was 84 mg), as determined by the investigator based on efficacy and tolerability. Participants ≥65 years of age (induction phase dose titration of ESK) 28 mg ESK on Day 1. 28 or 56 mg on Day 4. The dose could remain at 28 mg or be increased to 56 mg, as determined by the investigator based on efficacy and tolerability. 28, 56 or 84 mg on Day 8, 11, 15, 18, 22, and 25. The dose could remain the same or be increased or reduced by 28 mg from the previous dosing session, as determined by the investigator based on efficacy and tolerability. Optimisation/maintenance phase Participants entering from studies TRANSFORM-1 (NCT02417064), TRANSFORM-2 (NCT02418585) or ESKETINTRD3006 (US sites only) will self-administer ESK NS (same dose) once weekly. Participants entering from study TRANSFORM-3 (NCT02422186) will self-administer ESK NS (28 mg in week 1; 28 or 56 mg in week 2; and 28, 56 or 84 mg in week 3 and 4) once weekly. After Week 4 (starting at Week 5), based on the Investigator's clinical judgment, the dose of ESK for all participants can be adjusted based upon efficacy and tolerability.
Comparator(s)	N/A
Follow-up time	The median ESK NS exposure was 45.8 months[85].The median ESK NS exposure was 45.8 months[85].
Is the study used in the health economic model?	Not included in the health economic model. The study has been included in this application to provide safety data from a large population (N=1,148) and from a long follow-up.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint: number of participants with TEAEs. **Other endpoints:** The following endpoints are not included in this application:

Trial name: SUSTAIN-3	NCT number: NCT02782104
	Primary endpoints were CFB in computerised cognitive battery domain score: detection test score; CFB in computerised cognitive battery domain score: identification test score; CFB in computerised cognitive battery domain score: one card learning test score; CFB in computerised cognitive battery domain score: one back test score; CFB in computerised cognitive battery domain score: Groton Maze learning test score; CFB in Hopkins verbal learning test-revised score; percentage of participants based on C-SSRS score; CFB in heart rate; CFB in systolic and diastolic blood pressure; CFB in respiratory rate; and CFB in blood oxygen saturation. Secondary endpoints were CFB in MADRS total score; CFB in Participant-Reported Depressive Symptoms Using the PHQ-9 total score; CFB in CGI-S score; CFB in Sheehan Disability Scale total score; CFB in participant-reported HRQoL as assessed by EQ-5D-5L Valuation Index Score; CFB as assessed by EQ 5D-5L: sum score; and CFB in participant-reported health related quality of life using the Quality of Life in Depression Scale. The exploratory endpoints were medical resource utilisation (including Healthcare Resource Use Questionnaire results); CFB over time for depression response and remission rates to a second induction phase in eligible participants who had relapsed in SUSTAIN-1, assessed using the MADRS and PHQ-9; participant treatment satisfaction; and participant trade-off preferences for key benefit and harm outcomes associated with treatment-resistant depression treatment, using a stated-choice preference survey.
Method of analysis	Safety data for the all enrolled analysis set (all participants who were eligible to enter the study and who received at least one dose of study intervention) are included in this application. Only numbers and percentages are presented, and as such no specific method of analysis has been applied.
Subgroup analyses	A pre-specified subgroup analysis was conducted for computerised cognitive battery and Hopkins verbal learning test-revised based on age (<65 years of age and ≥65 years of age).
Other relevant information	N/A

Abbreviations: CFB, change from baseline; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; ESK, esketamine; NS, nasal spray; N/A, not applicable; PHQ-9, Patient Health Questionnaire 9-item; TEAE, treatment-emergent adverse event.

Source: ClinicalTrials.gov, 2016[77]; Janssen Research & Development, 2024[39].Source: ClinicalTrials.gov, 2016[77]; Janssen Research & Development, 2024[39].

Appendix B. Efficacy results per study

Results per study

Table 56 Results per study

Results of ESCAPE-TRD (NCT04338321) subgroup with 3+ prior treatment failures											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Remission by MADRS total score (Week 8)	QTP XR + OAD	129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Remission was tested between study intervention arms using a CMH chi-square test. Remission was analysed using the NRI approach.	Janssen EMEA, 2023[66]
	ESK NS + OAD	132	[redacted]								
Remission by MADRS total score (Week 12)	QTP XR + OAD	129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Janssen EMEA, 2024[66]
	ESK NS + OAD	132	[redacted]								
Response rate (Week 8)	QTP XR + OAD	129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Response was tested between study intervention arms using a CMH chi-square test. Response was analysed using the NRI approach.	Janssen EMEA, 2024[66]
	ESK NS + OAD	132	[redacted]								

Results of ESCAPE-TRD (NCT04338321) subgroup with 3+ prior treatment failures											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Response rate (Week 32)	QTP XR + OAD	129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Janssen EMEA, 2024[66]
	ESK NS + OAD	132	[redacted]								
LSM for CFB in MADRS score, Week 8	QTP XR + OAD	129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CFB in MADRS total score was analysed using ANCOVA models with treatment and baseline total MADRS scores. The analysis was conducted using only on-treatment visits (not retrieved drop-outs after treatment discontinuation).	Janssen EMEA, 2024[66]
	ESK NS + OAD	132	[redacted]								
LSM for CFB in MADRS score, Week 32	QTP XR + OAD	129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Missing data were imputed using a BOCF approach. This assumes that patients discontinuing treatment see their depression severity go back to its baseline level (i.e. CFB = 0).	Janssen EMEA, 2024[66]
	ESK NS + OAD	132	[redacted]								

Results of ESCAPE-TRD (NCT04338321) subgroup with 3+ prior treatment failures											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Relapse-free after remission (Week 32)	QTP XR + OAD	129	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Relapse-free after remission was tested between study intervention arms using a CMH chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]). Relapse-free after remission was analysed using the NRI approach.	Janssen EMEA, 2023[65]
	ESK NS + OAD	132	[redacted]								

Abbreviations: ANCOVA, analysis of covariance; BOCF, Baseline Observation Carried Forward; CFB, change from baseline: CI, confidence interval; ESK, esketamine; MADRS; CMH, Cochran-Mantel-Haenszel; LSM, least squares mean; MADRS, Montgomery-Asberg Depression Rating Scale: MMRM, mixed models for repeated measures; NS, nasal spray; N/A, not applicable; OAD, oral antidepressant; OR, odds ratio; QTP, quetiapine; XR, extended-release.

Sources: Janssen EMEA, 2023[65]; Janssen EMEA, 2024[66]. Sources: Janssen EMEA, 2023[65]; Janssen EMEA, 2024[66].

Appendix C. Comparative analysis of efficacy

N/A

Appendix D. Extrapolation

All relevant information of extrapolations of treatment effects and transition probabilities is presented in Section 7.

D.1 Extrapolation of [effect measure 1]

Not applicable.

D.1.1 Data input

Not applicable.

D.1.2 Model

Not applicable.

D.1.3 Proportional hazards

Not applicable.

D.1.4 Evaluation of statistical fit (AIC and BIC)

Not applicable.

D.1.5 Evaluation of visual fit

Not applicable.

D.1.6 Evaluation of hazard functions

Not applicable.

D.1.7 Validation and discussion of extrapolated curves

Not applicable.

D.1.8 Adjustment of background mortality

Not applicable.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of [effect measure 2]

Not applicable.

Appendix E. Serious adverse events

Table 57 Serious TEAEs in ESCAPE-TRD (subgroup, patients with 3+ prior treatment failures)

	QTP XR + OAD (N=128) (subgroup, ESCAPE-TRD) n (%)	ESK NS + OAD (N=131) (subgroup, ESCAPE-TRD) n (%)
Cardiac disorders	[redacted]	
Acute coronary syndrome		
Eye disorders		
Retinal detachment		
Infections and infestations		
Cystitis		
Pilonidal disease		
Injury, poisoning and procedural complications		
Tendon rupture		
Psychiatric disorders		
Alcoholism		
Anxiety		
Depression		
Major depression		
Somatic symptom disorder		
Suicidal ideation		
Suicide attempt		
Respiratory, thoracic and mediastinal disorders		
Nasal turbinate hypertrophy		

Abbreviations: ESK, esketamine; NS, nasal spray; OAD, oral antidepressants; QTP, quetiapine; TEAE, treatment-emergent adverse event: XR, extended-release.

Notes: n (%) indicates the number and percentage of patients experiencing any serious TEAE.

Source: Janssen EMEA, 2024[66]Source: Janssen EMEA, 2024[66]

Table 58 Serious TEAEs in ESCAPE-TRD (full safety population, treatment phase)

	QTP XR + OAD (N=336) (ITT, ESCAPE-TRD)	ESK NS + OAD (N=334) (ITT, ESCAPE-TRD) n (%)

	n (%)	
Serious TEAEs	[redacted]	
Psychiatric disorders		
Depression		
Suicidal ideation		
Suicide attempt		
Anxiety		
Major depression		
Somatic symptom disorder		
Alcoholism		
Conversion disorder		
Infections and infestations		
Bronchitis		
Coronavirus disease 2019		
Cystitis		
Pilonidal disease		
Nervous system disorders		
Cerebrovascular accident		
Dizziness		
Generalised tonic-clonic seizure		
Cardiac disorders		
Acute coronary syndrome		
Atrial fibrillation		
Gastrointestinal disorders		
Abdominal pain		
Pancreatitis		
Blood and lymphatic system disorders		
Lymphadenopathy mediastinal		
Eye disorders		
Retinal detachment		
General disorders and administration site conditions		
Death		
Injury, poisoning and procedural complications		
Tendon rupture		

Renal and urinary disorders	[redacted]
Nephrolithiasis	
Respiratory, thoracic and mediastinal disorders	
Nasal turbinate hypertrophy	

Abbreviations: ITT, intention-to-treat; ESK, esketamine; NS, nasal spray; OAD, oral antidepressant; QTP, quetiapine; TEAE, treatment-emergent adverse event; XR, extended-release.

Source: Janssen EMEA, 2023, Table 21[65].Source: Janssen EMEA, 2023, Table 21[65].

Table 59 presents serious TEAEs in SUSTAIN-3 reported by more than 2 (0.2%) participants in the 'All Enrolled Analysis Set' defined in section 6.1.2.1 for the combined study phases.

Table 59 Serious TEAEs in SUSTAIN-3 (induction and maintenance phase)

	ESK NS (N=1,148) n (%)
Serious TEAEs	[redacted]
Depression	
Suicide attempt	
Suicidal ideation	
Cholelithiasis	
Coronavirus disease 2019	
Pneumonia	
Nephrolithiasis	
Anxiety	
Atrial fibrillation	
Myocardial infarction	
Back pain	
Major depression	
Cellulitis	
Urinary tract infection	
Intentional overdose	
Lower limb fracture	
Headache	
Cholecystitis	
Intervertebral disc protrusion	
Osteoarthritis	

Abbreviations: ESK, esketamine; NS, nasal spray; TEAE, treatment-emergent adverse event.

Notes: Serious TEAEs reported by more than 2 (0.2%) participants in SUSTAIN-3 are presented in this table.

Sources: Janssen Research & Development, 2023[39].Sources: Janssen Research & Development, 2023[39].

Appendix F. Health-related quality of life

A scenario analysis was conducted to explore the use of utility values derived from the ITT analysis set in the CEM (Refer to Table 60, below).

Table 60 Overview of health state utility values used in the scenario analysis

	Results (SE)*	Instrument	Tariff (value set) used	Comments
HSUVs				
MDE, cycle 1	0.430 (0.010)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
MDE, cycle 2	0.582 (0.014)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
MDE, cycle 3	0.616 (0.020)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
MDE, cycle 4	0.568 (0.027)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
MDE, cycle 5	0.575 (0.039)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Response	0.738 (0.007)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 1	0.819 (0.008)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 2	0.828 (0.009)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 3	0.833 (0.009)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 4	0.854 (0.009)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 5	0.853 (0.010)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 6	0.859 (0.012)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 7	0.885 (0.013)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 8	0.884 (0.014)	EQ-5D-5L	DK	Estimate is based on mean of both trial arms obtained from the ESCAPE-TRD trial[65].
Remission, cycle 9	0.884 (0.014)	EQ-5D-5L	DK	Assumed equal to remission cycle 8 utility

	Results (SE)*	Instrument	Tariff (value set) used	Comments
Recovery	0.884 (0.014)	EQ-5D-5L	DK	Assumed equal to remission cycle 8 utility

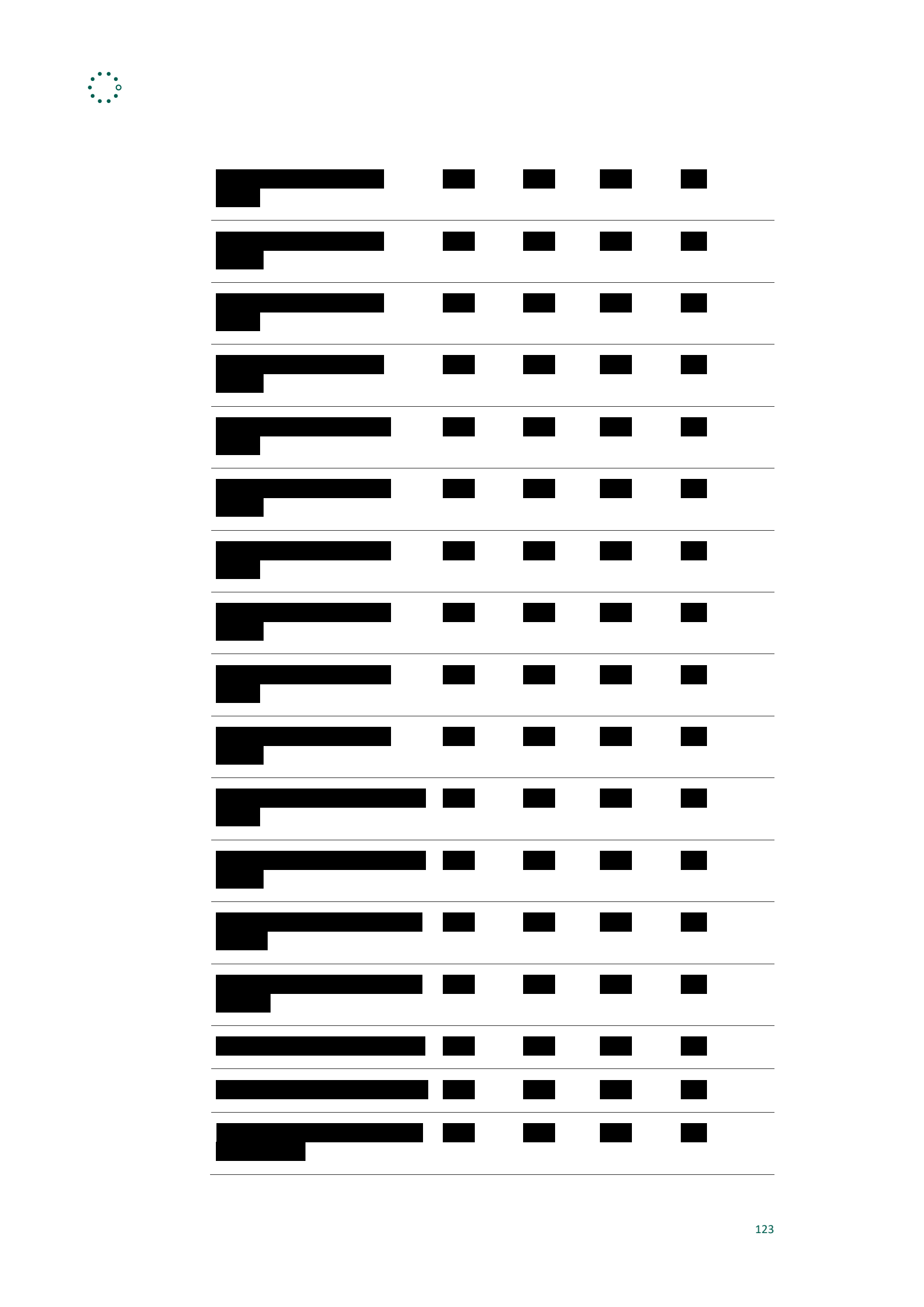
Abbreviations: EQ-5D-5L, European Quality of Life Group, 5-Dimension, 5-Level; HSUV, health-state utility value; MDE, major depressive episode; SE, standard error.
*Patients could have contributed more than one utility score for a health state

Appendix G. Probabilistic sensitivity analyses

Table 61 shows the distributional assumptions of model parameters (point estimate, and lower and upper bound.

Table 61. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Settings				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risk of clinical events (ESK NS+ OAD/QTP XR + OAD)				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



[redacted]

Risk of clinical events – subsequent treatment (line 2/line 3/line 4 in subsequent treatment)

[redacted]

[redacted]

Discontinuation

[redacted]

[redacted]

Health state utilities				
Utilities - MDE cycle 1	0.432	0.401	0.464	Beta
Utilities - MDE cycle 2	0.560	0.512	0.607	Beta
Utilities - MDE cycle 3	0.605	0.541	0.668	Beta
Utilities - MDE cycle 4	0.555	0.471	0.638	Beta
Utilities - MDE cycle 5	0.574	0.465	0.679	Beta
Utilities - Response	0.733	0.710	0.756	Beta
Utilities - Remission cycle 1	0.805	0.775	0.833	Beta
Utilities - Remission cycle 2	0.818	0.783	0.851	Beta
Utilities - Remission cycle 3	0.831	0.800	0.860	Beta

Utilities - Remission cycle 4	0.857	0.826	0.885	Beta
Utilities - Remission cycle 5	0.868	0.835	0.898	Beta
Utilities - Remission cycle 6	0.860	0.819	0.896	Beta
Utilities - Remission cycle 7	0.883	0.839	0.920	Beta
Utilities - Remission cycle 8	0.884	0.828	0.930	Beta
Utilities - Remission cycle 9	0.884	0.828	0.930	Beta
Utilities - Recovery	0.884	0.828	0.930	Beta
Disutilities by AE				
Anxiety	-0.129	-0.116	-0.142	Normal
Diarrhoea	-0.044	-0.040	-0.048	Normal
Dizziness	-0.085	-0.077	-0.094	Normal
Dry mouth	-0.010	-0.009	-0.011	Normal
Fatigue	-0.085	-0.077	-0.094	Normal
Feeling abnormal	-0.085	-0.077	-0.094	Normal
Feeling drunk	-0.085	-0.077	-0.094	Normal
Headache	-0.115	-0.104	-0.127	Normal
Illusion	-0.085	-0.077	-0.094	Normal
Insomnia	-0.129	-0.116	-0.142	Normal
Nausea	-0.065	-0.059	-0.072	Normal
Somnolence	-0.085	-0.077	-0.094	Normal
Throat irritation	-0.010	-0.009	-0.011	Normal
Vertigo	-0.085	-0.077	-0.094	Normal
Vision blurred	-0.050	-0.045	-0.055	Normal

Vomiting	-0.065	-0.059	-0.072	Normal
Sedation	-0.085	-0.077	-0.094	Normal
Confusional state	-0.085	-0.077	-0.094	Normal
Unit costs per AE				
Anxiety	4234.000	3444.951	5103.196	Gamma
Blood pressure increased	2240.000	1822.553	2699.848	Gamma
Delusional perception	2861.000	2327.824	3448.333	Gamma
Derealisation	2571.000	2091.868	3098.799	Gamma
Diarrhoea	4977.000	4049.486	5998.726	Gamma
Dissociation	4234.000	3444.951	5103.196	Gamma
Dizziness	2571.000	2091.868	3098.799	Gamma
Dizziness postural	2571.000	2091.868	3098.799	Gamma
Dry mouth	1286.000	1046.341	1550.002	Gamma
Dysgeusia	2012.000	1637.044	2425.042	Gamma
Fatigue	1957.000	1592.293	2358.752	Gamma
Feeling abnormal	5271.000	4288.696	6353.081	Gamma
Feeling drunk	5271.000	4288.696	6353.081	Gamma
Headache	5271.000	4288.696	6353.081	Gamma
Hypoaesthesia	2012.000	1637.044	2425.042	Gamma
Hypoaesthesia oral	2012.000	1637.044	2425.042	Gamma
Illusion	2861.000	2327.824	3448.333	Gamma
Insomnia	2012.000	1637.044	2425.042	Gamma
Nausea	4977.000	4049.486	5998.726	Gamma

Paraesthesia	2012.000	1637.044	2425.042	Gamma
Paraesthesia oral	2012.000	1637.044	2425.042	Gamma
Somnolence	2012.000	1637.044	2425.042	Gamma
Vertigo	8274.000	6732.057	9972.565	Gamma
Vision blurred	1085.000	882.799	1307.739	Gamma
Vomiting	4977.000	4049.486	5998.726	Gamma
Sedation	1957.000	1592.293	2358.752	Gamma
Confusional state	2012.000	1637.044	2425.042	Gamma
Direct medical costs				
Cumulative Medical Resource Utilisation - MDE	9970.784	8112.628	12017.681	Gamma
Cumulative Medical Resource Utilisation - Response	5688.550	4628.432	6856.350	Gamma
Cumulative Medical Resource Utilisation - Remission	1406.317	1144.235	1695.018	Gamma
Cumulative Medical Resource Utilisation - Recovery	1406.317	1144.235	1695.018	Gamma
Cumulative Medical Resource Utilisation - MDE (without treatment)	9970.784	8112.628	12017.681	Gamma
Cumulative Medical Resource Utilisation - Response (without treatment)	5688.550	4628.432	6856.350	Gamma
Cumulative Medical Resource Utilisation - Remission (without treatment)	1406.317	1144.235	1695.018	Gamma
Indirect medical costs				
Cumulative Indirect Travel Costs - MDE	324.681	264.173	391.334	Gamma
Cumulative Indirect Travel Costs - Response	185.238	150.717	223.265	Gamma

Cumulative Indirect Travel Costs - Remission	45.794	37.260	55.195	Gamma
Cumulative Indirect Travel Costs - Recovery	45.794	37.260	55.195	Gamma
Cumulative Indirect Patient Costs - MDE	3288.437	2675.604	3963.519	Gamma
Cumulative Indirect Patient Costs - Response	1876.125	1526.490	2261.274	Gamma
Cumulative Indirect Patient Costs - Remission	463.813	377.377	559.029	Gamma
Cumulative Indirect Patient Costs - Recovery	463.813	377.377	559.029	Gamma
Mortality				
Excess mortality for TRD patients, MDE	0.005	0.002	0.007	Normal
Excess mortality for TRD patients, Response	0.002	0.001	0.004	Normal

Abbreviations: AD, antidepressant; AE, adverse event; ESK, esketamine; MDE, major depressive episode; QTP, quetiapine; TRD, treatment resistant depression; Tx, treatment.

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

N/A

Table 62 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

Table 63 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA web-site	N/A	N/A	N/A

Abbreviations:

Table 64 Conference material included in the literature search

Conference	Source of ab-stracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

H.1.1 Search strategies

N/A

Table 65 of search strategy table for [name of database]

No.	Query	Results
#1	N/A	N/A

No.	Query	Results
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

H.1.2 Systematic selection of studies

N/A

Table 66 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

N/A

Table 67 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A
Study 2	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded full text references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Objective

An economic SLR was conducted to identify publications reporting preference-based HSUVs associated with depression (including TRD and MDD) and other related conditions. To avoid repetition the HRQoL and HSUVs is reported in the same SLR below.

I.1.1 Information sources

The population of interest for the economic evaluation and UK-based resource/cost study SLRs was restricted to patients with MDD/TRD. However, a decision was taken to broaden the population of interest to patients with depression regardless of severity for the HSUV SLR. This ensured that the scope of the HSUV SLR was aligned with the HRQoL search conducted as part of two previous relevant documents:

- NICE clinical guideline CG90 (Depression in adults: recognition and management), originally published in 2008 and updated in July 2016 (5) [Population of interest: adults (aged 18 years and older) with mild, moderate or severe depression, including people with chronic depression]
- NICE single technology appraisal (STA) for vortioxetine for the treatment of major depressive episodes (MDEs) (TA367) (6), published November 2015.

The approach adopted for the current SLR of HSUVs (conducted in July 2018) was to leverage the search strategies undertaken for the CG90 guideline to identify utility evidence published since July 2016. The disease-specific search terms used in the CG90 economic search strategies were combined with a bespoke HSUV-specific filter to identify potentially relevant citations (the original CG90 search strategy was not restricted to identifying utility studies). Subsequent updates of the July 2018 search were conducted in April 2019, September 2019, and January 2020. Relevant HSUV publications published prior to July 2016 and meeting the eligibility criteria for inclusion in the CG90 clinical guideline and vortioxetine STA are also summarised in the current report to provide a comprehensive summary of reported utilities in patients with depression.

July 2018 – January 2020 updates

On 5th July 2018, electronic searches were performed via the Ovid platform across Embase, MEDLINE (including various subcategories), the Cochrane Library (covering HTA, NHS EED, Cochrane Database of Systematic Reviews, DARE, and CENTRAL), and PsycInfo to identify evidence published from 2016 onwards. Supplementary searches included reference lists, conference proceedings, and additional grey literature. On 4th April 2019,

the searches were updated to include evidence published within six months of the NICE STA submission date. The same databases and search platforms were utilised, covering evidence up to July 2018, with additional hand-searching of reference lists, conference proceedings, and grey literature. On 19th September 2019, the searches were refreshed to identify evidence published within six months of the SMC submission date. The scope included all previous databases and sources, with updated conference proceedings and grey literature. On 29th January 2020, a final update was conducted to capture evidence published within six months of the most recent timeline. Searches were performed using the same databases and supplemented by hand-searching reference lists, conference proceedings (September 2019 onwards), and grey literature sources as outlined by NICE.

Vortioxetine NICE submission (TA367)

Electronic searches of the following databases were conducted on the 29th of May 2014: Embase, MEDLINE (including MEDLINE In-Process & Other Non-Indexed Citations), the Cochrane Library (incorporating the HTA database and the National Health Service Economic Evaluation Database [NHS EED]), EconLit, and PsycINFO. A date restriction was applied from 2008 to 2014.

CG90

A SLR was conducted as part of the CG90 update to find utility data for depression-related health states.

All sources used for the searches above are detailed in Table 68.

Table 68 Sources included in the search for HSUVs and HRQoL

Database	Platform/source	Relevant period for the search	Latest date of search completion
Embase	Ovid platform	1974 to present	29.01.2020
Medline	Ovid platform	1946 to present	29.01.2020
The Cochrane Library	Ovid platform	Q4 2016 to present	29.01.2020
PsycINFO	Ovid platform	1987 to present	29.01.2020
EconLit	Ovid platform	2008 to 2014	29.05.2014

Abbreviations:

The electronic databases searches were supplemented by hand searching of reference lists of included studies, relevant conference proceedings, and additional grey literature sources specified by NICE (Table 69 and Table 70).

Table 69 Bibliographic databases included in the literature search for HSUVs and HRQoL

Database	Platform	Relevant period for the search	Latest date of search completion
American Psychiatry Association	www.psychiatry.org	2016-2020	29.01.2020
Anxiety and Depression Association of America Conference	www.adaa.org	2016-2020	29.01.2020
European Congress of Psychiatry	www.epa-congress.org	2016-2020	29.01.2020
International Conference on Management of Depression	www.idias.org	2016-2020	29.01.2020
International Society for Pharmacoeconomics and Outcomes Research, European and International Congresses	www.ispor.org	2016-2020	29.01.2020
The Royal College of Psychiatrists	www.rcpsych.ac.uk	2016-2020	29.01.2020
WPA World Congress of Psychiatry	www.wcp-congress.com	2016-2020	29.01.2020

Table 70 Other sources included in the literature search for HSUVs and HRQoL

Database	Platform	Relevant period for the search	Latest date of search completion
EuroQoL website	www.euroqol.org	September 2019 onwards	29.01.2020
University of Sheffield School of Health and Related Research Health Utilities Database (ScHARRHUD)	www.sheffield.ac.uk/scharr	September 2019 onwards	29.01.2020
HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA)	www.database.inahta.org	September 2019 onwards	29.01.2020

Database	Platform	Relevant period for the search	Latest date of search completion
National Institute for Health Research Health Technology Assessment (NIHR HTA)	www.journalslibrary.nihr.ac.uk	September 2019 onwards	29.01.2020
The Institute for Clinical and Economic Review (ICER)	www.icer.org	September 2019 onwards	29.01.2020

I.1.2 Search strategies

The search strings for the July 2018, April 2019, September 2019, and January 2020 SLRs are reported below.

I.1.2.1 July 2018 update

Table 71 HSUVs and HRQoL search strategy for Embase (July 5, 2018)

#	Searches	Results
1	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	713794
2	((affective or mood) adj disorder*).mp.	66735
3	*depression/ or *agitated depression/ or *atypical depression/ or *depressive psychosis/ or *dysphoria/ or *dysthymia/ or *endogenous depression/ or *involutional depression/ or *late life depression/ or *major depression/ or *masked depression/ or *melancholia/ or "*mixed anxiety and depression"/ or "*mixed depression and dementia"/ or *premenstrual dysphoric disorder/ or *reactive depression/ or *recurrent brief depression/ or *seasonal affective disorder/ or *treatment resistant depression/	166179
4	1 or 2 or 3	741137
5	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	15599
6	(Health utilities index or HUI).mp.	2982
7	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1515
8	(short form 6D or short-form 6D).mp.	287
9	(standard gamble or ("SG" adj2 "standard gamble")).mp.	1034
10	(15D or 16D or 17D).mp.	3631
11	exp short form 12/ or exp short form 20/ or exp short form 36/	27367
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	22
13	(medical outcome adj1 (survey or stud*)).mp.	1036
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	3421
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	27538
16	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	79257
17	(QoL or HRQoL or HRQL).mp.	82413
18	exp "quality of life"/	424147

#	Searches	Results
19	(health related quality of life or health-related quality of life).mp.	52290
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	88299
21	17 or 18 or 19 or 20	436921
22	health state$.mp.	9329
23	utilit*.mp.	246476
24	Patient Preference/ or preference.mp.	134104
25	(map$ or regression).mp.	1520854
26	exp health status/	206509
27	health survey/	182930
28	exp daily life activity/	77594
29	("Activities of Daily Living" or "IADL").mp.	33857
30	Psychometrics.mp. or exp psychometry/	84711
31	("health year equivalent" or "HYE").mp.	102
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2323937
33	21 and 32	106958
34	16 or 33	165552
35	4 and 34	37245
36	limit 35 to yr="2016 -Current"	10331

Table 72 HSUVs and HRQoL search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (July 5, 2018)

#	Searches	Results
1	DEPRESSION/	102339
2	exp Depressive Disorder/	99365
3	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	492084
4	((affective or mood) adj disorder*).mp.	39422
5	1 or 2 or 3 or 4	510459
6	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	8290
7	(Health utilities index or HUI).mp.	1427
8	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1045
9	(short form 6D or short-form 6D).mp.	125
10	(standard gamble or ("SG" adj2 "standard gamble")).mp.	797
11	(15D or 16D or 17D).mp.	2606
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	18
13	(medical outcome adj1 (survey or stud*)).mp.	764
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	3688
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	17375
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	34745
17	(QoL or HRQoL or HRQL).mp.	46189
18	exp "Quality of Life"/	163195

#	Searches	Results
19	(health related quality of life or health-related quality of life).mp.	36312
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	38478
21	17 or 18 or 19 or 20	186076
22	health state$.mp.	5503
23	utilit*.mp.	177443
24	PATIENT PREFERENCE/ or preference.mp.	97111
25	(map$ or regression).mp.	1284775
26	exp Health Status/	288448
27	exp Health Surveys/	504724
28	exp "Activities of Daily Living"/	63246
29	("Activities of Daily Living" or "IADL").mp.	70497
30	exp PSYCHOMETRICS/ or psychometric*.mp.	85058
31	("health year equivalent" or "HYE").mp.	44
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2287296
33	21 and 32	169128
34	16 or 33	194878
35	5 and 34	30076
36	limit 35 to yr="2016 -Current"	6709

Table 73 HSUVs and HRQoL search strategy for Cochrane Library (July 5, 2018)

#	Searches	Results
1	exp depressive disorder/	10402
2	(depres* or dysphori* or dysthymi* or melancholi* or "seasonal affective disorder* " or "affective disorder*" or "mood disorder*").ti,ab,kw.	57672
3	1 or 2	58299
4	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	4874
5	(Health utilities index or HUI).mp.	469
6	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	502
7	(short form 6D or short-form 6D).mp.	45
8	(standard gamble or ("SG" adj2 "standard gamble")).mp.	282
9	(15D or 16D or 17D).mp.	219
10	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	11
11	(medical outcome adj1 (survey or stud*)).mp.	198
12	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	524
13	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	2926
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	9481
15	(QoL or HRQoL or HRQL).mp.	14708
16	(health related quality of life or health-related quality of life).mp.	11641
17	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	16172
18	15 or 16 or 17	30814

#	Searches	Results
19	health state$.mp.	2181
20	utilit*.mp.	16679
21	preference*.mp.	14237
22	(map$ or regression).mp.	63348
23	health status.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	11284
24	health survey*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	5308
25	("Activities of Daily Living" or "IADL").mp.	8743
26	psychometric*.mp.	5630
27	("health year equivalent" or "HYE").mp.	14
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	114394
29	18 and 28	9541
30	14 or 29	16689
31	3 and 30	3527
32	limit 31 to yr="2016 -Current" [Limit not valid in DARE; records were retained]	1291

Table 74 HSUVs and HRQoL search strategy for PsycINFO (July 5, 2018)

#	Searches	Results
1	exp Major Depression/	115976
2	exp Atypical Depression/	179
3	exp "DEPRESSION (EMOTION)"/	13004
4	exp Seasonal Affective Disorder/	1028
5	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	294878
6	((affective or mood) adj disorder*).mp.	37952
7	1 or 2 or 3 or 4 or 5 or 6	312317
8	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	2642
9	(Health utilities index or HUI).mp.	952
10	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	254
11	(short form 6D or short-form 6D).mp.	48
12	(standard gamble or ("SG" adj2 "standard gamble")).mp.	204
13	(15D or 16D or 17D).mp.	195
14	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	12
15	(medical outcome adj1 (survey or stud*)).mp.	525
16	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	3270
17	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	19749
18	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	26929
19	(QoL or HRQoL or HRQL).mp.	13433
20	exp "Quality of Life"/	38042
21	(health related quality of life or health-related quality of life).mp.	10023
22	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	12118

#	Searches	Results
23	19 or 20 or 21 or 22	45057
24	health state$.mp.	1384
25	utilit*.mp.	50029
26	preference*.mp.	82566
27	(map$ or regression).mp.	202761
28	health status.mp.	17031
29	health survey*.mp.	19670
30	exp "Activities of Daily Living"/	5486
31	("Activities of Daily Living" or "IADL").mp.	14489
32	exp PSYCHOMETRICS/ or psychometric*.mp.	74427
33	("health year equivalent" or "HYE").mp.	39
34	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	425762
35	23 and 34	16253
36	18 or 35	40758
37	7 and 36	17147
38	limit 37 to yr="2016 -Current"	3956

I.1.2.2 April 2019 update

Table 75 HSUVs and HRQoL search strategy for Embase (April 4, 2019)

#	Searches	Results
1	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	731656
2	((affective or mood) adj disorder*).mp.	69210
3	*depression/ or *agitated depression/ or *atypical depression/ or *depressive psychosis/ or *dysphoria/ or *dysthymia/ or *endogenous depression/ or *involutional depression/ or *late life depression/ or *major depression/ or *masked depression/ or *melancholia/ or "*mixed anxiety and depression"/ or "*mixed depression and dementia"/ or *premenstrual dysphoric disorder/ or *reactive depression/ or *recurrent brief depression/ or *seasonal affective disorder/ or *treatment resistant depression/	165898
4	1 or 2 or 3	760114
5	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	17594
6	(Health utilities index or HUI).mp.	3071
7	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1616
8	(short form 6D or short-form 6D).mp.	301
9	(standard gamble or ("SG" adj2 "standard gamble")).mp.	1059
10	(15D or 16D or 17D).mp.	3746
11	exp short form 12/ or exp short form 20/ or exp short form 36/	30629
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	25
13	(medical outcome adj1 (survey or stud*)).mp.	1076
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	3734
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	29683

#	Searches	Results
16	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	86824
17	(QoL or HRQoL or HRQL).mp.	89629
18	exp "quality of life"/	454511
19	(health related quality of life or health-related quality of life).mp.	56750
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	96320
21	17 or 18 or 19 or 20	468611
22	health state$.mp.	10088
23	utilit*.mp.	262464
24	Patient Preference/ or preference.mp.	140676
25	(map$ or regression).mp.	1611926
26	exp health status/	215775
27	health survey/	182765
28	exp daily life activity/	81129
29	("Activities of Daily Living" or "IADL").mp.	36148
30	Psychometrics.mp. or exp psychometry/	85682
31	("health year equivalent" or "HYE").mp.	107
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2443853
33	21 and 32	114958
34	16 or 33	179061
35	4 and 34	40749
36	limit 35 to yr="2018 -Current"	5397

Table 76 HSUVs and HRQoL search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (April 4, 2019)

#	Searches	Results
1	DEPRESSION/	107728
2	exp Depressive Disorder/	102832
3	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	510609
4	((affective or mood) adj disorder*).mp.	40829
5	1 or 2 or 3 or 4	529616
6	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	9195
7	(Health utilities index or HUI).mp.	1516
8	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1101
9	(short form 6D or short-form 6D).mp.	130
10	(standard gamble or ("SG" adj2 "standard gamble")).mp.	813
11	(15D or 16D or 17D).mp.	2634
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	18
13	(medical outcome adj1 (survey or stud*)).mp.	789
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	4204
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	18406

#	Searches	Results
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	37331
17	(QoL or HRQoL or HRQL).mp.	49678
18	exp "Quality of Life"/	173824
19	(health related quality of life or health-related quality of life).mp.	38997
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	41040
21	17 or 18 or 19 or 20	198377
22	health state$.mp.	5843
23	utilit*.mp.	188098
24	PATIENT PREFERENCE/ or preference.mp.	102150
25	(map$ or regression).mp.	1353665
26	exp Health Status/	305125
27	exp Health Surveys/	523925
28	exp "Activities of Daily Living"/	95015
29	("Activities of Daily Living" or "IADL").mp.	72969
30	exp PSYCHOMETRICS/ or psychometric*.mp.	88985
31	("health year equivalent" or "HYE").mp.	48
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2424635
33	21 and 32	180288
34	16 or 33	207781
35	5 and 34	32478
36	limit 35 to yr="2018 -Current"	3265

Table 77 HSUVs and HRQoL search strategy for Cochrane Library (April 4, 2019)

#	Searches	Results
1	exp depressive disorder/	10823
2	(depres* or dysphori* or dysthymi* or melancholi* or "seasonal affective disorder* " or "affective disorder*" or "mood disorder*").ti,ab,kw.	75011
3	1 or 2	75629
4	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	8480
5	(Health utilities index or HUI).mp.	547
6	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	535
7	(short form 6D or short-form 6D).mp.	55
8	(standard gamble or ("SG" adj2 "standard gamble")).mp.	291
9	(15D or 16D or 17D).mp.	293
10	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	11
11	(medical outcome adj1 (survey or stud*)).mp.	246
12	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	1087
13	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	4660
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	15287
15	(QoL or HRQoL or HRQL).mp.	21119
16	(health related quality of life or health-related quality of life).mp.	15579

#	Searches	Results
17	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	24080
18	15 or 16 or 17	44987
19	health state$.mp.	2488
20	utilit*.mp.	19703
21	preference*.mp.	17322
22	(map$ or regression).mp.	74652
23	health status.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	14051
24	health survey*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	7205
25	("Activities of Daily Living" or "IADL").mp.	10549
26	psychometric*.mp.	6299
27	("health year equivalent" or "HYE").mp.	15
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	137261
29	18 and 28	12324
30	14 or 29	24414
31	3 and 30	6055
32	limit 31 to yr="2018 -Current" [Limit not valid in DARE; records were retained]	903

Table 78 HSUVs and HRQoL search strategy for PsycINFO (April 4, 2019)

#	Searches	Results
1	exp Major Depression/	119292
2	exp Atypical Depression/	180
3	exp "DEPRESSION (EMOTION)"/	13448
4	exp Seasonal Affective Disorder/	1043
5	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	306542
6	((affective or mood) adj disorder*).mp.	38990
7	1 or 2 or 3 or 4 or 5 or 6	324409
8	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	2832
9	(Health utilities index or HUI).mp.	984
10	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	268
11	(short form 6D or short-form 6D).mp.	48
12	(standard gamble or ("SG" adj2 "standard gamble")).mp.	208
13	(15D or 16D or 17D).mp.	201
14	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	12
15	(medical outcome adj1 (survey or stud*)).mp.	537
16	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	3772
17	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	20899
18	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	28788
19	(QoL or HRQoL or HRQL).mp.	14159
20	exp "Quality of Life"/	39225

#	Searches	Results
21	(health related quality of life or health-related quality of life).mp.	10573
22	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	12674
23	19 or 20 or 21 or 22	46863
24	health state$.mp.	1431
25	utilit*.mp.	52110
26	preference*.mp.	85842
27	(map$ or regression).mp.	212636
28	health status.mp.	17510
29	health survey*.mp.	20446
30	exp "Activities of Daily Living"/	5607
31	("Activities of Daily Living" or "IADL").mp.	14962
32	exp PSYCHOMETRICS/ or psychometric*.mp.	77688
33	("health year equivalent" or "HYE").mp.	40
34	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	444344
35	23 and 34	16985
36	18 or 35	43195
37	7 and 36	18263
38	limit 37 to yr="2018 -Current"	1639

I.1.2.3 September 2019 update

Table 79 HSUVs and HRQoL search strategy for Embase (September 19, 2019)

#	Searches	Results
1	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	760494
2	((affective or mood) adj disorder*).mp.	71795
3	*depression/ or *agitated depression/ or *atypical depression/ or *depressive psychosis/ or *dysphoria/ or *dysthymia/ or *endogenous depression/ or *involutional depression/ or *late life depression/ or *major depression/ or *masked depression/ or *melancholia/ or "*mixed anxiety and depression"/ or "*mixed depression and dementia"/ or *premenstrual dysphoric disorder/ or *reactive depression/ or *recurrent brief depression/ or *seasonal affective disorder/ or *treatment resistant depression/	170856
4	1 or 2 or 3	790089
5	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	18971
6	(Health utilities index or HUI).mp.	3205
7	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1693
8	(short form 6D or short-form 6D).mp.	309
9	(standard gamble or ("SG" adj2 "standard gamble")).mp.	1088
10	(15D or 16D or 17D).mp.	3918
11	exp short form 12/ or exp short form 20/ or exp short form 36/	33074
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	25
13	(medical outcome adj1 (survey or stud*)).mp.	1106

#	Searches	Results
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	4024
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	31617
16	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	92954
17	(QoL or HRQoL or HRQL).mp.	95370
18	exp "quality of life"/	480098
19	(health related quality of life or health-related quality of life).mp.	60301
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	103740
21	17 or 18 or 19 or 20	495496
22	health state$.mp.	10593
23	utilit*.mp.	276560
24	Patient Preference/ or preference.mp.	147202
25	(map$ or regression).mp.	1701253
26	exp health status/	225892
27	health survey/	187519
28	exp daily life activity/	84795
29	("Activities of Daily Living" or "IADL").mp.	37949
30	Psychometrics.mp. or exp psychometry/	88758
31	("health year equivalent" or "HYE").mp.	112
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2568624
33	21 and 32	121449
34	16 or 33	189979
35	4 and 34	43745
36	(Mar* 2019 or Apr* 2019 or May* 2019 or Jun* 2019 or Jul* 2019 or Aug* 2019 or Sep* 2019 or Oct* 2019).dp.	323927
37	35 and 36	1337
38	limit 35 to dd=20190301-20191031	1567
39	37 or 38	2198

Table 80 HSUVs and HRQoL search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (September 19, 2019)

#	Searches	Results
1	DEPRESSION/	111496
2	exp Depressive Disorder/	105124
3	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	524149
4	((affective or mood) adj disorder*).mp.	41821
5	1 or 2 or 3 or 4	543596
6	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	9858
7	(Health utilities index or HUI).mp.	1575
8	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1144
9	(short form 6D or short-form 6D).mp.	134
10	(standard gamble or ("SG" adj2 "standard gamble")).mp.	829

#	Searches	Results
11	(15D or 16D or 17D).mp.	2703
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	18
13	(medical outcome adj1 (survey or stud*)).mp.	803
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	4569
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	19229
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	39320
17	(QoL or HRQoL or HRQL).mp.	52182
18	exp "Quality of Life"/	181187
19	(health related quality of life or health-related quality of life).mp.	40907
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	42794
21	17 or 18 or 19 or 20	207251
22	health state$.mp.	6081
23	utilit*.mp.	195883
24	PATIENT PREFERENCE/ or preference.mp.	105716
25	(map$ or regression).mp.	1402936
26	exp Health Status/	316431
27	exp Health Surveys/	536233
28	exp "Activities of Daily Living"/	97370
29	("Activities of Daily Living" or "IADL").mp.	74690
30	exp PSYCHOMETRICS/ or psychometric*.mp.	91358
31	("health year equivalent" or "HYE").mp.	50
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2505898
33	21 and 32	188007
34	16 or 33	216923
35	5 and 34	34241
36	(2019 Mar* or 2019 Apr* or 2019 May* or 2019 Jun* or 2019 Jul* or 2019 Aug* or 2019 Sep* or 2019 Oct*).dp.	684023
37	35 and 36	1221
38	limit 35 to ed=20190301-20191031	1828
39	37 or 38	2742

Table 81 HSUVs and HRQoL search strategy for Cochrane Library (September 19, 2019)

#	Searches	Results
1	exp depressive disorder/	11125
2	(depres* or dysphori* or dysthymi* or melancholi* or "seasonal affective disorder* " or "affective disorder*" or "mood disorder*").ti,ab,kw.	78224
3	1 or 2	78853
4	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	8967
5	(Health utilities index or HUI).mp.	564
6	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	539
7	(short form 6D or short-form 6D).mp.	55

#	Searches	Results
8	(standard gamble or ("SG" adj2 "standard gamble")).mp.	291
9	(15D or 16D or 17D).mp.	311
10	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	11
11	(medical outcome adj1 (survey or stud*)).mp.	250
12	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	1190
13	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	4987
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	16198
15	(QoL or HRQoL or HRQL).mp.	22380
16	(health related quality of life or health-related quality of life).mp.	16416
17	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	25626
18	15 or 16 or 17	47649
19	health state$.mp.	2548
20	utilit*.mp.	20441
21	preference*.mp.	18065
22	(map$ or regression).mp.	78133
23	health status.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	14583
24	health survey*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	7484
25	("Activities of Daily Living" or "IADL").mp.	10964
26	psychometric*.mp.	6463
27	("health year equivalent" or "HYE").mp.	15
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	143157
29	18 and 28	12896
30	14 or 29	25715
31	3 and 30	6465
32	limit 31 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	373

Table 82 HSUVs and HRQoL search strategy for PsycINFO (September 19, 2019)

#	Searches	Results
1	exp Major Depression/	124729
2	exp Atypical Depression/	185
3	exp "DEPRESSION (EMOTION)"/	13894
4	exp Seasonal Affective Disorder/	1058
5	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	328607
6	((affective or mood) adj disorder*).mp.	40274
7	1 or 2 or 3 or 4 or 5 or 6	346252
8	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	3130
9	(Health utilities index or HUI).mp.	1023
10	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	284
11	(short form 6D or short-form 6D).mp.	55

#	Searches	Results
12	(standard gamble or ("SG" adj2 "standard gamble")).mp.	212
13	(15D or 16D or 17D).mp.	216
14	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	12
15	(medical outcome adj1 (survey or stud*)).mp.	553
16	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	4558
17	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	22542
18	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	31527
19	(QoL or HRQoL or HRQL).mp.	15137
20	exp "Quality of Life"/	41320
21	(health related quality of life or health-related quality of life).mp.	11406
22	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	13369
23	19 or 20 or 21 or 22	49403
24	health state$.mp.	1498
25	utilit*.mp.	54498
26	preference*.mp.	89672
27	(map$ or regression).mp.	225162
28	health status.mp.	33360
29	health survey*.mp.	33887
30	exp "Activities of Daily Living"/	5794
31	("Activities of Daily Living" or "IADL").mp.	26810
32	exp PSYCHOMETRICS/ or psychometric*.mp.	187934
33	("health year equivalent" or "HYE").mp.	45
34	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	580090
35	23 and 34	21667
36	18 or 35	50118
37	7 and 36	20937
38	limit 37 to yr="2019 -Current"	1406

I.1.2.4 January 2020 update

Table 83 HSUVs and HRQoL search strategy for Embase (January 29, 2020)

#	Searches	Results
1	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	774108
2	((affective or mood) adj disorder*).mp.	72976
3	*depression/ or *agitated depression/ or *atypical depression/ or *depressive psychosis/ or *dysphoria/ or *dysthymia/ or *endogenous depression/ or *involutional depression/ or *late life depression/ or *major depression/ or *masked depression/ or *melancholia/ or "*mixed anxiety and depression"/ or "*mixed depression and dementia"/ or *premenstrual dysphoric disorder/ or *reactive depression/ or *recurrent brief depression/ or *seasonal affective disorder/ or *treatment resistant depression/	172716

#	Searches	Results
4	1 or 2 or 3	804248
5	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	19736
6	(Health utilities index or HUI).mp.	3277
7	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1729
8	(short form 6D or short-form 6D).mp.	318
9	(standard gamble or ("SG" adj2 "standard gamble")).mp.	1104
10	(15D or 16D or 17D).mp.	4017
11	exp short form 12/ or exp short form 20/ or exp short form 36/	33874
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	24
13	(medical outcome adj1 (survey or stud*)).mp.	1116
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	4172
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	32645
16	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	95735
17	(QoL or HRQoL or HRQL).mp.	98526
18	exp "quality of life"/	473675
19	(health related quality of life or health-related quality of life).mp.	62329
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	107461
21	17 or 18 or 19 or 20	494170
22	health state$.mp.	10939
23	utilit*.mp.	285308
24	Patient Preference/ or preference.mp.	151137
25	(map$ or regression).mp.	1752388
26	exp health status/	230823
27	health survey/	189699
28	exp daily life activity/	86462
29	("Activities of Daily Living" or "IADL").mp.	38951
30	Psychometrics.mp. or exp psychometry/	90175
31	("health year equivalent" or "HYE").mp.	115
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2638873
33	21 and 32	119544
34	16 or 33	194363
35	4 and 34	45218
36	(Sep* 2019 or Oct* 2019 or Nov* 2019 or Dec* 2019 or Jan* 2020).dp.	169125
37	35 and 36	659
38	limit 35 to dd=20190901-20200131	1073
39	37 or 38	1382

Table 84 HSUVs and HRQoL search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (January 29, 2020)

#	Searches	Results
1	DEPRESSION/	114643

#	Searches	Results
2	exp Depressive Disorder/	106714
3	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	534764
4	((affective or mood) adj disorder*).mp.	42579
5	1 or 2 or 3 or 4	554541
6	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	10355
7	(Health utilities index or HUI).mp.	1621
8	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	1158
9	(short form 6D or short-form 6D).mp.	136
10	(standard gamble or ("SG" adj2 "standard gamble")).mp.	835
11	(15D or 16D or 17D).mp.	2773
12	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	18
13	(medical outcome adj1 (survey or stud*)).mp.	817
14	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	4828
15	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	19933
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	40883
17	(QoL or HRQoL or HRQL).mp.	54182
18	exp "Quality of Life"/	187399
19	(health related quality of life or health-related quality of life).mp.	42525
20	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	44238
21	17 or 18 or 19 or 20	214389
22	health state$.mp.	6262
23	utilit*.mp.	201994
24	PATIENT PREFERENCE/ or preference.mp.	108602
25	(map$ or regression).mp.	1444021
26	exp Health Status/	326424
27	exp Health Surveys/	547367
28	exp "Activities of Daily Living"/	99422
29	("Activities of Daily Living" or "IADL").mp.	76075
30	exp PSYCHOMETRICS/ or psychometric*.mp.	93344
31	("health year equivalent" or "HYE").mp.	51
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	2573806
33	21 and 32	194459
34	16 or 33	224448
35	5 and 34	35683
36	(2019 Sep* or 2019 Oct* or 2019 Nov* or 2019 Dec* or 2020 Jan*).dp.	518106
37	35 and 36	890
38	limit 35 to ed=20190901-20200131	1350
39	37 or 38	2072

Table 85 HSUVs and HRQoL search strategy for Cochrane Library (January 29, 2020)

#	Searches	Results
1	exp depressive disorder/	11311
2	(depres* or dysphori* or dysthymi* or melancholi* or "seasonal affective disorder* " or "affective disorder*" or "mood disorder*").ti,ab,kw.	80924
3	1 or 2	81565
4	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	9450
5	(Health utilities index or HUI).mp.	574
6	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	544
7	(short form 6D or short-form 6D).mp.	56
8	(standard gamble or ("SG" adj2 "standard gamble")).mp.	292
9	(15D or 16D or 17D).mp.	329
10	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	11
11	(medical outcome adj1 (survey or stud*)).mp.	253
12	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	1293
13	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	5295
14	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	17075
15	(QoL or HRQoL or HRQL).mp.	23414
16	(health related quality of life or health-related quality of life).mp.	17116
17	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	27030
18	15 or 16 or 17	49947
19	health state$.mp.	2597
20	utilit*.mp.	21084
21	preference*.mp.	18687
22	(map$ or regression).mp.	81046
23	health status.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	15007
24	health survey*.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	7740
25	("Activities of Daily Living" or "IADL").mp.	11278
26	psychometric*.mp.	6586
27	("health year equivalent" or "HYE").mp.	15
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	148079
29	18 and 28	13433
30	14 or 29	26953
31	3 and 30	6914
32	limit 31 to yr="2019 -Current" [Limit not valid in DARE; records were retained]	776

Table 86 HSUVs and HRQoL search strategy for PsycINFO (January 29, 2020)

#	Searches	Results
1	exp Major Depression/	124729
2	exp Atypical Depression/	185
3	exp "DEPRESSION (EMOTION)"/	13894
4	exp Seasonal Affective Disorder/	1058

#	Searches	Results
5	(depres* or dysphori* or dysthymi* or melancholi* or seasonal affective disorder*).mp.	328607
6	((affective or mood) adj disorder*).mp.	40274
7	1 or 2 or 3 or 4 or 5 or 6	346252
8	(EuroQOL 5-Dimension or Euroqol 5D or EQ-5D or EQ5D or Euroqol).mp.	3130
9	(Health utilities index or HUI).mp.	1023
10	(time trade off or time trade-off or ("TTO" adj2 "time trade")).mp.	284
11	(short form 6D or short-form 6D).mp.	55
12	(standard gamble or ("SG" adj2 "standard gamble")).mp.	212
13	(15D or 16D or 17D).mp.	216
14	("quality of well-being index" or "quality of wellbeing index" or "quality of well being index").mp.	12
15	(medical outcome adj1 (survey or stud*)).mp.	553
16	(Psychological General Well-Being or PGWB or Clinical Outcomes in Routine Evaluation or Depression Anxiety Distress Scale or DASS* or Kessler Psychological Distress Scale).mp.	4558
17	(Patient Health Questionnaire or PHQ* or Generalised Anxiety Disorder Assessment or GAD or General Health Questionnaire or GHQ).mp.	22542
18	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	31527
19	(QoL or HRQoL or HRQL).mp.	15137
20	exp "Quality of Life"/	41320
21	(health related quality of life or health-related quality of life).mp.	11406
22	((quality of life or QoL) adj10 (question$ or instrument or scale$1or score$1)).mp.	13369
23	19 or 20 or 21 or 22	49403
24	health state$.mp.	1498
25	utilit*.mp.	54498
26	preference*.mp.	89672
27	(map$ or regression).mp.	225162
28	health status.mp.	33360
29	health survey*.mp.	33887
30	exp "Activities of Daily Living"/	5794
31	("Activities of Daily Living" or "IADL").mp.	26810
32	exp PSYCHOMETRICS/ or psychometric*.mp.	187934
33	("health year equivalent" or "HYE").mp.	45
34	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	580090
35	23 and 34	21667
36	18 or 35	50118
37	7 and 36	20937
38	limit 37 to yr="2019 -Current"	1406

I.1.3 Eligibility criteria

The eligibility criteria applied throughout the July 2018, April 2019, September 2019, and January 2020 SLR updates are detailed in Table 87. The inclusion/exclusion of citations (both at the title/abstract phase and full publication review) was conducted by two

independent analysts. Any disputes were referred to the project manager and resolved by consensus.

Relevant data were extracted into a pre-approved data extraction template by a reviewer. A second reviewer checked the data extraction, and any inconsistencies were resolved through discussion.

The inclusion/exclusion of citations (both at the title/abstract phase and full publication review) was conducted by two independent analysts. Any disputes were referred to the project manager and resolved by consensus.

Relevant data were extracted into a pre-approved data extraction template by a reviewer. A second reviewer checked the data extraction, and any inconsistencies were resolved through discussion.

Table 87 Eligibility criteria for the HSUVs and HRQoL use systematic literature review

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with depression (with a particular focus on patients who have progressed to TRD) and patients with related conditions (dysphoria, dysthymia, melancholia, SAD, mood disorder, GAD)	Paediatric patients (<18 years) and patients with comorbid depression
Intervention	No restriction	-
Outcomes	Outcomes of interest included: • HSUVs elicited directly (SG/TTO) or using preference-based instruments • HRQOL data measured using generic or disease-specific instruments • Mapping algorithms	Outcomes not listed
Study design	Eligible study designs included: • Utility elicitation studies • Clinical studies • Observational studies • Longitudinal studies	• Reviews/editorials • Budget impact analyses
Territory of interest	No restriction – although primary focus was UK	-
Date of publication	July 2018 update: 2016 onwards April 2019 update: July 2018 onwards September 2019 update: April 2019 onwards January 2020 update: September 2019 onwards	July 2018 update: Pre-2016 April 2019 update: Pre-July 2018 September 2019: Pre-April 2019 January 2020: Pre-September 2019
Language of publication	English language publications or foreign language publications with an English abstract	Foreign language publications without an English abstract

I.1.4 Systematic selection of studies

I.1.4.1 July 2018 update

The electronic databases identified a total of 22,287 citations. Following removal of 5,194 duplicates, 17,093 citations were screened on the basis of title and abstract. A total of 53 citations which potentially reported HSUVs of interest and were thus considered to be potentially relevant were obtained for full text review. At this stage, a further 25 citations were excluded. Hand searching yielded three additional publications reporting relevant utilities, resulting in a total of 31 publications that were eligible for inclusion in the HSUV review update. Of the 31 included publications, 29 were full publications and were extracted in detail. The remaining two citations were presented as abstracts only; due to limited reporting and the difficulties associated with meaningful quality assessment of abstracts, these studies were not extracted and were tagged[113,114].

In addition, 266 studies reporting disease-specific HRQOL data were tagged following the title/abstract review phase, and hand searching yielded two additional publications reporting relevant HRQOL data.

I.1.4.2 April 2019 update

In April 2019, the electronic databases identified a total of 11,204 citations. Following removal of 2,388 duplicates, 8,816 citations were screened on the basis of title and abstract. A total of 28 citations which potentially reported HSUVs of interest were obtained for full text review. At this stage, a further 23 citations were excluded. Hand searching yielded three additional publications for inclusion. This resulted in a total of eight publications that were eligible for inclusion in the April 2019 HSUV update. All eight included studies were presented as full publications.

In addition, 242 studies reporting disease-specific HRQoL data were tagged following the title/abstract review phase.

I.1.4.3 September 2019 update

In September 2019, the electronic databases identified a total of 6,198 citations. Following removal of 742 duplicates, 5,456 citations were screened on the basis of title and abstract. A total of 17 citations which potentially reported HSUVs of interest were obtained for full text review. At this stage, a further ten citations were excluded. Hand searching did not yield any additional citations for inclusion. This resulted in a total of seven publications that were eligible for inclusion in the September 2019 HSUV update. Of the seven included publications, six were full publications and one was presented as a conference abstract only. Due to limited reporting and the difficulties associated with meaningful quality assessment of abstracts, this study was not extracted and was tagged.

In addition, 101 studies reporting disease-specific HRQOL data were tagged following the title/abstract review phase.

I.1.4.4 January 2020 update

In January 2020, the electronic databases identified a total of 5,636 citations. Following removal of 583 duplicates, 5,053 citations were screened on the basis of title and abstract. A total of 26 citations which potentially reported HSUVs of interest were obtained for full text review. At this stage, a further 17 citations were excluded. Hand searching did not yield any additional citations for inclusion. This resulted in a total of nine publications that were eligible for inclusion in the January 2020 HSUV update. Of the nine included studies, seven were full publications and two were conference abstracts[115,116]. Due to limited reporting and the difficulties associated with meaningful quality assessment of abstracts, these studies were tagged and not extracted.

In addition, 97 studies reporting the use of disease-specific and/or generic HRQOL instruments in the population of interest were tagged.

The PRISMA flow diagram for the study selection process used in the July 2018, April 2019, September 2019, and January 2020 SLR updates is presented in Figure 13.

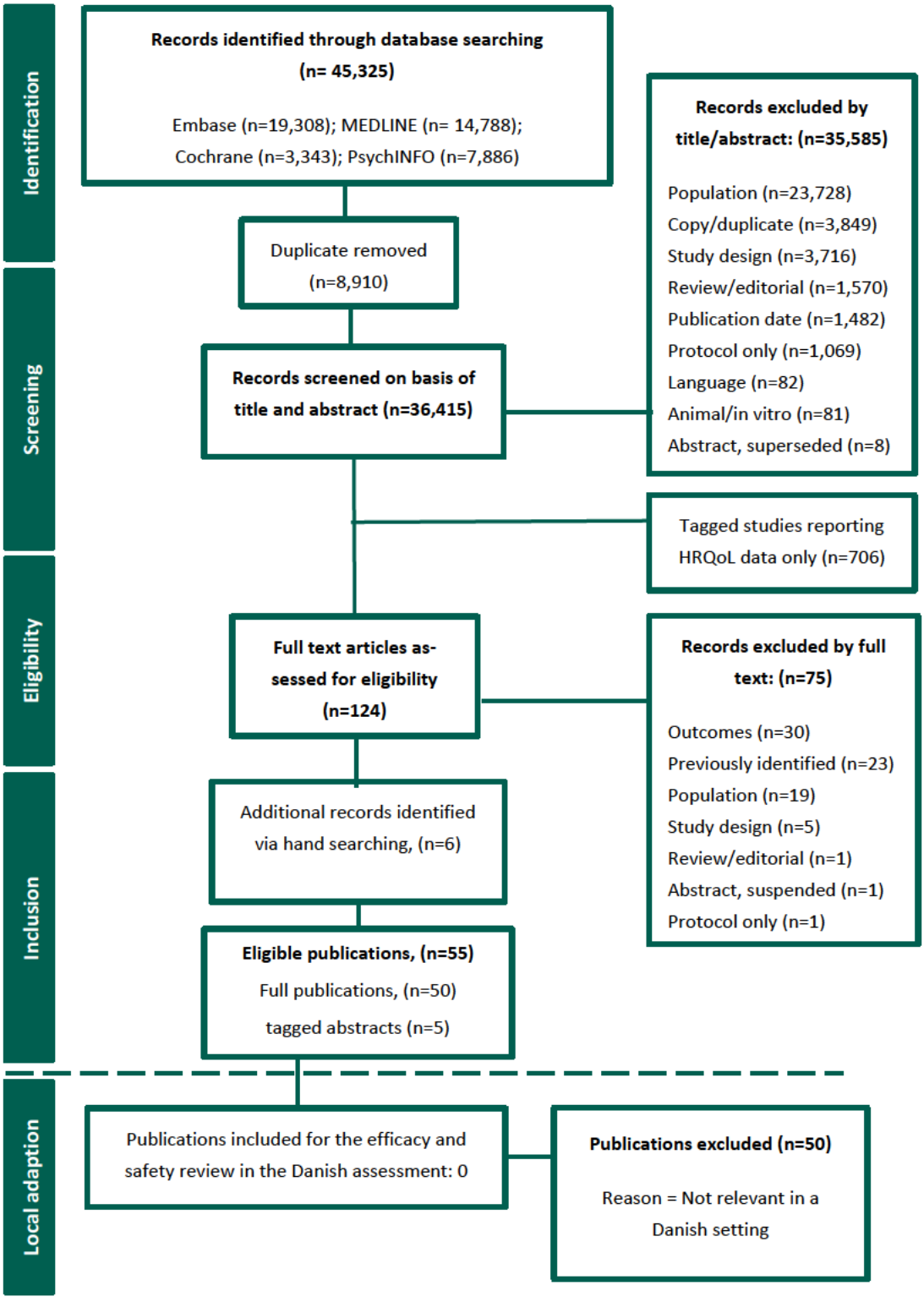


Figure 13 PRISMA diagram for the HSUVs and HRQoL SLR

I.1.4.5 Vortioxetine NICE submission (TA367)

The electronic database searches identified a total of 5,404 citations. Following removal of 1,659 duplicates, 3,745 citations were screened on the basis of title and abstract. A total of 322 publications were retained for full text screening. Following full text screening, 23 publications were retained for data extraction. However, only those studies reporting HSUV data of potential value for populating the model were discussed further in the submission document: this consisted of four studies reporting HSUVs and one study reporting disutilities. Details of these five unique studies and the REVIVE trial only have been retained in the current report.

The PRISMA flow diagram for the TA367 SLR is presented in Figure 14.

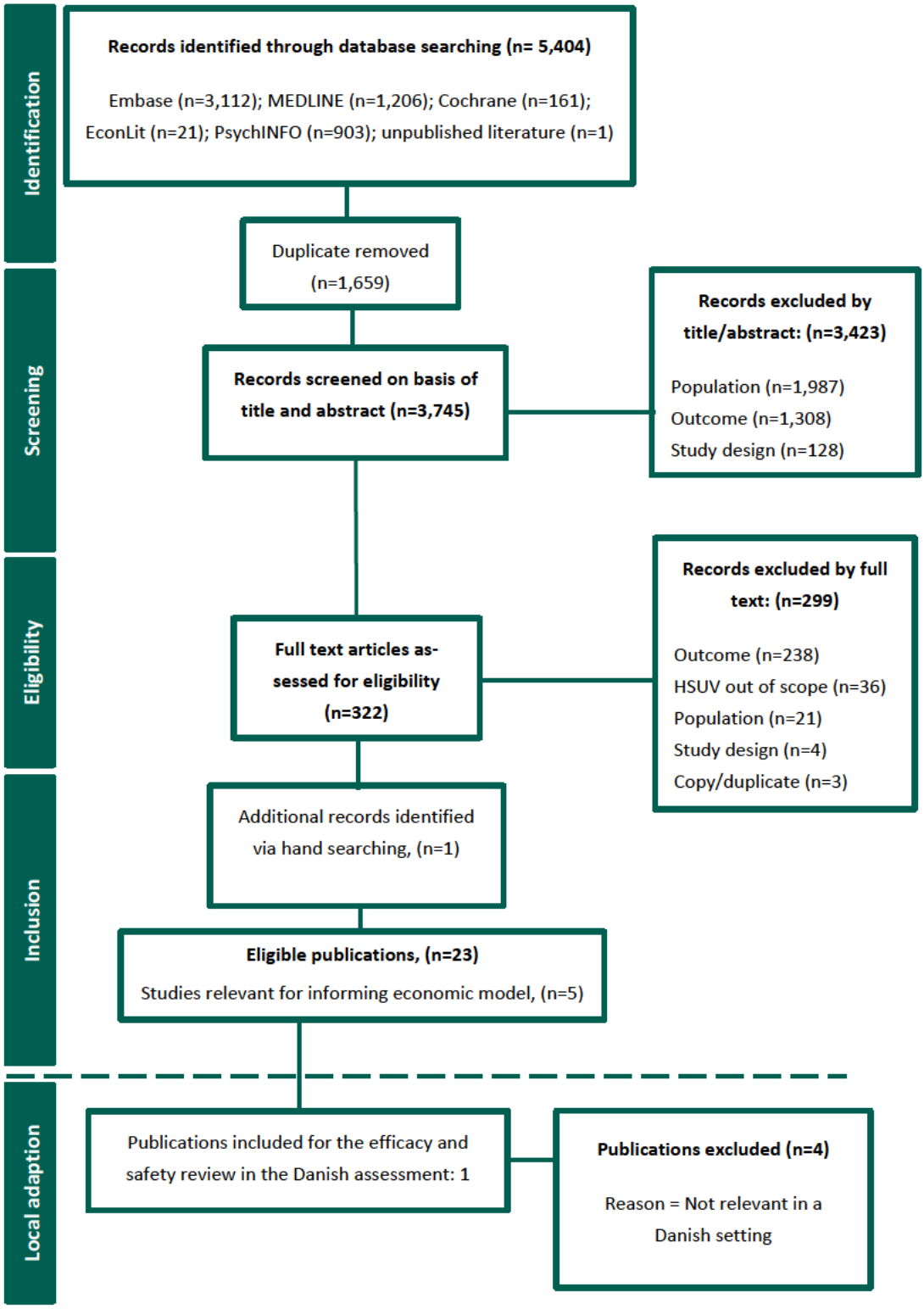


Figure 14 PRISMA diagram for the Vortioxetine NICE submission (TA367)SLR

I.1.4.6 CG90

Five unique studies reporting HSUVs for depression were identified (see Table 347 of the updated CG90 report, May 2018)[117-121].[117-121]. Of these, two were also identified in the vortioxetine submission[119,120]; therefore, three unique studies were extracted as part of the CG90 review[119,120].[117,118,121]. A PRISMA flow diagram summarising the study selection process was not available from the updated CG90 report.

Table 89 provides an overview of the publications included in the SLR updates conducted in July 2018, April 2019, September 2019, and January 2020, as well as the Vortioxetine NICE submission (TA367) and the CG90 guidelines. Table 90 details the publications excluded during full-text screening from the SLR updates in July 2018, April 2019, September 2019, and January 2020, along with the reasons for their exclusion. However, full-text exclusions for the Vortioxetine NICE submission (TA367) and the CG90 guidelines are not available.

I.1.5 Included publications

Of the 55 studies included in the global SLR, one study was used in the current submission (Table 88).

Table 88 List of studies from the global HSUV and HRQoL systematic literature review included in the local adaptation

Reference	Title
Sullivan et al., 2004	A comparison of the direct costs and cost effectiveness of serotonin reuptake inhibitors and associated adverse drug reactions

I.1.6 Excluded full text references

The global SLR identified 55 relevant studies. However, as detailed in the local adaptation section below, 54 of the publications included in the global SLR were excluded in the current submission, and these are therefore also considered 'excluded'. A list of the 54 studies included in the global SLR is provided in Table 89.

Table 89 List of studies included in the global HSUV and HRQoL systematic literature review, excluded from the local adaptation

Reference	Title
Fedgchin, 2019	Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1)
Heslin, 2019	Psychometric properties of the five-level EuroQoL-5 dimension and Short Form-6 dimension measures of health-related quality of life in a population of pregnant women with depression
Lee, 2019	Neurofeedback Treatment on Depressive Symptoms and Functional Recovery in Treatment-Resistant Patients with Major Depressive Disorder: an Open-Label Pilot Study
Mihalopoulos, 2019	Health state utility values of high prevalence mental disorders in Australia: results from the National Survey of Mental Health and Wellbeing

Murata, 2019	Alterations of mental defeat and cognitive flexibility during cognitive behavioral therapy in patients with major depressive disorder: a single-arm pilot study
Sumiyoshi, 2019	Relationship of cognitive impairment with depressive symptoms and psychosocial function in patients with major depressive disorder: Cross-sectional analysis of baseline data from PERFORM-J
Yan, 2019	Cost-effectiveness analysis of a randomized study of depression treatment options in primary care suggests stepped-care treatment may have economic benefits
Abdin, 2019	A comparison of the reliability and validity of SF-6D, EQ-5D and HUI3 utility measures in patients with schizophrenia and patients with depression in Singapore
Grochtdreis, 2019	Cost-effectiveness analysis of collaborative treatment of late-life depression in primary care (GermanIMPACT)
Hensel, 2019	A Web-Based Mental Health Platform for Individuals Seeking Specialized Mental Health Care Services: Multicenter Pragmatic Randomized Controlled Trial
Jaffe, 2019	The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study
Shearer, 2019	Refractory depression - cost-effectiveness of radically open dialectical behaviour therapy: findings of economic evaluation of RefraMED trial
Usuba, 2019	Trend of the burden of chronic illnesses: using the Canadian Community Health Survey
Aznar-Lou, 2019	Diagnostic accuracy and treatment approach to depression in primary care: Predictive factors
Bounthavong, 2018	Economic evaluation of home-based telebehavioural health care compared to in-person treatment delivery for depression
Chatterton, 2018	Economic evaluation of a dietary intervention for adults with major depression (the "SMILES" trial)
Morales, 2018	Differences in sleep functioning between individuals with seasonal affective disorder and major depressive disorder in Finland
Rubio, 2019	Cost-effectiveness of antidepressants versus active monitoring for mild-to-moderate major depressive disorder: a multisite non-randomized-controlled trial in primary care (INFAP study)
Segal, 2018	Cost effectiveness and cost-utility analysis of a group-based diet intervention for treating major depression-the HELFIMED trial
Simon, 2018	Comparative economic evaluation of quetiapine plus lamotrigine combination vs quetiapine monotherapy (and folic acid vs placebo) in patients with bipolar depression (CEQUEL)

Yamabe, 2019	Health-related quality of life outcomes, economic burden, and associated costs among diagnosed and undiagnosed depression patients in Japan
Biesheuval-Leliefeld, 2017	Effectiveness of supported self-help in recurrent depression: A randomized controlled trial in primary care
Bjorkelund, 2018	Clinical effectiveness of care managers in collaborative care for patients with depression in Swedish primary health care: a pragmatic cluster randomized controlled trial
Driessen, 2017	Cognitive-behavioral versus psychodynamic therapy for major depression: Secondary outcomes of a randomized clinical trial
Engel, 2018	The impact of depression on health-related quality of life and wellbeing: identifying important dimensions and assessing their inclusion in multi-attribute utility instruments
Eriksson, 2017	Long-term effects of Internet-delivered cognitive behavioral therapy for depression in primary care-The PRIM-NET controlled trial
Gamst Klaussen, 2018	Assessment of outcome measures for cost-utility analysis in depression: mapping depression scales onto the EQ-5D-5L
Hange, 2017	The impact of internet-based cognitive behavior therapy on work ability in patients with depression - A randomized controlled study
Haro, 2018	Real-world outcomes in patients with depression treated with duloxetine or a selective serotonin reuptake inhibitor in East Asia
Helvik, 2016a	Health-related quality of life in older depressed psychogeriatric patients: one year follow-up
Helvik, 2016b	Are coping strategies and locus of control orientation associated with health-related quality of life in older adults with and without depression?
Hiranyatheb, 2016	The impact of residual symptoms on relapse and quality of life among Thai depressive patients
Hong, 2016	Real-world outcomes in patients with depression treated with duloxetine or a selective serotonin reuptake inhibitor in East Asia
Iglesias-Gonzalez, 2018	Effectiveness of watchful waiting versus antidepressants for patients diagnosed of mild to moderate depression in primary care: A 12-month pragmatic clinical trial (INFAP study)
Jia, 2018	Associations of Smoking, Physical Inactivity, Heavy Drinking, and Obesity with Quality-Adjusted Life Expectancy among US Adults with Depression

Kamagata, 2018	Improvements in Quality-Adjusted Life Years and Cost-Utility After Pharmacotherapy for Premenstrual Dysphoric Disorder: A Retrospective Study
Kendrick, 2017	Patient-reported outcome measures for monitoring primary care patients with depression: PROMDEP feasibility randomised trial
Kim, 2016	Development of a Korean version of the perceived deficits questionnaire-depression for patients with major depressive disorder
Kivelitz, 2017	Effectiveness of telephone-based aftercare case management for adult patients with unipolar depression compared to usual care: A randomized controlled trial
Kolovos, 2017	Utility scores for different health states related to depression: individual participant data analysis
Kuga, 2017	An observational study of duloxetine versus SSRI monotherapy in japanese patients with major depressive disorder: Subgroup analyses of treatment effectiveness for pain, depressive symptoms, and quality of life
Markkula, 2016	Prognosis of depressive disorders in the general population- results from the longitudinal Finnish Health 2011 Study
Mitchell, 2017	Assessing the validity of the ICECAP-A capability measure for adults with depression
Ock, 2016	Estimating the severity distribution of disease in South Korea using EQ-5D-3L: a cross-sectional study
Pan, 2018	Evaluating health-related quality of life impact of chronic conditions among older adults from a rural town in Suzhou, China
Richards, 2016	PHASE: a randomised, controlled trial of supervised self-help cognitive behavioural therapy in primary care
Saragoussi, 2018	Long-term follow-up on health-related quality of life in major depressive disorder: A 2-year european cohort study
Villoro, 2016	Quality of life and use of health care resources among patients with chronic depression
Wikberg, 2017	Use of a self-rating scale to monitor depression severity in recurrent GP consultations in primary care - does it really make a difference? A randomised controlled study
Yamada, 2017	Reduction of quality-adjusted life years (QALYs) in patients with premenstrual dysphoric disorder (PMDD)
Boulenger, 2013	The burden of treatment change in Major Depressive Disorder: Comparison of switch versus non-switch patients in the PERFORM study.
Mann, 2009	Putting the 'Q' in depression QALYs: a comparison of utility measurement using EQ-5D and SF-6D health related quality of life measures

Sapin, 2004	Usefulness of EQ-5D in assessing health status in primary care patients with major depressive disorder
Winter, 2011	Health-related quality of life and its determinants in the urban Russian population with major depressive disorder: a cross-sectional study
Kaltenthaler, 2006	Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation
Koeser, 2015	Modelling the cost-effectiveness of pharmacotherapy compared with cognitive-behavioural therapy and combination therapy for the treatment of moderate to severe depression in the UK
Sobocki, 2006	Cost of depression in Europe

Table 90 Studies excluded based on full text review from the HSUVs and HRQoL systematic literature review

No.	Publication	Exclusion reason
Studies excluded in July 2018 update (n=25)		
1	Agyapong VI, Juhas M, Ohinmaa A, Omeje J, Mrklas K, Suen VY, et al. Randomized controlled pilot trial of supportive text messages for patients with depression. BMC Psychiatry 2017; 17: ArtID 286.	Outcome;: HSUV/HRQOL data not reported
2	Ascef BO, Haddad JPA, Alvares J, Guerra AA, Costa EA, Acurcio FA, et al. Health-related quality of life of patients of Brazilian primary health care. Revista de saude publica 2017; 51(Supplement 2):22s.	Study design; multiple linear regression
3	Ascef BO, Izidoro JB, Alvares J, Haddad JP, Silveira MR. Health-related quality of life of users of primary care in Brazil. Value in Health 2016; 19(7):A633.	Outcomes; HSUV/HRQOL data not reported
4	Bastardo YM, Mendoza FJ. Socioeconomic status, quality of life, depression and post-traumatic stress disorder in college students. Value in Health 2016; 19(3):A191-A2.	Outcomes; HSUV/HRQOL data not reported
5	Bosanquet K, Adamson J, Atherton K, Bailey D, Baxter C, Beresford-Dent J, et al. Collaborative care for screen-positive elders with major depression (CASPER plus): A multicentred randomized controlled trial of clinical effectiveness and cost-effectiveness. Health Technology Assessment 2017; 21(67):1-251.	Study design

No.	Publication	Exclusion reason
6	Brabyn S, Araya R, Barkham M, Bower P, Cooper C, Duarte A, et al. The second randomised evaluation of the effectiveness, cost-effectiveness and acceptability of computerised therapy (REEACT-2) trial: Does the provision of telephone support enhance the effectiveness of computer-delivered cognitive behaviour therapy? a randomised controlled trial. Health Technology Assessment 2016; 20(89):1-92.	Study design
7	Camacho E, Shields G, Lovell K, Coventry P, Morrison A, Davies L. A (five-)level playing field for mental health conditions?: Exploratory analysis of EQ-5D-5L-derived utility values. Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care & Rehabilitation 2017.	Patient population; comorbid depression
8	Castro A, Lopez-del-Hoyo Y, Peake C, Mayoral F, Botella C, Garcia-Campayo J, et al. Adherence predictors in an internet-based intervention program for depression. Cognitive Behaviour Therapy 2018; 47(3):246-61.	Outcomes; HSUV/HRQOL data not reported
9	Cheon EJ, Choi JH, Lee GW, Koo BH, Seo WS, Kim HG, et al. Neurofeedback treatment on depressive symptoms and functional recovery and brain-derived neurotrophic factor in treatment-resistant major depression. European Neuropsychopharmacology 2017; 27(Supplement 4):S851.	Outcomes; HSUV/HRQOL data not reported
10	Filipcic I, Filipcic IS, Gajsak T, Sucic S, Milovac Z, Zecevic Penic S, et al. Efficacy and tolerability of repetitive transcranial magnetic stimulation with and without the Brainsway H1-coil in treatment of major depressive disorder: Presentation of the protocol and interim analysis. European Archives of Psychiatry and Clinical Neuroscience 2017; 267(Supplement 2):S159-S60.	Outcomes; HSUV/HRQOL data not reported
11	Gajsak T, Filipcic I, Milovac Z, Sucic S, Zecevic Penic S, Ivezic E, et al. Transcranial magnetic stimulation has different short-term efficacy on different major depressive disorder symptoms: A nested prospective cohort study in Croatia. European Archives of Psychiatry and Clinical Neuroscience 2017; 267(Supplement 2):S159.	Outcomes; HSUV/HRQOL data not reported
12	Gilbody S, Brabyn S, Lovell K, Kessler D, Devlin T, Smith L, et al. Telephone-supported computerised cognitive-behavioural therapy: REEACT-2 large-scale pragmatic randomised controlled trial. British Journal of Psychiatry 2017; 210(5):362-7.	Outcomes; HSUV/HRQOL data not reported
13	Grafe V, Greiner W. Internet based treatment of depressive symptoms-a health economic evaluation of costs and benefits. Value in Health 2017; 20(9):A714.	Outcomes; HSUV/HRQOL data not reported
14	Guligowska A, Piglowska M, Fife E, Kostka J, Soltysik BK, Kroc L, et al. Inappropriate nutrients intake is associated with lower functional status and inferior quality of life in older adults with depression. Clinical Interventions in Aging 2016; 11:1505-17.	Patient population; comorbid depression

No.	Publication	Exclusion reason
15	Kenter RM, Cuijpers P, Beekman A, van Straten A. Effectiveness of a Web-Based Guided Self-help Intervention for Outpatients With a Depressive Disorder: Short-term Results From a Randomized Controlled Trial. Journal of Medical Internet Research 2016; 18(3):e80.	Outcomes; HSUV/HRQOL data not reported
16	Kim JM, Chalem Y, di Nicola S, Hong JP, Won SH, Milea D. A cross-sectional study of functional disabilities and perceived cognitive dysfunction in patients with major depressive disorder in South Korea: The PERFORM-K study. Psychiatry Research 2016; 239:353-61.	Outcomes; duplicate of data reported in Kim, 2016 (23)
17	Kimball SM, Mirhosseini N, Rucklidge J. Database analysis of depression and anxiety in a community sample-response to a micronutrient intervention. Nutrients 2018; 10(2):152.	Outcomes; HSUV/HRQOL data not reported
18	Lewis H, Adamson J, Atherton K, Bailey D, Birtwistle J, Bosanquet K, et al. Collaborative care and active surveillance for screen-positive ElderRs with subthreshold depression (CASPER): A multicentred randomised controlled trial of clinical effectiveness and cost-effectiveness. Health Technology Assessment 2017; 21(8):1-196.	Study design
19	Morrison R, Vairavan S, Tsiartas A, Smith J, Vergyri D, Cooper K, et al. Baseline speech and voice parameters and residual symptoms as predictors of relapse in subjects with recurrent major depressive disorder. Neuropsychopharmacology 2017; 43(Supplement 1):S367-S8.	Outcomes; HSUV/HRQOL data not reported
20	Papakostas GI, Nielsen RZ, Dragheim M, Tonnoir B. Efficacy and tolerability of vortioxetine versus agomelatine, categorized by previous treatment, in patients with major depressive disorder switched after an inadequate response. Journal of Psychiatric Research 2018; 101:72-9.	Outcomes; HSUV/HRQOL data not reported
21	Reinders P, Zoellner YF, Wood R, Holbrook T, Piercy J. Quantification of quality of life differences due to common diseases in the age group 50+ in the United Kingdom. Value in Health 2016; 19(7):A483.	Patient population
22	Richards DA, Bower P, Chew-Graham C, Gask L, Lovell K, Cape J, et al. Clinical effectiveness and cost-effectiveness of collaborative care for depression in UK primary care (CADET): A cluster randomised controlled trial. Health Technology Assessment 2016; 20(14):1-192.	Study design
23	Rubio-Valera M, March Pujol M, Fernandez A, Penarrubia-Maria M, Trave P, del Hoyo YL, et al. "Evaluation of a pharmacist intervention on patients initiating pharmacological treatment for depression: A randomized controlled superiority trial": Corrigendum. European Neuropsychopharmacology 2016; 26(6):1085.	Outcomes; HSUV/HRQOL data not reported

No.	Publication	Exclusion reason
24	Sun Y. The effectiveness of group Behavioral Activation with mindfulness in the treatment of Subthreshold Depression in primary care in Hong Kong. Dissertation Abstracts International: Section B: The Sciences and Engineering 2018; 79(2-B(E)).	Outcomes; HSUV/HRQOL data not reported
25	Trivedi M, Morrison R, Daly E, Singh JB, Fedgchin M, Jamieson C, et al. Biobehavioral prediction of relapse in major depression: A prospective, multicenter, observational study. Neuropsychopharmacology 2016; 41(Supplement 1):S517-S8.	Outcomes; HSUV/HRQOL data not reported
Studies excluded in April 2019 update (n=23)		
26	Bjorkelund C, Svenningsson I, Hange D, Udo C, Petersson EL, Ariai N, et al. Clinical effectiveness of care managers in collaborative care for patients with depression in Swedish primary health care: a pragmatic cluster randomized controlled trial. BMC Family Practice 2018; 19(1):28.	Included in previous July 2018 review
27	Caroff SM, Cutler A, Lenderking WR, Yeomans K, Shalhoub H, Ford AM, et al. Quality of life and functional impairment results: A prospective real-world dyskinesia screening study and registry in patients taking antipsychotic agents. Value in Health 2018; 21(Supplement 1):S188.	Outcomes
28	Engel L, Chen G, Richardson J, Mihalopoulos C. The impact of depression on health-related quality of life and well-being: identifying important dimensions and assessing their inclusion in multi-attribute utility instruments. Quality of Life Research 2018; 27(11):2873-84.	Included in previous July 2018 review
29	Enrique A, Burke J, Richards D, Timulak L. Quality of life outcomes in internet-delivered (space from depression) treatment for depression. Applied Research in Quality of Life 2018.	Outcomes
30	Escobar S. Group Mindfulness Meditation Based Cognitive Therapy Intervention for the Treatment of Late-Life Depression and Anxiety Symptoms: A Randomized Controlled Trial. American Journal of Geriatric Psychiatry 2019; 27(3 Supplement):S168.	Outcomes
31	Flink N, Honkalampi K, Lehto SM, Leppanen V, Viinamaki H, Lindeman S. Comparison of early maladaptive schemas between borderline personality disorder and chronic depression. Clinical Psychology & Psychotherapy 2018; 14:14.	Outcomes

No.	Publication	Exclusion reason
32	Gallagher P, McClenaghan A, Clarke M. 'Small goals but big impact': A mixed method evaluation of a healthy activity programme for people encountering mental health difficulties. Early Intervention in Psychiatry 2018; 12(Supplement 1):64.	Outcomes
33	Gamst-Klaussen T, Lamu AN, Chen G, Olsen JA. Assessment of outcome measures for cost-utility analysis in depression: Mapping depression scales onto the EQ-5D-5L. BJPsych Open 2018; 4(4):160-6.	Included in previous July 2018 review
34	Haro JM, Lamy FX, Jonsson B, Knapp M, Brignone M, Caillou H, et al. Characteristics of patients with depression initiating or switching antidepressant treatment: baseline analyses of the PERFORM cohort study. BMC Psychiatry 2018; 18(1):80.	Included in previous July 2018 review
35	He Y. C.02.02 Myth or fact: How can we achieve functional recovery in depression? European Neuropsychopharmacology 2019; 29(Supplement 1):S617-S8.	Outcomes
36	Hernandez Alava M, Wailoo A, Grimm S, Pudney S, Gomes M, Sadique Z, et al. EQ-5D-5L versus EQ-5D-3L: The Impact on Cost Effectiveness in the United Kingdom. Value in Health 2018; 21(1):49-56.	Population
37	Jaffe DH, Rive B, Denee T. The Burden of Suicidal Ideation in Europe from the Patient Perspective. Value in Health 2018; 21(Supplement 3):S286.	Outcomes
38	Jaffe DH. The burden of treatment-resistant depression in Europe from the patient perspective. Value in Health 2018; 21:S286.	Abstract; superseded by Jaffe, 2019 (47) identified by September 2019 update
39	Jalan D, Martin R, Mehra A, Tawata W, Williams SR, Carlton B, et al. Utility of intravenous ketamine as an alternative, effective depression treatment for hospitalized patients unable to receive electroconvulsive therapy due to medical risks. American Journal of Geriatric Psychiatry 2018; 26(3 Supplement 1):S162-S3.	Outcomes
40	Kamagata E, Yamada K. Improvements in Quality-Adjusted Life Years and Cost-Utility After Pharmacotherapy for Premenstrual Dysphoric Disorder: A Retrospective Study. Clinical Drug Investigation 2018; 38(1):49-55.	Included in previous July 2018 review
41	Klein NS, Bockting CL, Wijnen B, Kok GD, van Valen E, Riper H, et al. Economic Evaluation of an Internet-Based Preventive Cognitive Therapy With Minimal Therapist Support for Recurrent Depression: Randomized Controlled Trial. Journal of Medical Internet Research 2018; 20(11):e10437.	Population

No.	Publication	Exclusion reason
42	Lopez E, Steiner AJ, Manier K, Shapiro BB, Vanle B, Parisi T, et al. Quality of life and functioning of Hispanic patients with Major Depressive Disorder before and after treatment. Journal of Affective Disorders 2018; 225:117-22.	Included in previous July 2018 review
43	Perez-Cruzado D, Cuesta-Vargas AI, Vera-Garcia E, Mayoral-Cleries F. The relationship between quality of life and physical fitness in people with severe mental illness. Health and Quality of Life Outcomes 2018; 16(1):82.	Population
44	Rinaldi A, Rinaldi C, Coelho Pereira JA, Lotti Margotti M, Bittencourt MN, Barcessat ARP, et al. Radio electric asymmetric conveyer neuromodulation in depression, anxiety, and stress. Neuropsychiatry 2019; 15:469-80.	Outcomes
45	Saragoussi D, Christensen MC, Hammer-Helmich L, Rive B, Touya M, Haro JM. Long-term follow-up on health-related quality of life in major depressive disorder: A 2-year European cohort study. Neuropsychiatric Disease and Treatment 2018; 14:1339-50.	Included in previous July 2018 review
46	Stuhec M, Bratovic N. Role of the psychiatric clinical pharmacist on quality of life in elderly patients with mental health problems. European Neuropsychopharmacology 2019; 29(Supplement 1):S235.	Outcomes
47	Sun Y. The effectiveness of group Behavioral Activation with mindfulness in the treatment of Subthreshold Depression in primary care in Hong Kong. Dissertation Abstracts International: Section B: The Sciences and Engineering 2018; 79(2-B(E)).	Population
48	van den Noort M, Lim S, Litscher G, Bosch P. Transcranial magnetic stimulation for treating older patients with treatment-resistant depression. Journal of Affective Disorders 2018; 225:278-9.	Review; letter to editor
Studies excluded in September 2019 update (n=10)		
49	Alamgir, A. et al. A real-world follow-up of pain, depression and quality of life outcomes in a UK neuromodulation centre. British Journal of Pain 2019; 13(Suppl 2):32.	Population
50	Babinska, A. et al. No association between MRI changes in the lumbar spine and intensity of pain, quality of life, depressive and anxiety symptoms in patients with low back pain. Neurologia i Neurochirurgia Polska 2019; 53(1):74-82.	Population
51	Caroff, S. et al. Re-Kinect, a Real-World, Prospective Tardive Dyskinesia Screening Study: An Evaluation of Baseline Characteristics in Older Patients. American Journal of Geriatric Psychiatry 2019; 27(Suppl 3):S176-S178.	Population

No.	Publication	Exclusion reason
52	ChiCTR1900020586. The effect of cognitive behavioral self-help intervention on depressive residual symptoms. 2019.	Protocol only
53	Cutler, A. J. et al. Presence and Impact of Possible Tardive Dyskinesia in Patients Prescribed Antipsychotics: Results from the RE-KINECTStudy. CNS Spectrums 2019; 24(1):176-177.	Population
54	Escobar, S. et al. Group Mindfulness Meditation Based Cognitive Therapy Intervention for the Treatment of Late-Life Depression and Anxiety Symptoms: A Randomized Controlled Trial. American Journal of Geriatric Psychiatry 2019; 27 (Suppl 3):S168.	Outcomes
55	Liao, Y. et al. Health-related quality of life and health-adjusted life expectancy among patients with chronic non-communicable diseases, in Guangdong province. Chinese Journal of Epidemiology 2019; 40(4):406-411.	Population
56	Milla-Perseguer, M. et al. Measurement of health-related quality by multimorbidity groups in primary health care. Health and Quality of Life Outcomes 2019; 17:8.	Population
57	Wong, E. L. et al. Normative Profile of Health-Related Quality of Life for Hong Kong General Population Using Preference-Based Instrument EQ-5D-5L. Value in Health 2019; 22(8):916-924.	Population
58	Yamabe, K. et al. Health-related quality of life outcomes, economic burden, and associated costs among diagnosed and undiagnosed depression patients in Japan. ClinicoEconomics and Outcomes Research 2019; 11:233-243.	Identified by previous review
Studies excluded in January 2020 update (n=17)		
59	Bingham, K. S. et al. Health-related quality of life in remitted psychotic depression. Journal of Affective Disorders 2019; 256:373-379.	Identified by previous review
60	Bressington, D. et al. Feasibility of a group-based laughter yoga intervention as an adjunctive treatment for residual symptoms of depression, anxiety and stress in people with depression. Journal of Affective Disorders 2019; 248:42-51.	Identified by previous review
61	Conway, C. R. et al. Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment-Resistant Major Depression. Journal of Clinical Psychiatry 2018; 79(5):21.	Identified by previous review
62	Gao, K. et al. Correlation between depression/anxiety symptom severity and quality of life in patients with major depressive disorder or bipolar disorder. Journal of Affective Disorders 2019; 244:9-15.	Identified by previous review

No.	Publication	Exclusion reason
63	Gong, J. et al. Acupuncture and moxibustion for the elderly patients with depression: A randomized controlled trial. World Journal of Acupuncture – Moxibustion 2019; 29(3):169-173.	Identified by previous review
64	Izquierdo, A. et al. Community Partners in Care: 6- and 12-month Outcomes of Community Engagement versus Technical Assistance to Implement Depression Collaborative Care among Depressed Older Adults. Ethnicity & Disease 2018; 28(Suppl 2):339-348.	Identified by previous review
65	Jaffe, D. H. et al. The humanistic and economic burden of treatment-resistant depression in Europe: A cross-sectional study. BMC Psychiatry 2019; 19: ArtID 247.	Identified by previous review
66	Jelinek, L. et al. Long-term efficacy of Metacognitive Training for Depression (D-MCT): A randomized controlled trial. British Journal of Clinical Psychology 2019; 58(3):245-259.	Identified by previous review
67	Lex, H. et al. Quality of life across domains among individuals with treatment-resistant depression. Journal of Affective Disorders 2019; 243:401-407.	Identified by previous review
68	Morales-Munoz, I. et al. Differences in sleep functioning between individuals with seasonal affective disorder and major depressive disorder in Finland. Sleep Medicine 2018; 48:16-22.	Identified by previous review
69	Papakostas, G. I. et al. Efficacy and tolerability of vortioxetine versus agomelatine, categorized by previous treatment, in patients with major depressive disorder switched after an inadequate response. Journal of Psychiatric Research 2018; 101:72-79.	Identified by previous review
70	Ray, M. P. K. et al. Pmu105 Impact of Behavioral Interventions for Chronic Diseases on Health Utility: Assessment of Three Trials of Older Adults. Value in Health 2019; 22.	Identified by previous review
71	Shearer, J. et al. Refractory depression - cost-effectiveness of radically open dialectical behaviour therapy: findings of economic evaluation of RefraMED trial. BJPsych Open 2019; 5(5):e64.	Identified by previous review
72	Simon, J. et al. Pmh21 Cost-Effectiveness of the Predict Test: Results and Lessons Learned from a European Multinational Depression Trial. Value in Health 2019; 22(Supplement 3):S684.	Outcomes
73	Wang, G. et al. Pmh53 Impact of Cognitive Symptoms on Health-Related Quality of Life and Work Productivity in Chinese Patients with Major Depressive Disorder: Results from the Proact Study. Value in Health 2019; 22 (Supplement 3):S690.	Outcomes

No.	Publication	Exclusion reason
74	Zisook, S. et al. General Predictors and Moderators of Depression Remission: A VAST-D Report. American journal of psychiatry 2019; 176(5):348-357.	Identified by previous review
75	Zoun, M. H. H. et al. Effectiveness of a self-management training for patients with chronic and treatment resistant anxiety or depressive disorders on quality of life, symptoms, and empowerment: results of a randomized controlled trial. BMC psychiatry 2019; 19(1):46.	Identified by previous review

I.1.7 Local adaptation

To support this submission for ESK NS for the treatment of TRD in Denmark, the global SLR was adapted by excluding all studies not relevant to a Danish setting. The objective of the global SLR was to identify publications reporting preference-based HSUVs associated with depression (including TRD and MDD) and other related conditions. Only one of the identified sources from the global SLR were deemed eligible for inclusion in the local adaptation (Sullivan et al., 2004[78]). All other sources from the global SLR were omitted as inputs[78]). All other sources from the global SLR were omitted as inputs.

Targeted literature review – HSUV studies

In addition to the SLR, a targeted literature review (TLR) was conducted to identify and collect relevant inputs for the HSUV model. The TLR was conducted pragmatically, focusing only on disutility values not already covered by Sullivan et al[78] or the head-to-head ESCPAE-TRD trial[65]. One source was identified and used in the HSUV model (In addition to the SLR, a targeted literature review (TLR) was conducted to identify and collect relevant inputs for the HSUV model. The TLR was conducted pragmatically, focusing only on disutility values not already covered by Sullivan et al[78] or the head-to-head ESCPAE-TRD trial[65]. One source was identified and used in the HSUV model (Table 91).

Table 91 List of studies included to identify HSUV studies, TLR

Source name/database	Location/source	Search strategy	Date of search
Revicki DA, & Wood M. (1998) [79]	Patient-assigned health state utilities for depression-related outcomes: differences by depression severity and antidepressant medications	Hand search	N/A

I.1.8 Quality assessment

During data extraction, the quality of the studies generating utilities was assessed and recorded. This process is as recommended in NICE technical support documents (TSDs) 8-10[122], and enables justification of the use/non-use of different utility values or mapping algorithms in an economic model. The following issues were addressed: During data extraction, the quality of the studies generating utilities was assessed and recorded. This process is as recommended in NICE technical support documents (TSDs) 8-10[122], and enables justification of the use/non-use of different utility values or mapping algorithms in an economic model. The following issues were addressed:

- Whether response rates, loss to follow-up, or missing data level are likely to threaten the validity of the utility estimate.
- Whether the selection criteria yield a population similar to that being modelled.
- Whether the utility incorporated a decrement for quality-of-life loss from AEs.
- Whether the utility meets the NICE reference case (i.e. health states should be described by the patient and valued according to UK societal preferences).

Quality assessment of the included studies highlighted a number of limitations associated with the utility values reported; in particular, absence of details regarding the patient recruitment process, response rates to instruments, loss to follow up, and missing data are likely to restrict the usefulness of the studies for informing economic evaluation. The results are summarised in Table 92

Table 92 Quality assessment of the included studies in the HSUVs and HRQoL systematic literature review

Study	Sample size	Response rates to instruments?	Missing data?	Loss to follow up?	Comparable to population of patients with TRD?	Other considerations
Studies identified by January 2020 (n=7)						
Fedgchin, 2019 [123]	N=356 (randomised)	No	No	Yes – 1 patient was lost to follow up in the induction phase, and 3	The study sample included patients with TRD defined	None

				patients in the follow up phase	as failure of ≥2 previous antidepressants	
Heslin, 2019 [124]	N=545	Yes – only 30% of those eligible for study inclusion agreed to take part	Yes – of the 545 participants, 77% (N=421) had full data on measures required for the current analyses	NA – cross-sectional study	The study considered pregnant women with depression; most patients had mild/moderate depression	Single centre study
Lee, 2019 [125]	N=36 (patient with TRD, N=24; controls, N=12)	No	No	Yes – no patients were lost to follow up	The study sample included patients with TRD defined as failure of ≥2 previous antidepressants	None
Mihalopoulos, 2019 [126]	N=1,526 (of which N=150 had MDD)	Yes – reports response rate of 60% to the original survey from which patients were recruited	Yes – the % of missing data for AQoL-4D was small (21 missing/8,841 overall respondents)	NA – cross-sectional study	The study considered patients with affective disorders (including MDD); it is unclear if results are generalisable to patients with TRD	None
Murata, 2019 [127]	N=18	Yes – of 20 patients assessed for eligibility 19 were enrolled and started/completed CBT	No	Yes – one patient was excluded from the analysis (reason not stated)	The study considered patients with MDD; it is unclear if results are generalisable to patients with TRD.	Single-arm trial design; lack of long-term follow up data.
Sumiyoshi, 2019 [128]	N=518	No	No	NA – cross-sectional study	The study considered patients with MDD, of which 40.2% were relapsed; it is unclear if results are generalisable to patients with TRD.	None

Yan, 2019 [129]	N=206	No	No – reports methods for handling missing data only	No	The study considered patients with depressive symptoms based on the PHQ-9; it is unclear if results are generalisable to patients with TRD.	Study based in two primary care clinics
Studies identified by September 2019 update (n=6)						
Abdin, 2019 [130]	N=249	No	No	No	The study sample included patients with depression; no further details were provided, and it is unclear if results are generalisable to patients with TRD	None
Grochtdreis, 2019 [131]	N=246	No	No	No	The study sample included patients with late-life depression; it is unclear if results are generalisable to patients with TRD	None
Hensel, 2019 [132]	N=812	Yes – of 1,455 individuals approached, 975 consented, of which 812 completed the baseline assessment questionnaire	No	Yes – 236 lost to follow up in immediate treatment arm and 72 in delayed treatment arm	The study sample included patients with mood/anxiety disorders; it is unclear if results are generalisable to patients with depression or TRD	None
Jaffe, 2019 [27] [supplemented by Jaffe, 2018[133]]	N=3,308 MDD patients and N=48,752 controls	No	No	No	Yes, the study sample included patients with TRD defined as a failure of ≥2 antidepressants	None

Shearer, 2019 [134]	N=250	No	No	No	The study sample included patients with refractory depression; it is unclear if results are generalisable to patients with TRD	None
Usuba, 2019 [135]	NR	No	No	No	The study sample included patients with mood/anxiety disorders; it is unclear if results are generalisable to patients with TRD	None
Studies identified by April 2019 update (n=8)						
Aznar-Lou, 2019 [136]	N=263	No	Yes – the proportion of missing data was <3% in all variables	No	The study sample included patient with mild or moderate depression; 30.8% patients had MDD, however, patients who had received antidepressants in the prior 2 months were excluded	None
Bounthavong, 2018 [137]	N=121	No	Yes – missing BDI-II data at 3 months provided	No	Patients had a diagnosis of major or minor depressive disorder; however, it is unclear if patients were treatment resistant	Complete case analysis used for missing data
Chatterton, 2018 [138]	N=67	No	No	No	The study sample included patients diagnosed with an MDE; it is unclear if patients were treatment resistant.	None
Morales, 2018 [139]	N=526	No	No	No	The study sample included patients with SAD and/or	None

					MDD; it is unclear if results are generalisable to patients with TRD.	
Rubio, 2019 [140]	N=263	No	No	Yes – almost 26% of patients were lost to follow up	The study sample included patients with MDD; it is unclear if results are generalisable to patients with TRD.	None
Segal, 2018 [141]	N=152	No	No	No	Patients were diagnosed with MDD; however, it is unclear if they were treatment resistant.	None
Simon, 2018 [142]	N=201	No	Yes – number of missing responses provided for each treatment group	Yes – number of respondents at baseline and 12-/52-weeks follow up reported	The study sample included patients with bipolar depression; it is unclear if results are generalisable to patients with TRD.	None
Yamabe, 2019 [143]	N=83, 504	No	No	No	The study sample include patients with diagnosed or undiagnosed depression; it is unclear if result is generalisable to patients with TRD.	None
Studies identified by July 2018 SLR update (N=29)						
Biesheuval-Leliefeld, 2017 [144]	N=188	Yes – The number of patients completing the EQ-5D at 6 months follow up and 12 months follow up were reported: 1.0 Allocated to PCT +	No	Yes – 29 lost to follow up at 12 months for SPCT +TAU arm; 31/124 lost to follow up at 12 months for TAU arm	The study population consisted of patients with MDD; antidepressant medication use was reported; however, it is unclear whether patients had previously failed attempts.	None

		TAU: 6 months: 109/124 12 months: 98/124 2.0 Allocated to TAU: 6 months: 107/124 12 months: 95/124			Inclusion criteria included patients in full or partial remission.	
Bjorkeland, 2018 [145]	N=376	No	No	Yes – a total of 34 patients did not participate in the 3- and 6-month follow up (29 in the intervention group and 5 in the control group)	The study population consisted of patients with a new diagnosis of mild/moderate depression; it is unclear if the results are generalisable to patients with TRD.	None
Dreissen, 2017 [146]	N=341	Yes – the number (%) of patients completing the EQ-5D at baseline and follow up at weeks 22 and 52 were reported: 3.0 Allocated to CBT: Week 0: 121 (73.8%) Week 22: 67 (40.9%) Week 52 (47 (28.7%) 4.0 Allocated to psychodynamic therapy: Week 0: 140 (79.1%) Week 22: 82 (46.3%)	Yes – acknowledges impact of missing data on results, particularly at follow up	No – no details reported	The study population consisted of patients with MDD; it is unclear if patients had previously failed treatment attempts and could therefore be considered treatment-resistant.	None

	Week 52: 34 (19.2%)					
Engel, 2018 [147]	5.0 Individuals with depression: N=917 6.0 Healthy subjects: N=1,760	No	No	Unclear	It is unclear if the study population had TRD; previous treatment history was not described.	None
Eriksson, 2017 [148]	Analysed at 12 months: 7.0 ICBT: N=38 8.0 TAU: N=30	No	No	Yes – Loss to follow up reported at 3, 6, 12 months: 9.0 Allocated to ICBT: 3 months: N=16 6 months: N=13 12 months: N=14 10.0 Allocated to TAU-waiting list: 3 months: N=10 6 months: N=7 12 months: N=8	It is unclear if patients in the study had TRD, and details of previous treatment were not clear.	None
Gamst Klaussen, 2018 [149]	NR	No	No	No	It is unclear if the study population had TRD; previous treatment history was not described.	None
Hange, 2017 [150]	11.0 ICBT: N=46 12.0 TAU: N=31	No	No	No	The paper does not report whether patients had TRD, nor does it describe detail of success/unsuccess of previous antidepressant medication. The generalisability	None

					of the study population is therefore unclear.	
Haro, 2018 [151]	N=1,159	No	No	No	This paper focuses on a group of patients switching antidepressant treatment for the first time (reasons: lack of efficacy, AEs, patients' decision, lack of compliance) and so this cohort could be representative of patients with TRD, however, it is unclear how many patients had failed previous treatments.	None
Helvik, 2016a [152]	N=144	No	No	No	The paper does not report whether patients had TRD, nor does it describe detail of previous treatment history.	None
Helvik, 2016b [153]	N=108	No	No	Yes – only 108/144 were included in follow up (reasons given for loss to follow up reported in paper)	The paper does not report whether patients had TRD, nor does it describe detail of success/unsuccess of previous antidepressant medication.	None
Hiranyatheb, 2016 [154]	N=346	No	No	Yes – of 346 patients who completed baseline EQ-5D, 224 completed the questionnaire at 3 months	The study population consisted of patients with MDD; it is unclear if patients had previously failed treatment attempts.	None

				follow up, and 167 at 6 months follow up		
Hong, 2016 [155]	Overall: N=452 13.0 Duloxetine: N=227 14.0 SSRI: N=225	No	No	No	No – the study excluded patients who had a history of TRD	None
Iglesias-Gonzalez, 2018 [156]	N=265	No	Yes – missing data patterns were evaluated to assess the plausibility of data missing at random	Yes – loss to follow up reported at 6 and 12 months: 15.0 Allocated to antidepressant group: 6 months: N=29 12 months: N=40 16.0 Allocated to active monitoring group: 6 months: N=20 12 months: N=28	The study population consisted of patients with MDD; it is unclear if patients had previously failed treatment attempts.	None
Jia, 2018 [157]	N=24,826	NA	No	NA	It is unclear if the study population is representative of patients with TRD; patients were diagnosed with depression but there was no description of previous treatment.	None
Kamagata, 2018 [158]	N=49	No	No	No	The study population is unlikely to be representative of patients with TRD; patients had PMDD and were previously untreated.	None.

Kendrick, 2017 [159]	Analysed in either group at: 17.0 12 weeks: N=18 18.0 24 weeks: N=15	No	No	Yes – Loss to follow up reported at 12 weeks, 26 weeks: 19.0 Allocated to treatment arm: 12 weeks: N=4 26 weeks: N=7 20.0 Allocated to control arm: 12 weeks: N=7 26 weeks: N=10	It is unclear whether previous treatment was unsuccessful in patients; the paper states that previous treatment for depression was defined by the participating GPs rather than assessed independently.	None
Kim, 2016 [160]	N=312	No	No	No	It was not stated that patients had TRD, however, patients were previously on either a first-line therapy or on a first treatment switch from previous antidepressant monotherapy.	None
Kivelitz, 2017 [161]	Analysed at 21.0 3 months follow up: ACM: N=71 Usual care: N=68 22.0 6 months follow up: ACM: N=61 Usual care: N=56	No	No	Yes – loss to follow up reported at t2, t3: 23.0 Allocated to aftercare group N=99: t2: N=29 t3: N=10 24.0 Allocated to TAU group N=100: t2: N=27 t3: N=12	It is unclear whether previous treatment was unsuccessful in patients and so it is unclear whether patients had TRD; the paper states that 98/199 total participants were using antidepressants at baseline.	None

Kolovos, 2017 [162]	N=1,629 (of the 10 RCTs N=856 had been randomized to an intervention group and N=773 to a control group)	No	No – missing data did not refer to EQ-5D instrument	No	It is not clear whether patients had TRD, and details of previous treatment history were not provided.	None
Kuga, 2017 [163]	Overall: N=523 25.0 Duloxetine: N=273 26.0 SSRIs: N=250	No	No	No	It is unlikely that the study population is representative of patients with TRD; patients were diagnosed by the investigator with at least moderate depression and no previous treatment history/success was provided.	None
Markkula, 2016 [164]	N=4,620	No	No – missing data did not refer to EQ-5D instrument	Yes – Losses during follow-up (n = 1,379 from 7112 people who participated in baseline data collection) after baseline data collection	It is unclear if patients had TRD, and details of previously failed treatment were not reported.	None
Mitchell, 2017 [165]	N=617	No	No	No	It is unclear if the study population is representative of patients with TRD; patients had depression, and it was not reported whether patients had failed previous treatment.	None

Ock, 2016 [166]	N=90	Yes – there were 30 responders for each level of severity (mild, moderate, severe)	No	No	It is unclear if the study population is representative of patients with TRD; patients had MDD, and it was not reported whether patients had failed previous treatment.	None
Pan, 2018 [167]	N=65	No – no response rate reported for the preferred instruments	No	No	The study population consisted of patients with MDD; it is unclear if patients had previously failed treatment attempts.	None
Richards, 2016 [168]	N=440	No	Missing data did not refer to EQ-5D instruments	Yes – Follow up data reported at 6, 12, 18 months follow up	It is unclear if the study population had TRD; previous treatment history was not described. Participants who were taking medication had been doing so for a considerable time before entering the trial.	None
Saragoussi, 2018 [169]	N=1,159	Yes – the number (%) of patients completing the EQ-5D: 27.0 Month 0: N=264 28.0 Month 2: N=244 29.0 Month 6/12: N=360 30.0 Month 18/24: N=289	Unclear – authors report that missing data were not replaced in any of the analyses.	Unclear – loss to follow up not explicitly reported, however, declining patient data for EQ-5D reported in Figure 3c of the publication.	It is not clear whether patients were treatment resistant.	None
Villoro, 2016 [170]	N=14,691	No	No	No	It is unlikely that the study population is representative of patients with TRD; the	None

					Spanish National Health Survey does not differentiate between different types of chronic depression and so it unclear whether patients had TRD.	
Wikberg, 2017 [171]	N=173	No	No	Yes – loss to follow up reported at 3, 6, 12 months: 31.0 Allocated to intervention: 3 months: N=30 6 months: N=28 12 months: N=37 32.0 Allocated to control: 3 months: N=43 6 months: N=44 12 months: N=48	It is unclear if patients had TRD, and details of previously failed treatment were not reported.	None
Yamada, 2017 [172]	N=66 enrolled	No	No	No	It is unlikely that the study population is representative of patients with TRD; patients had previously untreated PMDD.	None
Studies identified by vortioxetine submission (n=5)						
Boulenger, 2013 (abstract PERFORM) [173]	N=947	NR	NR	NR	NR	None

Mann, 2009 [119]	N=114	No	No	No	The paper does not report whether patients had TRD, nor does it report details of previously failed treatment.	None
Sapin, 2004 [120]	N=226 completers	No	Missing data did not refer to EQ-5D instruments	Yes – among 250 included patients, 24 were lost to follow up (9.6%)	It is unclear if the study population are representative of a population of patients with TRD; patients were not treated with an antidepressant before inclusion.	None
Sullivan, 2004 [78]	N=14,888	Yes – EQ-5D responses for 14,888 individuals were available from MEPS	No	No	The population is unlikely to be representative of patients with TRD; participants were obtained from MEPS, and utilities were derived for health states relating to an initial episode of depression.	Economic evaluation; details regarding the elicitation of utilities was limited.
Winter, 2012 [174]	N=72 enrolled	No	No	No	The paper does not report whether patients had TRD, nor does it report details of any previously failed treatment.	None
Unique studies identified by CG90 (n=3)						
Kaltenthaler, 2006 [117]	N=62	No	No	No	The study population that Kaltenthaler refers to in Richards et al (2003) [175]study have mild to moderate anxiety and/or	None

					depression, but Kaltenthaler does not report whether patients have had previously failed treatment. The study population that Kaltenthaler refers to in Richards et al (2003) [175]study have mild to moderate anxiety and/or depression, but Kaltenthaler does not report whether patients have had previously failed treatment.	
Koeser, 2015 [118]	NR	No	Unclear – not clear if missing data was referring to EQ-5D data; authors reported that patients with a missing endpoint assessment in the acute and follow up phases would be assumed to be in the least favourable health status.	No	The study population consisted of patients with MDD; it is unclear if patients had previously failed treatment attempts.	None
Sobocki, 2006 [121]	N=398 completers	No	No	No – loss to follow up not explicitly reported, however, supplementary appendix S3 of the publication reports discontinuation rates per RCT for ITT sample.	The study population consisted of patients with depression being treated with antidepressant therapy; it is unclear if patients had previously failed treatment attempts.	None

I.1.9 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

Objective

To support the ongoing market access activities for ESK nasal spray for the treatment of TRD, Janssen commissioned a series of HTA-compatible SLRs to identify economic evaluations of relevant interventions and UK-based resource/cost data associated with TRD and MDD.

Findings from the SLRs will be used to support the development of the economic model for ESK nasal spray in this indication, to ensure that the proposed model structure and data inputs are robust and supported by the published literature.

This appendix summarises the methodology and findings of the SLR of cost/resource use studies.

J.1.1 Information sources

Between July 2018 and January 2020, a series of systematic literature reviews (SLRs) were conducted and updated to identify relevant evidence. Electronic searches were performed using the Ovid platform across the following databases: Embase, MEDLINE (including MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, and MEDLINE Daily), the Cochrane Library (incorporating the HTA database and NHS EED), EconLit, and PsycINFO (Table 94). These searches were supplemented by hand-searching reference lists of included studies, relevant conference proceedings, and additional grey literature sources as specified by NICE (Table 94).

The initial search was conducted on 4th July 2018, covering conference proceedings from the last three years. Updates were subsequently performed on 4th April 2019, 19th September 2019, and 29th January 2020. Each update included new conference proceedings from the periods following the prior search (July 2018, April 2019, and September 2019, respectively) (Table 95).

The population of interest is the same as described in Section I.1.1.

Table 93 Sources included in the search for cost/resource use

Database	Platform/source	Relevant period for the search	Latest date of search completion
Embase	Ovid platform	1974 to present	29.01.2020
Medline	Ovid platform	1946 to present	29.01.2020

Database	Platform/source	Relevant period for the search	Latest date of search completion
The Cochrane Library	Ovid platform	Q4 2016 to present	29.01.2020
EconLit	Ovid platform	1886 to present	29.01.2020
PsycINFO	Ovid platform	1987 to present	29.01.2020

Abbreviations:

Table 94 Bibliographic databases included in the literature search for cost/resource use

Database	Platform	Relevant period for the search	Latest date of search completion
American Psychiatry Association	www.psychiatry.org	2016-2020	29.01.2020
Anxiety and Depression Association of America Conference	www.adaa.org	2016-2020	29.01.2020
European Congress of Psychiatry	www.epa-congress.org	2016-2020	29.01.2020
International Conference on Management of Depression	www.idias.org	2016-2020	29.01.2020
International Society for Pharmacoeconomics and Outcomes Research, European and International Congresses	www.ispor.org	2016-2020	29.01.2020
The Royal College of Psychiatrists	www.rcpsych.ac.uk	2016-2020	29.01.2020
WPA World Congress of Psychiatry	www.wcp-congress.com	2016-2020	29.01.2020

Table 95 Other sources included in the literature search for cost/resource use

Database	Platform	Relevant period for the search	Latest date of search completion
EconPapers within Research Papers in Economics (RePEc)	www.econpapers.repec.org	September 2019 onwards	29.01.2020

Database	Platform	Relevant period for the search	Latest date of search completion
HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA)	www.database.inahta.org	September 2019 onwards	29.01.2020
National Institute for Health Research Health Technology Assessment (NIHR HTA)	www.journalslibrary.nihr.ac.uk	September 2019 onwards	29.01.2020

J.1.2 Search strategies

The search strings for the July 2018, April 2019, September 2019, and January 2020 SLRs are reported below.

J.1.2.1 July 2018 update

The search strategies for the original cost/resource use SLR are shown below.

Table 96 Cost/resource use search strategy for Embase (July 5, 2018)

#	Searches	Results
1	exp major depression/	55267
2	exp treatment resistant depression/	2109
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	85141
4	(MDD* or MDE* or TRD*).mp.	21917
5	1 or 2 or 3 or 4	90671
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	3498
7	exp "cost benefit analysis"/	78170
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	80326
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	9347
10	"cost utility analysis"/ or economic evaluation/	20880
11	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	136975
12	"cost effectiveness analysis"/	133915
13	6 or 7 or 8 or 9 or 10 or 11 or 12	217550
14	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	30823
15	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	63595
16	exp decision theory/ or "decision tree"/	11516
17	decision tree.mp.	13257
18	economic model.mp.	3351
19	(markov or deterministic).mp.	38400
20	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	281537
21	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	1116

#	Searches	Results
22	(incremental-cost or incremental cost).mp.	15186
23	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	20768
24	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	399296
25	14 and 24	9998
26	13 or 25	218677
27	5 and 26	960
28	exp economics/	242996
29	exp "Costs and Cost Analysis"/	322445
30	exp 'cost allocation'/	322445
31	exp "cost benefit analysis"/	78170
32	exp "cost control"/	62449
33	exp 'cost savings'/	62449
34	exp "cost of illness"/	17615
35	exp 'cost sharing'/	322445
36	exp 'medical savings accounts'/	322445
37	exp "health care cost"/	264830
38	exp 'direct service costs'/	264830
39	exp "drug cost"/	71759
40	exp 'employer health costs'/	264830
41	exp "hospital cost"/	34062
42	exp 'health expenditures'/	264830
43	exp 'capital expenditures'/	264830
44	exp 'value of life'/	344035
45	exp 'economics, medical'/	776207
46	exp 'economics, hospital'/	776207
47	exp 'economics, nursing'/	776207
48	exp 'economics, pharmaceutical'/	193026
49	exp budget/	25593
50	exp fee/	39501
51	(fiscal or funding or financial or finance).ab,ti.	159523
52	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	328605
53	fee.ti,ab.	13307
54	fees.ti,ab.	8547
55	(value adj2 (money or monetary)).ti,ab.	2789
56	exp quality adjusted life year/	21372
57	(quality adjusted life year* or qualy*).ti,ab.	15229
58	exp hospitalization/	311010
59	exp "consumer satisfaction"/	45465
60	"patient acceptance of health care"/	55117
61	"disease management"/	17916
62	clinical practice/	242427
63	"health care rationing"/	119387
64	((clinical or critical or patient) adj1 path*).ab,ti.	38109
65	(managed adj2 (care or clinical or network)).ti,ab.	21685
66	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	52902

#	Searches	Results
67	cost*.mp.	925081
68	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	2530302
69	exp Scotland/	2612
70	exp England/	11777
71	exp Wales/	1808
72	exp Northern Ireland/	752
73	exp United Kingdom/	409460
74	(northern adj2 (ireland or irish)).mp.	6163
75	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	810997
76	69 or 70 or 71 or 72 or 73 or 74 or 75	815467
77	68 and 76	145145
78	5 and 77	560
79	27 or 78	1406

Table 97 Cost/resource use search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (July 5, 2018)

#	Searches	Results
1	exp Depressive Disorder, Major/	26079
2	exp Depressive Disorder, Treatment-Resistant/	836
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonre-spon* or major) adj3 depressi*).mp.	56794
4	(MDD* or MDE* or TRD*).mp.	14805
5	1 or 2 or 3 or 4	60525
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	656
7	exp Cost-Benefit Analysis/	73197
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	75183
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	2568
10	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	10776
11	6 or 7 or 8 or 9 or 10	79341
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	16120
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	57929
14	exp Decision Theory/	11097
15	exp Decision Trees/	10215
16	decision tree.mp.	5598
17	economic model.mp.	1893
18	(markov or deterministic).mp.	34656
19	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	185661
20	((patient level or patient-level or discrete event or discrete-event) adj1 simu-lat*).mp.	666
21	(incremental-cost or incremental cost).mp.	9333
22	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	11791

#	Searches	Results
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	295356
24	12 and 23	5321
25	11 or 24	80846
26	5 and 25	369
27	exp ECONOMICS/	561448
28	exp "Costs and Cost Analysis"/	216037
29	exp "Cost Allocation"/	1986
30	exp "Cost Control"/	31727
31	exp "Cost Savings"/	10764
32	exp "Cost of Illness"/	23545
33	exp "Cost Sharing"/	4205
34	exp Medical Savings Accounts/	523
35	exp Health Care Costs/	58438
36	exp Direct Service Costs/	1138
37	exp Drug Costs/	14650
38	exp Employer Health Costs/	1085
39	exp Hospital Costs/	9863
40	exp Health Expenditures/	19475
41	exp Capital Expenditures/	1977
42	exp "Value of Life"/	5603
43	exp ECONOMICS, MEDICAL/	14030
44	exp ECONOMICS, NURSING/	3980
45	exp ECONOMICS, HOSPITAL/	22911
46	exp ECONOMICS, PHARMACEUTICAL/	2772
47	exp Budgets/	13307
48	exp "Fees and Charges"/	29301
49	(fiscal or funding or financial or finance).ab,ti.	123054
50	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	253190
51	fee.ti,ab.	10114
52	fees.ti,ab.	6757
53	(value adj2 (money or monetary)).ti,ab.	2001
54	exp Quality-Adjusted Life Years/	10198
55	(quality adjusted life year* or qualy*).ti,ab.	10148
56	exp Hospitalization/	208282
57	exp "Patient Acceptance of Health Care"/	133727
58	exp Disease Management/	58210
59	exp Resource Allocation/ or exp HEALTH CARE RATIONING/	16396
60	((clinical or critical or patient) adj1 path*).ab,ti.	25237
61	(managed adj2 (care or clinical or network)).ti,ab.	17992
62	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	37283
63	cost*.mp.	607128
64	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63	1535775
65	exp SCOTLAND/	23495

#	Searches	Results
66	exp ENGLAND/	101011
67	exp WALES/	13461
68	exp Northern Ireland/	4587
69	exp United Kingdom/	344949
70	(northern adj2 (ireland or irish)).mp.	6757
71	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	2209362
72	65 or 66 or 67 or 68 or 69 or 70 or 71	2228626
73	64 and 72	177234
74	5 and 73	541
75	26 or 74	844

Table 98 Cost/resource use search strategy for Cochrane Library (July 5, 2018)

#	Searches	Results
1	exp Depressive Disorder, Major/	113
2	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	227
3	(MDD* or MDE* or TRD*).mp.	30
4	1 or 2 or 3	230

Table 99 Cost/resource use search strategy for EconLit (July 5, 2018)

#	Searches	Results
1	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	78
2	(MDD* or MDE* or TRD*).mp.	53
3	1 or 2	122

Table 100 Cost/resource use search strategy for PsycINFO (July 5, 2018)

#	Searches	Results
1	exp Major Depression/	115976
2	exp Treatment Resistant Depression/	1989
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	121987
4	(MDD* or MDE* or TRD*).mp.	10285
5	1 or 2 or 3 or 4	126867
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	23
7	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	1057
8	(cost utility analys* or (cost-utility adj1 analys*)).mp.	339
9	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	1233
10	6 or 7 or 8 or 9	2507
11	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	2601
12	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	2446
13	exp Decision Theory/	975
14	decision tree.mp.	1062
15	economic model.mp.	391
16	(markov or deterministic).mp.	5799

#	Searches	Results
17	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	24180
18	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	136
19	(incremental-cost or incremental cost).mp.	785
20	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	2052
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	36062
22	11 and 21	559
23	10 or 22	2867
24	5 and 23	171
25	exp ECONOMICS/	22397
26	exp "COSTS AND COST ANALYSIS"/	22885
27	exp "Cost Containment"/	540
28	exp Health Care Costs/	9162
29	exp BUDGETS/	978
30	exp FEE FOR SERVICE/	312
31	(fiscal or funding or financial or finance).ab,ti.	58072
32	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	103174
33	fee.ti,ab.	1931
34	fees.ti,ab.	1413
35	(value adj2 (money or monetary)).ti,ab.	802
36	(quality adjusted life year* or qaly or qualy*).ti,ab.	1240
37	exp Hospitalization/	16493
38	exp Consumer Satisfaction/	4613
39	exp Disease Management/	6050
40	exp Clinical Practice/	17793
41	((clinical or critical or patient) adj1 path*).ab,ti.	1381
42	(managed adj2 (care or clinical or network)).ti,ab.	4775
43	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	11816
44	cost*.mp.	96246
45	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	282813
46	(northern adj2 (ireland or irish)).mp.	2329
47	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	167000
48	46 or 47	168752
49	45 and 48	16038
50	5 and 49	378
51	24 or 50	530

J.1.2.2 April 2019 update

The searches for the April 2019 update are shown below. Note: the Cochrane Library databases (HTA and NHS EED) are only updated to 2016. No citations were therefore identified from these databases for the updated SLR, and the search strategy has not been included.

Table 101 Cost/resource use search strategy for Embase (September 19, 2019)

#	Searches	Results
1	exp major depression/	57815
2	exp treatment resistant depression/	2456
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	88673
4	(MDD* or MDE* or TRD*).mp.	23573
5	1 or 2 or 3 or 4	94554
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	3640
7	exp "cost benefit analysis"/	80228
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	82461
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	9882
10	"cost utility analysis"/ or economic evaluation/	21959
11	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	142932
12	"cost effectiveness analysis"/	139736
13	6 or 7 or 8 or 9 or 10 or 11 or 12	225995
14	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	32427
15	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	65627
16	exp decision theory/ or "decision tree"/	12479
17	decision tree.mp.	14381
18	economic model.mp.	3774
19	(markov or deterministic).mp.	41446
20	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	296111
21	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	1215
22	(incremental-cost or incremental cost).mp.	16556
23	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	22672
24	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	420116
25	14 and 24	10702
26	13 or 25	227209
27	5 and 26	984
28	exp economics/	244885
29	exp "Costs and Cost Analysis"/	327939
30	exp 'cost allocation'/	327939
31	exp "cost benefit analysis"/	80228
32	exp "cost control"/	64487
33	exp 'cost savings'/	64487
34	exp "cost of illness"/	18122
35	exp 'cost sharing'/	327939
36	exp 'medical savings accounts'/	327939
37	exp "health care cost"/	272605
38	exp 'direct service costs'/	272605
39	exp "drug cost"/	73517
40	exp 'employer health costs'/	272605

#	Searches	Results
41	exp "hospital cost"/	34862
42	exp 'health expenditures'/	272605
43	exp 'capital expenditures'/	272605
44	exp 'value of life'/	348924
45	exp 'economics, medical'/	787753
46	exp 'economics, hospital'/	787753
47	exp 'economics, nursing'/	787753
48	exp 'economics, pharmaceutical'/	191723
49	exp budget/	26953
50	exp fee/	38405
51	(fiscal or funding or financial or finance).ab,ti.	171331
52	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	346305
53	fee.ti,ab.	13896
54	fees.ti,ab.	8767
55	(value adj2 (money or monetary)).ti,ab.	2950
56	exp quality adjusted life year/	23264
57	(quality adjusted life year* or qualy*).ti,ab.	16640
58	exp hospitalization/	325632
59	exp "consumer satisfaction"/	46526
60	"patient acceptance of health care"/	53881
61	"disease management"/	17763
62	clinical practice/	256795
63	"health care rationing"/	116360
64	((clinical or critical or patient) adj1 path*).ab,ti.	39274
65	(managed adj2 (care or clinical or network)).ti,ab.	22134
66	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	57251
67	cost*.mp.	970111
68	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	2614401
69	exp Scotland/	3488
70	exp England/	15937
71	exp Wales/	2417
72	exp Northern Ireland/	991
73	exp United Kingdom/	397755
74	(northern adj2 (ireland or irish)).mp.	6338
75	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	815440
76	69 or 70 or 71 or 72 or 73 or 74 or 75	820216
77	68 and 76	149337
78	5 and 77	593
79	27 or 78	1466
80	limit 79 to yr="2018 -Current"	121

Table 102 Cost/resource use search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (September 19, 2019)

#	Searches	Results
1	exp Depressive Disorder, Major/	27484
2	exp Depressive Disorder, Treatment-Resistant/	993
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonre-spon* or major) adj3 depressi*).mp.	59477
4	(MDD* or MDE* or TRD*).mp.	16027
5	1 or 2 or 3 or 4	63418
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	686
7	exp Cost-Benefit Analysis/	75917
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	77974
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	2770
10	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	11453
11	6 or 7 or 8 or 9 or 10	82384
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	17088
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	59595
14	exp Decision Theory/	11396
15	exp Decision Trees/	10501
16	decision tree.mp.	6174
17	economic model.mp.	1989
18	(markov or deterministic).mp.	36727
19	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	194870
20	((patient level or patient-level or discrete event or discrete-event) adj1 simu-lat*).mp.	718
21	(incremental-cost or incremental cost).mp.	10060
22	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	12745
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	309154
24	12 and 23	5684
25	11 or 24	84008
26	5 and 25	387
27	exp ECONOMICS/	575134
28	exp "Costs and Cost Analysis"/	223275
29	exp "Cost Allocation"/	1994
30	exp "Cost Control"/	32248
31	exp "Cost Savings"/	11126
32	exp "Cost of Illness"/	24847
33	exp "Cost Sharing"/	4316
34	exp Medical Savings Accounts/	527
35	exp Health Care Costs/	60714
36	exp Direct Service Costs/	1162
37	exp Drug Costs/	15168
38	exp Employer Health Costs/	1088
39	exp Hospital Costs/	10221

#	Searches	Results
40	exp Health Expenditures/	20487
41	exp Capital Expenditures/	1987
42	exp "Value of Life"/	5642
43	exp ECONOMICS, MEDICAL/	14090
44	exp ECONOMICS, NURSING/	3986
45	exp ECONOMICS, HOSPITAL/	23445
46	exp ECONOMICS, PHARMACEUTICAL/	2854
47	exp Budgets/	13480
48	exp "Fees and Charges"/	29663
49	(fiscal or funding or financial or finance).ab,ti.	130991
50	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	269349
51	fee.ti,ab.	10552
52	fees.ti,ab.	7076
53	(value adj2 (money or monetary)).ti,ab.	2139
54	exp Quality-Adjusted Life Years/	10843
55	(quality adjusted life year* or qualy*).ti,ab.	10979
56	exp Hospitalization/	218527
57	exp "Patient Acceptance of Health Care"/	139385
58	exp Disease Management/	62431
59	exp Resource Allocation/ or exp HEALTH CARE RATIONING/	16683
60	((clinical or critical or patient) adj1 path*).ab,ti.	26361
61	(managed adj2 (care or clinical or network)).ti,ab.	18168
62	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	39872
63	cost*.mp.	639913
64	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63	1609596
65	exp SCOTLAND/	23946
66	exp ENGLAND/	102757
67	exp WALES/	13642
68	exp Northern Ireland/	4710
69	exp United Kingdom/	351359
70	(northern adj2 (ireland or irish)).mp.	6947
71	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	2143562
72	65 or 66 or 67 or 68 or 69 or 70 or 71	2163198
73	64 and 72	174244
74	5 and 73	537
75	26 or 74	859
76	limit 75 to yr="2018 -Current"	52
77	from 76 keep 1-52	52

Table 103 Cost/resource use search strategy for EconLit (September 19, 2019)

#	Searches	Results
1	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonre-spon* or major) adj3 depressi*).mp.	80
2	(MDD* or MDE* or TRD*).mp.	59

#	Searches	Results
3	1 or 2	130
4	limit 3 to yr="2018 -Current"	7

Table 104 Cost/resource use search strategy for PsycINFO (September 19, 2019)

#	Searches	Results
1	exp Major Depression/	119292
2	exp Treatment Resistant Depression/	2082
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	125681
4	(MDD* or MDE* or TRD*).mp.	10870
5	1 or 2 or 3 or 4	130715
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	24
7	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	1086
8	(cost utility analys* or (cost-utility adj1 analys*)).mp.	357
9	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	1279
10	6 or 7 or 8 or 9	2597
11	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	2701
12	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	2546
13	exp Decision Theory/	1010
14	decision tree.mp.	1114
15	economic model.mp.	404
16	(markov or deterministic).mp.	5995
17	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	25049
18	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	141
19	(incremental-cost or incremental cost).mp.	819
20	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	2151
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	37382
22	11 and 21	588
23	10 or 22	2977
24	5 and 23	176
25	exp ECONOMICS/	22980
26	exp "COSTS AND COST ANALYSIS"/	23404
27	exp "Cost Containment"/	550
28	exp Health Care Costs/	9363
29	exp BUDGETS/	992
30	exp FEE FOR SERVICE/	317
31	(fiscal or funding or financial or finance).ab,ti.	60563
32	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	106951
33	fee.ti,ab.	1991
34	fees.ti,ab.	1452
35	(value adj2 (money or monetary)).ti,ab.	837
36	(quality adjusted life year* or qaly or qualy*).ti,ab.	1302
37	exp Hospitalization/	16932

#	Searches	Results
38	exp Consumer Satisfaction/	4745
39	exp Disease Management/	6302
40	exp Clinical Practice/	18316
41	((clinical or critical or patient) adj1 path*).ab,ti.	1426
42	(managed adj2 (care or clinical or network)).ti,ab.	4807
43	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	12264
44	cost*.mp.	99965
45	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	293214
46	(northern adj2 (ireland or irish)).mp.	2387
47	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	171514
48	46 or 47	173307
49	45 and 48	16621
50	5 and 49	396
51	24 or 50	552
52	limit 51 to yr="2018 -Current"	31

J.1.2.3 September 2019 update

The searches for the September 2019 update are shown below. Note: the Cochrane Library databases (HTA and NHS EED) are only updated to 2016. No citations were therefore identified from these databases for the updated SLR, and the search strategy has not been included.

Table 105 Cost/resource use search strategy for Embase (January 29, 2020)

#	Searches	Results
1	exp major depression/	60634
2	exp treatment resistant depression/	2723
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	92483
4	(MDD* or MDE* or TRD*).mp.	24910
5	1 or 2 or 3 or 4	98666
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	3770
7	exp "cost benefit analysis"/	82270
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	84590
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	10300
10	"cost utility analysis"/ or economic evaluation/	22852
11	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	148887
12	"cost effectiveness analysis"/	145530
13	6 or 7 or 8 or 9 or 10 or 11 or 12	234215
14	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	33887
15	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	68121
16	exp decision theory/ or "decision tree"/	13320
17	decision tree.mp.	15351
18	economic model.mp.	4008

#	Searches	Results
19	(markov or deterministic).mp.	43921
20	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	310167
21	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	1268
22	(incremental-cost or incremental cost).mp.	17598
23	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	24066
24	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	440153
25	14 and 24	11266
26	13 or 25	235504
27	5 and 26	1028
28	exp economics/	247854
29	exp "Costs and Cost Analysis"/	338344
30	exp 'cost allocation'/	338344
31	exp "cost benefit analysis"/	82270
32	exp "cost control"/	66294
33	exp 'cost savings'/	66294
34	exp "cost of illness"/	18560
35	exp 'cost sharing'/	338344
36	exp 'medical savings accounts'/	338344
37	exp "health care cost"/	281907
38	exp 'direct service costs'/	281907
39	exp "drug cost"/	75437
40	exp 'employer health costs'/	281907
41	exp "hospital cost"/	36224
42	exp 'health expenditures'/	281907
43	exp 'capital expenditures'/	281907
44	exp 'value of life'/	362508
45	exp 'economics, medical'/	814897
46	exp 'economics, hospital'/	814897
47	exp 'economics, nursing'/	814897
48	exp 'economics, pharmaceutical'/	196551
49	exp budget/	27784
50	exp fee/	39237
51	(fiscal or funding or financial or finance).ab,ti.	181704
52	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	363436
53	fee.ti,ab.	14608
54	fees.ti,ab.	9183
55	(value adj2 (money or monetary)).ti,ab.	3091
56	exp quality adjusted life year/	24718
57	(quality adjusted life year* or qualy*).ti,ab.	17725
58	exp hospitalization/	345458
59	exp "consumer satisfaction"/	48105
60	"patient acceptance of health care"/	55968
61	"disease management"/	18064

#	Searches	Results
62	clinical practice/	270775
63	"health care rationing"/	118193
64	((clinical or critical or patient) adj1 path*).ab,ti.	41062
65	(managed adj2 (care or clinical or network)).ti,ab.	22427
66	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	60691
67	cost*.mp.	1014292
68	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	2731404
69	exp Scotland/	4149
70	exp England/	18907
71	exp Wales/	2918
72	exp Northern Ireland/	1203
73	exp United Kingdom/	406368
74	(northern adj2 (ireland or irish)).mp.	6657
75	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	841000
76	69 or 70 or 71 or 72 or 73 or 74 or 75	846023
77	68 and 76	155068
78	5 and 77	621
79	27 or 78	1535
80	limit 79 to yr="2019 -Current"	84

Table 106 Cost/resource use search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (January 29, 2020)

#	Searches	Results
1	exp Depressive Disorder, Major/	28432
2	exp Depressive Disorder, Treatment-Resistant/	1079
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonre-spon* or major) adj3 depressi*).mp.	61389
4	(MDD* or MDE* or TRD*).mp.	16824
5	1 or 2 or 3 or 4	65480
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	713
7	exp Cost-Benefit Analysis/	77768
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	79921
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	2919
10	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	11960
11	6 or 7 or 8 or 9 or 10	84606
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	17785
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	60850
14	exp Decision Theory/	11591
15	exp Decision Trees/	10689
16	decision tree.mp.	6566
17	economic model.mp.	2051
18	(markov or deterministic).mp.	38057

#	Searches	Results
19	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	201361
20	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	755
21	(incremental-cost or incremental cost).mp.	10587
22	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	13428
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	318856
24	12 and 23	5944
25	11 or 24	86290
26	5 and 25	402
27	exp ECONOMICS/	583916
28	exp "Costs and Cost Analysis"/	228014
29	exp "Cost Allocation"/	1999
30	exp "Cost Control"/	32545
31	exp "Cost Savings"/	11372
32	exp "Cost of Illness"/	25620
33	exp "Cost Sharing"/	4378
34	exp Medical Savings Accounts/	530
35	exp Health Care Costs/	62271
36	exp Direct Service Costs/	1174
37	exp Drug Costs/	15492
38	exp Employer Health Costs/	1088
39	exp Hospital Costs/	10531
40	exp Health Expenditures/	21148
41	exp Capital Expenditures/	1987
42	exp "Value of Life"/	5657
43	exp ECONOMICS, MEDICAL/	14122
44	exp ECONOMICS, NURSING/	3993
45	exp ECONOMICS, HOSPITAL/	23849
46	exp ECONOMICS, PHARMACEUTICAL/	2887
47	exp Budgets/	13560
48	exp "Fees and Charges"/	29880
49	(fiscal or funding or financial or finance).ab,ti.	138210
50	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	280559
51	fee.ti,ab.	10914
52	fees.ti,ab.	7291
53	(value adj2 (money or monetary)).ti,ab.	2230
54	exp Quality-Adjusted Life Years/	11347
55	(quality adjusted life year* or qualy*).ti,ab.	11567
56	exp Hospitalization/	225406
57	exp "Patient Acceptance of Health Care"/	143519
58	exp Disease Management/	65119
59	exp Resource Allocation/ or exp HEALTH CARE RATIONING/	16883
60	((clinical or critical or patient) adj1 path*).ab,ti.	27282
61	(managed adj2 (care or clinical or network)).ti,ab.	18301

#	Searches	Results
62	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	41743
63	cost*.mp.	663444
64	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63	1662648
65	exp SCOTLAND/	24208
66	exp ENGLAND/	104003
67	exp WALES/	13798
68	exp Northern Ireland/	4761
69	exp United Kingdom/	355986
70	(northern adj2 (ireland or irish)).mp.	7084
71	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	2145210
72	65 or 66 or 67 or 68 or 69 or 70 or 71	2165047
73	64 and 72	176373
74	5 and 73	540
75	26 or 74	875
76	limit 75 to yr="2019 -Current"	28

Table 107 Cost/resource use search strategy for EconLit (January 29, 2020)

#	Searches	Results
1	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	82
2	(MDD* or MDE* or TRD*).mp.	62
3	1 or 2	135
4	limit 3 to yr="2019 -Current"	5

Table 108 Cost/resource use search strategy for PsycINFO (January 29, 2020)

#	Searches	Results
1	exp Major Depression/	122334
2	exp Treatment Resistant Depression/	2187
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	128930
4	(MDD* or MDE* or TRD*).mp.	11405
5	1 or 2 or 3 or 4	134058
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	25
7	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	1116
8	(cost utility analys* or (cost-utility adj1 analys*)).mp.	372
9	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	1319
10	6 or 7 or 8 or 9	2677
11	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	2768
12	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	2617
13	exp Decision Theory/	1051
14	decision tree.mp.	1172
15	economic model.mp.	414
16	(markov or deterministic).mp.	6155

#	Searches	Results
17	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	25680
18	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	144
19	(incremental-cost or incremental cost).mp.	850
20	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	2223
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	38407
22	11 and 21	610
23	10 or 22	3070
24	5 and 23	182
25	exp ECONOMICS/	65633
26	exp "COSTS AND COST ANALYSIS"/	37439
27	exp "Cost Containment"/	559
28	exp Health Care Costs/	20033
29	exp BUDGETS/	1023
30	exp FEE FOR SERVICE/	325
31	(fiscal or funding or financial or finance).ab,ti.	61971
32	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	109346
33	fee.ti,ab.	2027
34	fees.ti,ab.	1491
35	(value adj2 (money or monetary)).ti,ab.	859
36	(quality adjusted life year* or qaly or qualy*).ti,ab.	1348
37	exp Hospitalization/	17281
38	exp Consumer Satisfaction/	4850
39	exp Disease Management/	6420
40	exp Clinical Practice/	19391
41	((clinical or critical or patient) adj1 path*).ab,ti.	1467
42	(managed adj2 (care or clinical or network)).ti,ab.	4823
43	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	12548
44	cost*.mp.	107371
45	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	325428
46	(northern adj2 (ireland or irish)).mp.	2433
47	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	177742
48	46 or 47	179566
49	45 and 48	18493
50	5 and 49	456
51	24 or 50	616
52	limit 51 to yr="2019 -Current"	19

J.1.2.4 January 2020 update

The searches for the January 2020 update are shown below. Note: the Cochrane Library databases (HTA and NHS EED) are only updated to 2016. No citations were therefore identified from these databases for the updated SLR, and the search strategy has not been included.

Table 109 Cost/resource use search strategy for Embase (January 29, 2020)

#	Searches	Results
1	exp major depression/	62014
2	exp treatment resistant depression/	2915
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	94385
4	(MDD* or MDE* or TRD*).mp.	25892
5	1 or 2 or 3 or 4	100797
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	3838
7	exp "cost benefit analysis"/	83618
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	85986
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	10610
10	"cost utility analysis"/ or economic evaluation/	23475
11	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	151946
12	"cost effectiveness analysis"/	148480
13	6 or 7 or 8 or 9 or 10 or 11 or 12	238916
14	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	34927
15	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	69629
16	exp decision theory/ or "decision tree"/	13887
17	decision tree.mp.	16031
18	economic model.mp.	4196
19	(markov or deterministic).mp.	45925
20	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	317576
21	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	1323
22	(incremental-cost or incremental cost).mp.	18340
23	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	25108
24	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	451786
25	14 and 24	11643
26	13 or 25	240245
27	5 and 26	1047
28	exp economics/	250379
29	exp "Costs and Cost Analysis"/	345138
30	exp 'cost allocation'/	345138
31	exp "cost benefit analysis"/	83618
32	exp "cost control"/	67809
33	exp 'cost savings'/	67809
34	exp "cost of illness"/	18926
35	exp 'cost sharing'/	345138
36	exp 'medical savings accounts'/	345138
37	exp "health care cost"/	287947
38	exp 'direct service costs'/	287947
39	exp "drug cost"/	77929
40	exp 'employer health costs'/	287947

#	Searches	Results
41	exp "hospital cost"/	36993
42	exp 'health expenditures'/	287947
43	exp 'capital expenditures'/	287947
44	exp 'value of life'/	370187
45	exp 'economics, medical'/	833416
46	exp 'economics, hospital'/	833416
47	exp 'economics, nursing'/	833416
48	exp 'economics, pharmaceutical'/	202007
49	exp budget/	28756
50	exp fee/	40344
51	(fiscal or funding or financial or finance).ab,ti.	188158
52	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	375399
53	fee.ti,ab.	15216
54	fees.ti,ab.	9463
55	(value adj2 (money or monetary)).ti,ab.	3190
56	exp quality adjusted life year/	25700
57	(quality adjusted life year* or qualy*).ti,ab.	18486
58	exp hospitalization/	355996
59	exp "consumer satisfaction"/	49205
60	"patient acceptance of health care"/	56833
61	"disease management"/	18026
62	clinical practice/	277456
63	"health care rationing"/	121779
64	((clinical or critical or patient) adj1 path*).ab,ti.	42062
65	(managed adj2 (care or clinical or network)).ti,ab.	22660
66	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	63189
67	cost*.mp.	1046087
68	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67	2807417
69	exp Scotland/	4508
70	exp England/	20591
71	exp Wales/	3200
72	exp Northern Ireland/	1300
73	exp United Kingdom/	416289
74	(northern adj2 (ireland or irish)).mp.	6777
75	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	859112
76	69 or 70 or 71 or 72 or 73 or 74 or 75	864332
77	68 and 76	160578
78	5 and 77	644
79	27 or 78	1576
80	(Sep* 2019 or Oct* 2019 or Nov* 2019 or Dec* 2019 or Jan* 2020).dp.	169125
81	79 and 80	23
82	limit 79 to dd=20190901-20200131	27

#	Searches	Results
83	81 or 82	34

Table 110 Cost/resource use search strategy for MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (January 29, 2020)

#	Searches	Results
1	exp Depressive Disorder, Major/	29089
2	exp Depressive Disorder, Treatment-Resistant/	1168
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	62887
4	(MDD* or MDE* or TRD*).mp.	17472
5	1 or 2 or 3 or 4	67115
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	727
7	exp Cost-Benefit Analysis/	79323
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	81545
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	3038
10	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	12429
11	6 or 7 or 8 or 9 or 10	86435
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	18334
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	61884
14	exp Decision Theory/	11790
15	exp Decision Trees/	10881
16	decision tree.mp.	6927
17	economic model.mp.	2105
18	(markov or deterministic).mp.	39211
19	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	206793
20	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	784
21	(incremental-cost or incremental cost).mp.	11014
22	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	14009
23	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	326978
24	12 and 23	6134
25	11 or 24	88145
26	5 and 25	411
27	exp ECONOMICS/	591718
28	exp "Costs and Cost Analysis"/	232059
29	exp "Cost Allocation"/	2003
30	exp "Cost Control"/	32851
31	exp "Cost Savings"/	11624
32	exp "Cost of Illness"/	26318
33	exp "Cost Sharing"/	4425
34	exp Medical Savings Accounts/	535
35	exp Health Care Costs/	63651
36	exp Direct Service Costs/	1180
37	exp Drug Costs/	15775

#	Searches	Results
38	exp Employer Health Costs/	1090
39	exp Hospital Costs/	10790
40	exp Health Expenditures/	21638
41	exp Capital Expenditures/	1987
42	exp "Value of Life"/	5683
43	exp ECONOMICS, MEDICAL/	14160
44	exp ECONOMICS, NURSING/	3996
45	exp ECONOMICS, HOSPITAL/	24183
46	exp ECONOMICS, PHARMACEUTICAL/	2912
47	exp Budgets/	13617
48	exp "Fees and Charges"/	30099
49	(fiscal or funding or financial or finance).ab,ti.	142926
50	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	289401
51	fee.ti,ab.	11174
52	fees.ti,ab.	7427
53	(value adj2 (money or monetary)).ti,ab.	2300
54	exp Quality-Adjusted Life Years/	11776
55	(quality adjusted life year* or qualy*).ti,ab.	12075
56	exp Hospitalization/	231877
57	exp "Patient Acceptance of Health Care"/	147243
58	exp Disease Management/	67325
59	exp Resource Allocation/ or exp HEALTH CARE RATIONING/	17054
60	((clinical or critical or patient) adj1 path*).ab,ti.	27973
61	(managed adj2 (care or clinical or network)).ti,ab.	18399
62	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	43198
63	cost*.mp.	682311
64	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63	1705184
65	exp SCOTLAND/	24450
66	exp ENGLAND/	105161
67	exp WALES/	13960
68	exp Northern Ireland/	4819
69	exp United Kingdom/	360240
70	(northern adj2 (ireland or irish)).mp.	7188
71	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	2152726
72	65 or 66 or 67 or 68 or 69 or 70 or 71	2172736
73	64 and 72	178194
74	5 and 73	549
75	26 or 74	892
76	(2019 Sep* or 2019 Oct* or 2019 Nov* or 2019 Dec* or 2020 Jan*).dp.	518106
77	75 and 76	8
78	limit 75 to ed=20190901-20200131	13
79	77 or 78	21

Table 111 Cost/resource use search strategy for EconLit (January 29, 2020)

#	Searches	Results
1	exp major depression/	62014
2	exp treatment resistant depression/	2915
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	94385
4	(MDD* or MDE* or TRD*).mp.	25892

Table 112 Cost/resource use search strategy for PsycINFO (January 29, 2020)

#	Searches	Results
1	exp Major Depression/	124729
2	exp Treatment Resistant Depression/	2248
3	((chronic or resistan* or untreatable or unrespon* or non-respon* or nonrespon* or major) adj3 depressi*).mp.	131409
4	(MDD* or MDE* or TRD*).mp.	11770
5	1 or 2 or 3 or 4	136660
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	25
7	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	1132
8	(cost utility analys* or (cost-utility adj1 analys*)).mp.	382
9	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	1350
10	6 or 7 or 8 or 9	2729
11	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	2844
12	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	2658
13	exp Decision Theory/	1088
14	decision tree.mp.	1200
15	economic model.mp.	420
16	(markov or deterministic).mp.	6268
17	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	26244
18	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	145
19	(incremental-cost or incremental cost).mp.	873
20	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	2291
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	39229
22	11 and 21	632
23	10 or 22	3137
24	5 and 23	188
25	exp ECONOMICS/	67102
26	exp "COSTS AND COST ANALYSIS"/	38142
27	exp "Cost Containment"/	575
28	exp Health Care Costs/	20420
29	exp BUDGETS/	1044
30	exp FEE FOR SERVICE/	333
31	(fiscal or funding or financial or finance).ab,ti.	63294
32	(economic* or pharmacoeconomic* or price* or pricing).ab,ti.	111268
33	fee.ti,ab.	2061

#	Searches	Results
34	fees.ti,ab.	1523
35	(value adj2 (money or monetary)).ti,ab.	872
36	(quality adjusted life year* or qaly or qualy*).ti,ab.	1389
37	exp Hospitalization/	17660
38	exp Consumer Satisfaction/	4931
39	exp Disease Management/	6599
40	exp Clinical Practice/	19765
41	((clinical or critical or patient) adj1 path*).ab,ti.	1497
42	(managed adj2 (care or clinical or network)).ti,ab.	4845
43	(resource* adj2 (allocat* or utili* or use*)).ti,ab.	12791
44	cost*.mp.	109462
45	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	331710
46	(northern adj2 (ireland or irish)).mp.	2478
47	(scot* or england or english or wales or welsh or united kingdom or UK).mp.	180338
48	46 or 47	182190
49	45 and 48	18845
50	5 and 49	464
51	24 or 50	630
52	limit 51 to yr="2019 -Current"	27

J.1.3 Eligibility criteria

The eligibility criteria applied throughout the original cost/resource use SLR, and subsequent updates are detailed in Table 113.

The inclusion/exclusion of citations (both at the title/abstract phase and full publication review) was conducted by two independent analysts. Any disputes were referred to the project manager and resolved by consensus.

Relevant data were extracted into a pre-approved data extraction template by a reviewer. A second reviewer checked the data extraction, and any inconsistencies were resolved through discussion.

Table 113 Eligibility criteria for the cost/resource use systematic literature review

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adult patients with MDD (with a particular focus on patients who have progressed to TRD)	Paediatric patients (<18 years), patients with related conditions (dysphoria, dysthymia, melancholia, SAD, mood disorder, GAD), and patients with comorbid depression
Intervention	No restriction	-
Study design	Eligible study designs included: • Cost studies • Clinical studies • Longitudinal studies	• Reviews/editorials • Economic evaluations • Budget impact analyses

	• Database studies	
Outcomes	Outcomes of interest included: • Direct costs • Direct healthcare costs per patient (over any time frame) • Resource use (e.g. specialist/unscheduled visits, hospitalisations) • Patients and family/caregiver costs • Influence of comorbidities • Suicide-related costs • Costs aligned with the following health states: ○ No response/MDE ○ Response ○ Remission ○ Recovery	Outcomes not listed in inclusion column
Territory of interest	UK	Non-UK
Date of publication	Original review: no restriction April 2019 update: post-July 2018 September 2019 update: post-April 2019 January 2020 update: post-September 2019	Original review: NA April 2019 update: pre-July 2018 September 2019 update: pre-April 2019 January 2020 update: pre-September 2019
Language of publication	English language publications or foreign language publications with an English abstract	Foreign language publications without an English abstract

J.1.4 Systematic selection of studies

The electronic databases identified a total of 3,132 citations. Following removal of 431 duplicates, 2,701 citations were screened based on title and abstract. Of these, 341 were potentially relevant and were obtained for full text review. At this stage, a further 323 citations were excluded. Hand searching yielded no additional publications, resulting in 22 publications for final inclusion in cost/resource use SLR.

The PRISMA flow diagram for the study selection process used in the SLR is presented in Figure 15.

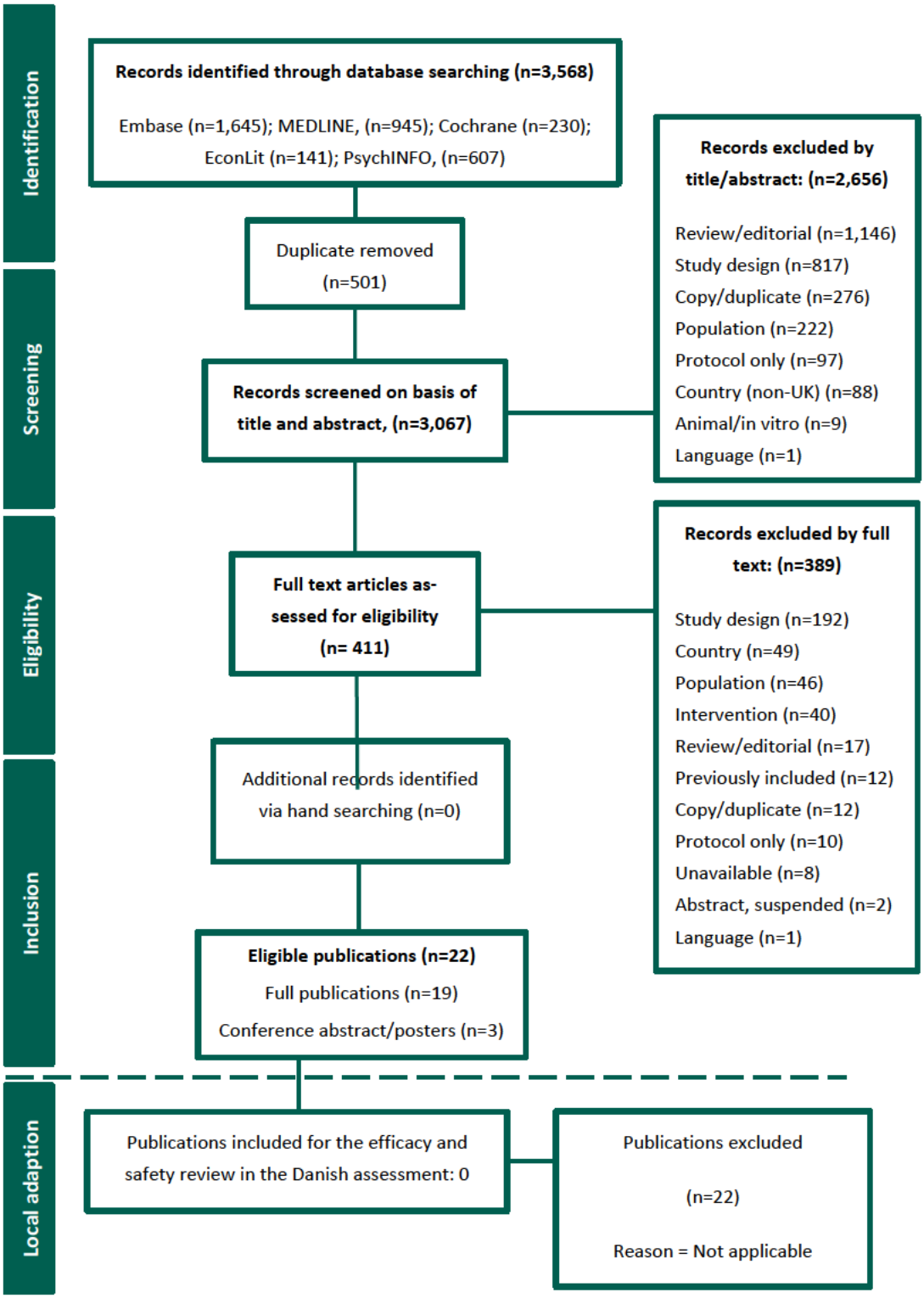


Figure 15 PRISMA diagram for the cost/resource use SLR

J.1.5 Excluded full-text references

The global SLR identified 22 relevant studies. However, as detailed in the local adaptation section below, none of the publications included in the global SLR were used in the current submission, and they are therefore considered 'excluded'. A list of the 22 studies included in the global SLR is provided in Table 114Table 114.

Table 114 List of studies included in the global cost/resource use systematic literature review, excluded from the local adaptation

Reference	Title
Byford, 2011	Impact of treatment success on health service use and cost in depression: Longitudinal database analysis.
Chiesa, 2002	Health service use costs by personality disorder following specialist and nonspecialist treatment: a comparative study
Denee, 2019	A Retrospective Chart Review Study to Quantify the Monthly Medical Resource Use and Costs of Treating Patients with Treatment Resistant Depression in the United Kingdom.
Diamoantopoulos, 2018	Costs and quality in the treatment of acute depression in primary care: A comparison between England, Germany and Switzerland
Gandjour, 2004	. Vagus nerve stimulation for treatment-resistant depression: A budget impact analysis in England
Jaffe, 2019	The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study
Jonsson, 1994	What price depression? The cost of depression and the cost-effectiveness of pharmacological treatment.
Kind, 1993	The costs of depression.
Kuyken, 2015	The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antide-pressant treatment in the prevention of depressive relapse/recurrence: results of a randomised controlled trial (the PRE-VENT study).
Lamy, 2015	Pharmacotherapeutic strategies for patients treated for depression in UK primary care: A database analysis.

McCracken, 2006	Health service use by adults with depression: Community survey in five European countries: Evidence from the ODIN study.
McCrone, 2017	The economic cost of treatment-resistant depression in patients referred to a specialist service.
McMahon, 2012	Chronic and recurrent depression in primary care: socio-demographic features, morbidity, and costs.
Painchault, 2014	Economic burden of major depressive disorder (MDD) in five European countries: Description of resource use by health state.
Richards, 2016	Cost and Outcome of Behavioural Activation versus Cognitive Behavioural Therapy for Depression (COBRA): a randomised, controlled, non-inferiority trial.
Shearer, 2019	Refractory depression - cost-effectiveness of radically open dialectical behaviour therapy: findings of economic evaluation of RefraMED trial.
Shi, 2012	Healthcare utilization among patients with depression before and after initiating duloxetine in the United Kingdom.
Sobocki, 2006	Cost of depression in Europe.
Thomas, 2003	Cost of depression among adults in England in 2000
Treglia, 1999	Fluoxetine and dothiepin therapy in primary care and health resource utilization: Evidence from the United Kingdom.
Vanoli, 2008	Adequacy of venlafaxine dose prescribing in major depression and hospital resources implications.
Wade, 2010	Healthcare expenditure in severely depressed patients treated with escitalopram, generic SSRIs or venlafaxine in the UK

A list of studies excluded from all the global cost/resource use SLR updates is provided in Table 115.

Table 115 List of studies excluded from the cost/resource use systematic literature review following full-text review

No.	Publication	Exclusion reason
Studies excluded in July 2018 update (n=323)		
1	Adilgozhina G, Abdukhakimova D, Zhumagali Y, Bektur C, Kostuyk A, Nurgozhin T. Pharmacoeconomic analysis of agomelatine for the treatment of major depressive disorder in Kazakhstan. Value in Health 2017; 20(5):A297.	Study design (included in economic evaluation SLR)
2	Alegre P, Nagy B, Nagy J. Economic evaluation of agomelatine in major depresive disorders in Hungary. Value in Health 2010; 13(7):A451.	Study design (included in economic evaluation SLR)
3	Alsultan M, Khurshid F, Alegre P. Economic evaluation of agomelatine in patients attending private hospitals in Saudi Arabia. European Psychiatry Conference 2012; 27(SUPPL. 1).	Study design (included in economic evaluation SLR)
4	Andrew Demitrack M, Bonneh-Barkay D, Brock DG, Waltman A, Nahas Z, et al. Health economic comparison of TMS and antidepressant medications in the treatment of major depression. Biological Psychiatry 2014; (1):45S-6S.	Copy/duplicate
5	Annemans L, Brignone M, Druais S, De Pauw A, Gauthier A, et al. Cost-effectiveness analysis of pharmaceutical treatment options in the first-line management of major depressive disorder in Belgium. PharmacoEconomics 2014; 32(5):479-93.	Study design (included in economic evaluation SLR)
6	Anonymous. Adjunctive CBT effective and cost-effective for treatment-resistant depression? Drug and Therapeutics Bulletin 2014; 52(9):100-1.	Study design (included in economic evaluation SLR)
7	Anonymous. Depression in the workplace is associated with high indirect costs related to absenteeism and impaired performance. Drugs and Therapy Perspectives 2008; 24(6):23-6.	Review/editorial
8	Anton SF, Revicki DA. The use of decision analysis in the pharmacoeconomic evaluation of an antidepressant: A cost-effective study of nefazodone. Psychopharmacology Bulletin 1995; 31(2):249-58.	Study design (included in economic evaluation SLR)
9	Antonuccio DO, Thomas M, Danton WG. A cost-effectiveness analysis of cognitive behavior therapy and fluoxetine (Prozac) in the treatment of depression. Behavior Therapy 1997; 28(2):187-210.	Study design (included in economic evaluation SLR)
10	Araya R, Flynn T, Rojas G, Fritsch R, Simon G. Cost-effectiveness of a primary care treatment program for depression in low-income women in Santiago, Chile. American Journal of Psychiatry 2006; 163(8):1379-87.	Intervention (economic evaluation)
11	Armstrong EP, Malone DC, Erder M. A Markov cost-utility analysis of escitalopram and duloxetine for the treatment of major depressive disorder. Current Medical Research and Opinion 2008; 24(4):1115-21.	Study design (included in economic evaluation SLR)
12	Armstrong EP, Skrepnek GH, Erder MH. Cost-utility comparison of escitalopram and sertraline in the treatment of major depressive disorder. Current Medical Research and Opinion 2007; 23(2):251-8.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
13	Ausejo M, Glennie J. A clinical and economic evaluation of selective serotonin reuptake inhibitors in major depression. Health Technology Assessment Database. 2016; (4).	Unavailable; unable to obtain
14	Aydemir O, Dilbaz N, Malhan S. Cost effectiveness of extended release quetiapine fumarate (quetiapine XR) monotherapy in Turkey in patients with major depressive disorder (MDD) who have failed previous antidepressant therapy. Value in Health 2011; 14(7):A291-A2.	Study design (included in economic evaluation SLR)
15	Aziz M, Mehringer AM, Mozurkewich E, Razik GN. Cost-utility of 2 maintenance treatments for older adults with depression who responded to a course of electroconvulsive therapy: Results from a decision analytic model. Canadian Journal of Psychiatry 2005; 50(7):389-97.	Unavailable; unable to obtain
16	Baca Baldomero E, Rubio-Terres C. Cost-effectiveness of venlafaxine for the treatment of depression and anxiety. Bibliographic review. [Spanish]. Actas Espanolas de Psiquiatria 2006; 34(3):193-201.	Study design (included in economic evaluation SLR)
17	Baladi J-F. Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part 2. The cost-effectiveness of SSRIs in treatment of depression (Structured abstract). Health Technology Assessment Database 2016; (4).	Study design (included in economic evaluation SLR)
18	Benedict A, Arellano J, De Cock E, Baird J. Economic evaluation of duloxetine versus serotonin selective reuptake inhibitors and venlafaxine XR in treating major depressive disorder in Scotland. Journal of Affective Disorders 2010; 120(1-3):94-104.	Study design (included in economic evaluation SLR)
19	Bentkover JD, Feighner JP. Cost Analysis of Paroxetine versus Imipramine in Major Depression. PharmacoEconomics 1995; 8(3):223-32.	Country (non-UK)
20	Berndt ER, Bir A, Busch SH, Frank RG, Normand S-LT. The Medical Treatment of Depression, 1991-1996: Productive Inefficiency, Expected Outcome Variations, and Price Indexes. National Bureau of Economic Research, Inc, NBER Working Papers 2000; 7816.	Country (non-UK)
21	Berndt ER, Busch SH, Frank RG. Price Indexes for Acute Phase Treatment of Depression. National Bureau of Economic Research, Inc, NBER Working Papers 1998; 6799.	Country (non-UK)
22	Berndt ER, Busch SH, Frank RG. Treatment Price Indexes for Acute Phase Major Depression. Medical care output and productivity Cutler, David M Berndt, Ernst R, eds, NBER Studies in Income and Wealth, vol 62 Chicago and London: University of Chicago Press2001. p. 463-505.	Country (non-UK)
23	Berndt ER. Changes in the Costs of Treating Mental Health Disorders: An Overview of Recent Research Findings. PharmacoEconomics 2004; 22:37-50.	Review/editorial
24	Biesheuvel-Leliefeld KE, Kersten SM, van der Horst HE, van Schaik A, Bockting CL, et al. Cost-effectiveness of nurse-led self-help for recurrent depression in the primary care setting: design of a pragmatic randomised controlled trial. BMC Psychiatry 2012; 12:59.	Protocol only
25	BlueCross BlueShield Association. Vagus nerve stimulation for treatment-resistant depression. Health Technology Assessment Database 2016; (4).	Unavailable; unable to obtain

No.	Publication	Exclusion reason
26	Bode K, Vogel R, Walker J, Kroger C. Health Care Costs of Borderline Personality Disorder and Matched Controls with Major Depressive Disorder: A Comparative Study Based on Anonymized Claims Data. European Journal of Health Economics 2017; 18(9):1125-35.	Country (non-UK)
27	Borghi J, Guest J. Economic impact of using mirtazapine compared to amitriptyline and fluoxetine in the treatment of moderate and severe depression in the UK. European Psychiatry 2000; 15(6):378-87.	Patient population
28	Bosanquet K, Adamson J, Atherton K, Bailey D, Baxter C, et al. Collaborative care for screen-positive elders with major depression (CASPER plus): A multicentred randomized controlled trial of clinical effectiveness and cost-effectiveness. Health Technology Assessment 2017; 21(67):1-251.	Intervention (economic evaluation)
29	Bosmans J, De Bruijne M, Van Hout H, Van Marwijk H, Beekman A, et al. Cost-effectiveness of a disease management program for major depression in elderly primary care patients. Journal of General Internal Medicine 2006; 21(10):1020-6.	Intervention (economic evaluation)
30	Bosmans JE, Brook OH, van Hout HP, de Bruijne MC, Nieuwenhuyse H, et al. Cost Effectiveness of a Pharmacy-Based Coaching Programme to Improve Adherence to Antidepressants. PharmacoEconomics 2007; 25(1):25-37.	Intervention (economic evaluation)
31	Bosmans JE, Hermens ML, de Bruijne MC, van Hout HP, Terluin B, et al. Cost-effectiveness of usual general practitioner care with or without antidepressant medication for patients with minor or mild-major depression. Journal of Affective Disorders 2008; 111(1):106-12.	Study design (included in economic evaluation SLR)
32	Bosmans JE, van Schaik DJ, Heymans MW, van Marwijk HW, van Hout HP, et al. Cost-effectiveness of interpersonal psychotherapy for elderly primary care patients with major depression. International Journal of Technology Assessment in Health Care 2007; 23(4):480-7.	Study design (included in economic evaluation SLR)
33	Brignone M, Atsou K, Reynaud-Mougin C, Chen W, Milea D. Cost-utility analysis evaluating vortioxetine versus venlafaxine XR and agomelatine in the treatment of major depressive disorder in Taiwan. Value in Health 2016; 19(7):A841-A2.	Study design (included in economic evaluation SLR)
3	Bruijniks SJ, Bosmans J, Peeters FP, Hollon SD, van Oppen P, et al. Frequency and change mechanisms of psychotherapy among depressed patients: study protocol for a multicenter randomized trial comparing twice-weekly versus once-weekly sessions of CBT and IPT. BMC Psychiatry 2015; 15:137.	Protocol only
35	Byford S, Barrett B, Roberts C, Wilkinson P, Dubicka B, et al. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive-behavioural therapy in adolescents with major depression. The British Journal of Psychiatry 2007; 191(6):521-7.	Patient population
36	Byford S, Barrett B, Roberts C, Wilkinson P, Dubicka B, et al. Cost-effectiveness of selective serotonin reuptake inhibitors and routine specialist care with and without cognitive behavioural therapy in adolescents with major depression. British Journal of Psychiatry 2007; 191:521-7.	Copy/duplicate

No.	Publication	Exclusion reason
37	Callander EJ, Lindsay DB, Scuffham PA. Employer benefits from an early intervention program for depression: A cost-benefit analysis. Journal of Occupational and Environmental Medicine 2017; 59(3):246-9.	Intervention (economic evaluation)
38	Canadian Coordinating Office for Health Technology Assessment. Duloxetine for major depressive disorder and stress urinary incontinence. Health Technology Assessment Database 2016; (4).	Unavailable; unable to obtain
39	Carlini DJ. Transcranial magnetic stimulation and antidepressant medication for the treatment of major depression: A cost-effectiveness comparison to assist patient-physician decision making. Dissertation Abstracts International Section A: Humanities and Social Sciences 2017; 78(5-A(E)).	Unavailable; unable to obtain
40	Casciano J, Arikian S, Tarride JE, Doyle JJ, Casciano R. A pharmacoeconomic evaluation of major depressive disorder (Italy). Epidemiologia e Psichiatria Sociale 1999; 8(3):220-31.	Review/editorial
41	Casciano R, Arikian SR, Tarride JE, Casciano J, Doyle JJ. Antidepressant selection for major depressive disorder: The budgetary impact on managed care. Drug Benefit Trends 2000; 12(5):6BH-17BH.	Study design (included in economic evaluation SLR)
42	Casciano R. A pharmacoeconomic evaluation of major depressive disorder. Managed care interface 2003; Suppl B:16-21.	Study design (included in economic evaluation SLR)
43	Centres for Reviews and Dissemination. Core discrete event simulation model for the evaluation of health care technologies in major depressive disorder. NHS Economic Evaluation Database 2015; (2).	Intervention (economic evaluation)
44	Centres for Reviews and Dissemination. Cost analysis of paroxetine versus imipramine in major depression. NHS Economic Evaluation Database 2015; (2).	Review/editorial
45	Centres for Reviews and Dissemination. Cost-effectiveness of mirtazapine relative to fluoxetine in the treatment of moderate and severe depression in France. NHS Economic Evaluation Database 2015; (2).	Patient population
46	Centres for Reviews and Dissemination. Cost-effectiveness of two vocational rehabilitation programs for persons with severe mental illness. NHS Economic Evaluation Database 2015; (2).	Patient population
47	Centres for Reviews and Dissemination. Medical costs and utilization in patients with depression treated with adjunctive atypical antipsychotic therapy. NHS Economic Evaluation Database 2015; (2).	Country (non-UK)
48	Chatterton ML, Mihalopoulos C, O'Neil A, Itsiopoulos C, Opie R, et al. Economic evaluation of a dietary intervention for adults with major depression (the "SMILES" trial). BMC Public Health 2018; 18(1):599.	Intervention (economic evaluation)

No.	Publication	Exclusion reason
49	Chereches RM, Litan CM, Zlati AM, Bloom JR. Does Co-morbid Depression Impact Diabetes Related Costs? Evidence from a Cross-Sectional Survey in a Low-Income Country. Journal of Mental Health Policy and Economics 2012; 15(3):127-38.	Country (non-UK)
50	Choi SE, Brignone M, Cho SJ, Jeon HJ, Jung R, et al. Cost-effectiveness of vortioxetine versus venlafaxine (extended release) in the treatment of major depressive disorder in South Korea. Expert Review of Pharmacoeconomics and Outcomes Research 2016; 16(5):629-38.	Study design (included in economic evaluation SLR)
51	Christensen MC, Munro V. Cost per successfully treated patient for vortioxetine versus duloxetine in adults with major depressive disorder: an analysis of the complete symptoms of depression and functional outcome. Current Medical Research and Opinion 2018; 34(4):593-600.	Study design (included in economic evaluation SLR)
52	Clapham E, Berg J, Ekman M, Jonsson L. Economic evaluation of agomelatine for major depressive disorder in Sweden. Value in Health 2009; 12(3):A176.	Study design (included in economic evaluation SLR)
53	Cocker F, Nicholson JM, Graves N, Oldenburg B, Palmer AJ, et al. Depression in working adults: Comparing the costs and health outcomes of working when Ill. PLoS ONE 2014; 9(9):e105430.	Intervention (economic evaluation)
54	Commander M, Disanyake L. Impact of functionalised community mental health teams on in-patient care. Psychiatric Bulletin 2006; 30(6):213-5.	Patient population
55	Coretti S, Izzo G, Vaggi M, Bellomo A, Mencacci C, et al. The cost of cognitive impairment in patient with major depressive disorder. Value in Health 2016; 19(7):A526.	Country (non-UK)
56	Corey-Lisle PK, Birnbaum H, Greenberg P, Marynchenko M, Dube S. Economic impact of olanzapine plus fluoxetine combination therapy among patients treated for depression: a pilot study. Psychopharmacology Bulletin 2003; 37(3):90-8.	Country (non-UK)
57	Crespo C, Blanca-Tamayo M, Villacampa A, Lobo S. Antidepressant treatment optimization with BrainChip test: Effectiveness and costs. International Journal of Neuropsychopharmacology 2012; (1):232.	Intervention (economic evaluation)
58	Croom KF, Plosker GL. Escitalopram: A Pharmacoeconomic Review of its Use in Depression. PharmacoEconomics 2003; 21(16):1185-209.	Review/editorial
59	Cseh A, Forgacs T. The Effects of Mental Health Parity Legislation on Mental Health Related Hospitalizations. Journal of Economics 2009; 35(1):1-20.	Country (non-UK)
60	Cui Z, Faries DE, Shen W, Able SL, Novick D. Longitudinal analysis of healthcare costs: A case study of patients with major depressive disorder treated with duloxetine. Journal of Medical Economics 2013; 16(5):623-32.	Country (non-UK)
61	Cui Z, Faries DE, Zhao Y, Novick D, Liu X. Trajectory analysis of healthcare costs for patients with major depressive disorder treated with high doses of duloxetine. Journal of Medical Economics 2011; 14(5):662-72.	Country (non-UK)

No.	Publication	Exclusion reason
62	Dalal AA, Shah M, Lunacsek O, Hanania NA. Clinical and economic burden of depression/anxiety in chronic obstructive pulmonary disease patients within a managed care population. COPD: Journal of Chronic Obstructive Pulmonary Disease 2011; 8(4):293-9.	Country (non-UK)
63	Dardennes R, Berdeaux G, Lafuma A, Fagnani F. Comparison of the cost-effectiveness of milnacipran (a SNRI) with TCAs and SSRIs: A modeling approach. European Psychiatry 1999; 14(3):152-62.	Study design (included in economic evaluation SLR)
64	Dardennes R, Lafuma A, Fagnani F, Pribil C, Bisserbe J, et al. Economic Assessment of a Maintenance Treatment Strategy in Prevention of Recurrent Depressive Disorder. Value in Health 2000; 3(1):40-7.	Study design (included in economic evaluation SLR)
65	Demitrack MA, Bonneh-Barkay D, Brock DG, Waltman A, Nahas Z, et al. Health economics comparison of TMS and antidepressant drugs in the treatment of major depression. CNS Spectrums 2015; 20(1):77.	Study design (included in economic evaluation SLR)
66	Demitrack MA, Brock DG, Nahas Z, Waltman A, Simpson AN, Simpson KN. TMS is a cost effective alternative to antidepressant medication in pharmacoresistant major depression: A propensity-score matched health economic analysis. Brain Stimulation 2015; 8(2):334.	Copy/duplicate
67	Demyttenaere K, Hemels ME, Hudry J, Annemans L. A cost-effectiveness model of escitalopram, citalopram, and venlafaxine as first-line treatment for major depressive disorder in Belgium. Clinical Therapeutics 2005; 27(1):111-24.	Study design (included in economic evaluation SLR)
68	Demyttenaere K, Hemels MEH, Hudry J, Annemans L. A cost-effectiveness model of escitalopram, citalopram, and venlafaxine as first-line treatment for major depressive disorder in Belgium. Clinical Therapeutics 2005; 27(1):111-24.	Copy/duplicate
69	Despiegel N, Danchenko N, Maman K. Cost-effectiveness of escitalopram versus venlafaxine in second-line treatment of major depressive disorder (MDD) in Sweden. Value in Health 2009; 12(3):A177.	Study design (included in economic evaluation SLR)
70	Di Matteo S, Colombo GL. Budget impact analysis in the treatment of major depressive disorder in various Italian regions: The role of venlafaxine. Value in Health 2009; 12(7):A366.	Country (non-UK)
71	Domino ME, Burns BJ, Silva SG, Kratochvil CJ, Vitiello B, et al. Cost-effectiveness of treatments for adolescent depression: Results from TADS. American Journal of Psychiatry 2008; 165(5):588-96.	Patient population
72	Domino ME, Foster EM, Vitiello B, Kratochvil CJ, Burns BJ, et al. Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the tads randomized trial. Journal of the American Academy of Child and Adolescent Psychiatry 2009; 48(7):711-20.	Patient population
73	Donohue JM, Belnap BH, Men A, He F, Roberts MS, Schulberg HC, et al. Twelve-month cost-effectiveness of telephone-delivered collaborative care for treating depression following CABG surgery: A randomized controlled trial. General Hospital Psychiatry 2014; 36(5):453-9.	Patient population
74	Doyle JJ, Casciano J, Arikian S, Tarride JE, Gonzalez MA, Casciano R. A multinational pharmacoeconomic evaluation of acute Major Depressive Disorder (MDD): A comparison of cost-effectiveness between venlafaxine, SSRIs and TCAs. Value in Health 2001; 4(1):16-31.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
75	Druais S, Gauthier A, Demyttenaere K, Brignone M, De Pauw A, Defraigne G, et al. An assessement of the cost-effectiveness of escitalopram versus multiple comparators as first line antidepressant in patients with major depressive disorder (MDD) in belgium. Value in Health 2012; 15(7):A338.	Study design (included in economic evaluation SLR)
76	Duarte A, Walker J, Walker S, Richardson G, Hansen C, Martin P, et al. Cost-effectiveness of integrated collaborative care for comorbid major depression in patients with cancer. Journal of Psychosomatic Research 2015; 79(6):465-70.	Intervention (economic evaluation)
77	Duarte A, Walker S, Littlewood E, Brabyn S, Hewitt C, et al. Cost-effectiveness of computerized cognitive-behavioural therapy for the treatment of depression in primary care: Findings from the Randomised Evaluation of the Effectiveness and Acceptability of Computerised Therapy (REEACT) trial. Psychological Medicine 2017; 47(10):1825-35.	Patient population
78	Edoka IP, Petrou S, Ramchandani PG. Healthcare costs of paternal depression in the postnatal period. Journal of Affective Disorders 2011; 133(1-2):356-60.	Patient population
79	Edwards SJ, Hamilton V, Nherera L, Trevor N. Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a systematic review and economic evaluation. Health Technology Assessment 2013; 17(54):1-190.	Copy/duplicate
80	Edwards SJ, Nherera L, Trevor N, Wakefield V. Cost-effectiveness of lithium versus an atypical anti-psychotic (AAP) used to augment treatment with a selective serotonin reuptake inhibitor (SSRI) in treatment resistant depression (TRD). Value in Health 2014; 17(7):A459.	Copy/duplicate
81	Edwards SJ. Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: A systematic review and economic evaluation. Health Technology Assessment 2013; 17(54):1-34.	Study design (included in economic evaluation SLR)
82	Egede LE, Frueh CB, Richardson LK, Acierno R, Mauldin PD, et al. Rationale and design: Telepsychology service delivery for depressed elderly veterans. Trials 2009; 10(22).	Protocol only
83	Einarson TR, Addis A, Iskedjian M. Pharmacoeconomic analysis of venlafaxine in the treatment of major depressive disorder. PharmacoEconomics 1997; 12(2 II):286-96.	Study design (included in economic evaluation SLR)
84	Einarson TR, Arikian S, Sweeney S, Doyle J. A model to evaluate the cost-effectiveness of oral therapies in the management of patients with major depressive disorders. Clinical Therapeutics 1995; 17(1):136-53.	Study design (included in economic evaluation SLR)
85	Entsuah R, Chitra R. A benefit-risk analysis of once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Psychopharmacology Bulletin 1997; 33(4):671-6.	Study design
86	Evitt L, Danchenko N, Atsou K, Brignone M, Diamand F, Campbell R. Cost-effectiveness evaluation of vortioxetine in major depressive episode in the UK setting. Value in Health 2016; 19(7):A525.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
87	Fantino B, Moore N, Verdoux H, Auray JP. Cost-effectiveness of escitalopram vs. citalopram in major depressive disorder. International Clinical Psychopharmacology 2007; 22(2):107-15.	Study design (included in economic evaluation SLR)
88	Felix J, Almeida J, Varandas P. A discrete event simulation model in major depressive disorder - cost-effectiveness analysis of agomelatine. Value in Health 2009; 12(7):A223.	Study design (included in economic evaluation SLR)
89	Fernandez JL, Montgomery S, Francois C. Evaluation of the cost effectiveness of escitalopram versus venlafaxine XR in major depressive disorder. PharmacoEconomics 2005; 23(2):155-67.	Study design (included in economic evaluation SLR)
90	Forder J, Kavanagh S, Fenyo A. A comparison of the cost-effectiveness of sertraline versus tricyclic antidepressants in primary care. Journal of Affective Disorders 1996; 38(2-3):97-111.	Study design (included in economic evaluation SLR)
91	Fortney JC, Pyne JM, Burgess JF, Jr. Population-level cost-effectiveness of implementing evidence-based practices into routine care. Health Services Research 2014; 49(6):1832-51.	Study design (included in economic evaluation SLR)
92	Francois C, Atsou K, Diamand F, Brignone M, Briquet B, et al. Cost-effectiveness evaluation, including cognitive outcomes, of vortioxetine in patients with major depressive disorder switching from first antidepressant therapy in the United States. Value in Health 2017; 20(5):A297.	Study design (included in economic evaluation SLR)
93	Francois C, Sintonen H, Toumi M. Introduction of escitalopram, a new SSRI in Finland: Comparison of cost-effectiveness between the other SSRIS and SNRI for the treatment of depression and estimation of the budgetary impact. Journal of Medical Economics 2002; 5(91-107):91-107.	Study design (included in economic evaluation SLR)
94	Frank RG, Berndt ER, Busch SH. Price Indexes for the Treatment of Depression. National Bureau of Economic Research, Inc, NBER Working Papers 1998; 6417.	Country (non-UK)
95	Freeman H, Arikian S, Lenox-Smith A. Pharmacoeconomic Analysis of Antidepressants for Major Depressive Disorder in the United Kingdom. PharmacoEconomics 2000; 18(2):143-48.	Study design (included in economic evaluation SLR)
96	Gabarron E, Garcia-Bayo I, Soler-Vila M, Carames E, Penarrubia-Maria MT, et al. Effectiveness and cost-effectiveness of antidepressant treatment in primary health care: A six-month randomised study comparing fluoxetine to imipramine. Journal of Affective Disorders 2006; 91(2-3):153-63.	Patient population
97	Gandjour A, Lauterbach KW. At What Time is a Reduction of Medical Under- or Overtreatment Sensible? Treatment of Acute Depression as an Example. [German]. Psychiatrische Praxis 2004; 31(3):157-62.	Language
98	Gangan N, Yang Y. Health services utilization and costs among employed adults with depression. Value in Health 2015; 18(3):A269.	Country (non-UK)

No.	Publication	Exclusion reason
99	Garfield K, Thomas L, Peters T, Wiles N, Hollinghurst S. Cost-effectiveness of cognitive behavioural therapy for treatment resistant depression: Challenges and solutions conducting an economic evaluation of the long-term follow-up of the cobalt trial. Trials Conference: 3rd International Clinical Trials Methodology Conference United Kingdom 2015; 16(Supplement 2).	Study design (included in economic evaluation SLR)
100	Gensichen J, Petersen JJ, von Korff M, Heider D, Baron S, et al. Cost-effectiveness of depression case management in small practices. The British Journal of Psychiatry 2013; 202(6):441-6.	Intervention (economic evaluation)
101	Gerhards S, de Graaf L, Jacobs L, Severens J, Huibers M, et al. Economic evaluation of online computerised cognitive-behavioural therapy without support for depression in primary care: Randomised trial. The British Journal of Psychiatry 2010; 196(4):310-8.	Patient population
102	Ghiasvand H, Moradi-Joo M, Abolhassani N, Ravaghi H, Raygani SM, et al. Economic evaluation of resistant major depressive disorder treatment in Iranian population: a comparison between repetitive Transcranial Magnetic Stimulation with electroconvulsive. Med J Islam Repub Iran 2016; 30:330.	Study design (included in economic evaluation SLR)
103	Golicki D, Pajak K, Dbrowska A, Niewada M. The cost-utility of agomelatine in major depressive disorder in Poland. Value in Health 2010; 13(7):A452-A3.	Study design (included in economic evaluation SLR)
104	Goorden M, Huijbregts KLM, Van Marwijk HWJ, Beekman ATF, Van Der Feltz-Cornelis CM, et al. Cost-utility of collaborative care for major depressive disorder in primary care in the Netherlands. Journal of Mental Health Policy and Economics 2015; (1):S16-S7.	Copy/duplicate
105	Goorden M, Huijbregts KM, van Marwijk HW, Beekman AT, van der Feltz-Cornelis CM, et al. Cost-utility of collaborative care for major depressive disorder in primary care in the Netherlands. Journal of Psychosomatic Research 2015; 79(4):316-23.	Intervention (economic evaluation)
106	Goorden M, Huijbregts KM, van Marwijk HW, Beekman AT, van der Feltz-Cornelis CM, et al. Cost-utility of collaborative care for major depressive disorder in primary care in the Netherlands. Journal of Psychosomatic Research 2015; 79(4):316-23.	Intervention (economic evaluation)
107	Goorden M, Vlasveld MC, Anema JR, van Mechelen W, Beekman AT, et al. Cost-utility analysis of a collaborative care intervention for major depressive disorder in an occupational healthcare setting. Journal of occupational rehabilitation 2014; 24(3):555-62.	Intervention (economic evaluation)
108	Gordon LG, Nguyen K. Cost-utility of repetitive transcranial magnetic stimulation versus antidepressant therapy for treatment-resistant depression. Value in Health 2015; 18(3):A45-A6.	Copy/duplicate
109	Greenberg P, Corey-Lisle PK, Birnbaum H, Marynchenko M, Claxton A. Economic implications of treatment-resistant depression among employees. PharmacoEconomics 2004; 22(6):363-73.	Country (non-UK)
110	Gureje O, Oladeji BD, Araya R, Montgomery AA. A cluster randomized clinical trial of a stepped care intervention for depression in primary care (STEPCARE)- study protocol. BMC Psychiatry 2015; 15(1):148.	Protocol only

No.	Publication	Exclusion reason
111	Haby MM, Tonge B, Littlefield L, Carter R, Vos T. Cost-effectiveness of cognitive behavioural therapy and selective serotonin reuptake inhibitors for major depression in children and adolescents. Australian and New Zealand Journal of Psychiatry 2004; 38(8):579-91.	Patient population
112	Haji Ali Afzali H, Karnon J, Gray J. A Proposed Model for Economic Evaluations of Major Depressive Disorder. European Journal of Health Economics 2012; 13(4):501-10.	Study design
113	Haji EO, Mann K, Dragicevic A, Muller MJ, Boland K, et al. Potential cost-effectiveness of therapeutic drug monitoring for depressed patients treated with citalopram. Therapeutic Drug Monitoring 2013; 35(3):396-401.	Country (non-UK)
114	Hay JW, Katon WJ, Ell K, Lee PJ, Guterman JJ. Cost-effectiveness analysis of collaborative care management of major depression among low-income, predominantly Hispanics with diabetes. Value in Health 2012; 15(2):249-54.	Intervention (economic evaluation)
115	Health Quality Ontario. Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment. Ontario Health Technology Assess Ser 2017; 17(15):1-167.	Study design (included in economic evaluation SLR)
116	Health Quality Ontario. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: An Economic Analysis. Ontario Health Technology Assess Ser 2016; 16(6):1-51.	Review/editorial
117	Health Technology Assessment Unit, University of Calgary. Repetitive transcranial magnetic stimulation for treatment resistant depression. Health Technology Assessment Database 2016; (4).	Study design (included in economic evaluation SLR)
118	Health Technology Assessment. A randomised pragmatic trial comparing the clinical and cost effectiveness of lithium and quetiapine augmentation in treatment resistant depression (Project record). Health Technology Assessment Database 2016; (4).	Unavailable; unable to obtain
119	Health Technology Assessment. Vortioxetine for the treatment of major depressive disorder (ID583) (Project record). Health Technology Assessment Database 2016; (4).	Study design (included in economic evaluation SLR)
120	Hemels ME, Kasper S, Walter E, Einarson TR. Cost-effectiveness analysis of escitalopram: a new SSRI in the first-line treatment of major depressive disorder in Austria. Curr Med Res Opin 2004; 20(6):869-78.	Study design (included in economic evaluation SLR)
121	Hollinghurst S, Carroll FE, Abel A, Campbell J, Garland A, et al. Cost-effectiveness of cognitive-behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: Economic evaluation of the CoBalT Trial. British Journal of Psychiatry 2014; 204(1):69-76.	Study design (included in economic evaluation SLR)
122	Hollinghurst S, Carroll FE, Abel A, Campbell J, Garland A, et al. "Cost-effectiveness of cognitive-behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: economic evaluation of the CoBalT Trial": Correction. The British Journal of Psychiatry 2014; 204(3):245.	Copy/duplicate

No.	Publication	Exclusion reason
123	Hollinghurst S, Kessler D, Peters TJ, Gunnell D. Opportunity cost of antidepressant prescribing in England: Analysis of routine data. BMJ: British Medical Journal 2005; 330(7498):999-1000.	Patient population
124	Hollinghurst S, Peters TJ, Kaur S, Wiles N, Lewis G, et al. Cost-effectiveness of therapist-delivered online cognitive-behavioural therapy for depression: Randomised controlled trial. The British Journal of Psychiatry 2010; 197(4):297-304.	Patient population
125	Hornberger J, Li Q, Quinn B. Cost-effectiveness of combinatorial pharmacogenomic testing for treatment-resistant major depressive disorder patients. The American Journal of Managed Care 2015; 21(6):e357-e65.	Intervention (economic evaluation)
126	Howard P, Knight C. A clinical- and cost-effectiveness comparison of venlafaxine and selective serotonin reuptake inhibitors (SSRIs) in the management of patients with major depressive disorder from the perspective of an Austrian sickness fund. Journal of Medical Economics 2004; 7(93-106):93-106.	Study design (included in economic evaluation SLR)
127	Huijbregts KML, De Jong FJ, Martens F, Ader HJ, Van Marwijk HWJ, et al. Effectiveness of collaborative care for depression in Dutch primary care. Journal of Psychosomatic Research 2010; 68(6):633-4.	Study design
128	Idrovo J, Rivas R, Zapata L. Cost-effectiveness of selective serotonin reuptake inhibitors in the treatment of major depression in Mexico. Value in Health 2009; 12(7):A487.	Study design (included in economic evaluation SLR)
129	Ignatyeva V, Avxentyeva M, Frolov M. The cost effectiveness of agomelatine in the treatment of major depressive disorder. Value in Health 2015; 18(7):A411.	Study design (included in economic evaluation SLR)
130	Institute for Clinical Effectiveness and Health Policy (IECS). Deep brain stimulation in patients with treatment-resistant depressive disorder, obsessive compulsive disorder and Tourette syndrome. Health Technology Assessment Database 2016; (4).	Unavailable; unable to obtain
131	Isik E, Dilbaz N, Savas H, Gonul AS, Saylan M, et al. Adjunctive antipsychotics in patients with major depressive disorder in turkey: A health economic perspective. Value in Health 2010; 13(7):A451.	Study design (included in economic evaluation SLR)
132	Ivanova JI, Birnbaum HG, Chen L, Duhig AM, Dayoub EJ, et al. Cost of post-traumatic stress disorder vs major depressive disorder among patients covered by Medicaid or private insurance. American Journal of Managed Care 2011; 17(8):e314-e23.	Country (non-UK)
133	Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. Current Medical Research and Opinion 2010; 26(10):2475-84.	Country (non-UK)
134	Jacke CO, Salize HJ. [Cost effectiveness of a health insurance based case management programme for patients with affective disorders]. Neuropsychiatrie 2014; 28(3):130-41.	Patient population

No.	Publication	Exclusion reason
135	Jahoda A, Hastings R, Hatton C, Cooper S-A, Dagnan D, et al. Comparison of behavioural activation with guided self-help for treatment of depression in adults with intellectual disabilities: A randomised controlled trial. The Lancet Psychiatry 2017; 4(12):909-19.	Intervention (economic evaluation)
136	Jonkers CC, Lamers F, Evers SM, Bosma H, Van Eijk JT. Cost-utility estimates in depression: does the valuation method matter? J Ment Health Policy Econ 2010; 13(4):189-97.	Patient population
137	Jung R, Brignone M, Campbell R, Francois C, Milea D. Cost-utility of vortioxetine versus venlafaxine XR in the treatment of major depressive disorder in South Korea. Value in Health 2015; 18(3):A121-A2.	Study design (included in economic evaluation SLR)
138	Karyotaki E, Smit Y, Cuijpers P, Debauche M, DeKeyser T, et al. The long-term efficacy of psychotherapy, alone or in combination with antidepressants, in the treatment of adult major depression. Health Technology Assessment Database 2016; (4).	Review/editorial
139	Katon WJ, Schoenbaum M, Fan MY, Callahan CM, Williams J, Jr., et al. Cost-effectiveness of improving primary care treatment of late-life depression. Archives of General Psychiatry 2005; 62(12):1313-20.	Patient population
140	Katz P, Heiman F, Ripellino C. C-quality: A cost and quality of life pharmacoeconomic analysis of antidepressants in major depressive disorder in Italy. Value in Health 2013; 16(7):A549.	Study design (included in economic evaluation SLR)
141	Katz P, Mencacci C, Di Sciascio G, Ripellino C, Heiman F. Cost-effectiveness analysis of depression in Italy. Value in Health 2012; 15(7):A338.	Study design (included in economic evaluation SLR)
142	Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, et al. Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: The THREAD (THREshold for AntiDepressant response) study. Health Technology Assessment 2009; 13(22):1-159.	Patient population
143	Kendrick T, Peveler R, Longworth L, Baldwin D, Moore M, et al. Cost-effectiveness and cost-utility of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine: Randomised controlled trial. The British Journal of Psychiatry 2006; 188(4):337-45.	Patient population
144	Kendrick T, Stevens L, Bryant A, Goddard J, Stevens A, et al. Hampshire depression project: changes in the process of care and cost consequences. British Journal of General Practice 2001; 51(472):911-3.	Study design
145	Keyloun KR, Devine B. Estimating the cost-effectiveness of vortioxetine versus desvenlafaxine as first line therapy for mild to moderate major depressive disorder in remitted patients. Value in Health 2015; 18(3):A121.	Study design (included in economic evaluation SLR)
146	Khoo AL, Zhou HJ, Teng M, Lin L, Zhao YJ, et al. Network meta-analysis and cost-effectiveness analysis of new generation antidepressants. CNS Drugs 2015; 29(8):695-712.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
147	Klug G, Hermann G, Fuchs-Nieder B, Panzer M, Haider-Stipacek A, Zapotoczky HG, et al. Clinically and economically effectiveness of home treatment for elderly patients with depression: Randomised controlled trial. Journal of Mental Health Policy and Economics 2011; (1):S15.	Intervention (economic evaluation)
148	Knapp M, Romeo R, Mogg A, Eranti S, Pluck G, et al. Cost-effectiveness of transcranial magnetic stimulation vs. electroconvulsive therapy for severe depression: a multi-centre randomised controlled trial. Journal of Affective Disorders 2008; 109(3):273-85.	Patient population
149	Koeser L, Donisi V, Goldberg D, McCrone P. Modelling the cost-effectiveness of pharmacotherapy compared with cognitive-behavioural therapy and combination therapy for the treatment of moderate to severe depression in the UK. Psychological Medicine 2015; 45(14):3019-31.	Study design (included in economic evaluation SLR)
150	Kolovos S, Kenter RM, Bosmans JE, Beekman AT, Cuijpers P, et al. Economic evaluation of Internet-based problem-solving guided self-help treatment in comparison with enhanced usual care for depressed outpatients waiting for face-to-face treatment: A randomized controlled trial. Journal of Affective Disorders 2016; 200:284-92.	Intervention (economic evaluation)
151	Kolovos S, van Dongen JM, Riper H, Buntrock C, Cuijpers P, Ebert DD, et al. Cost effectiveness of guided Internet-based interventions for depression in comparison with control conditions: An individual-participant data meta-analysis. Depression and Anxiety 2018; 35(3):209-19.	Intervention (economic evaluation)
152	Kongsakon R, Bunchapattanasakda C. The treatment of major depressive disorders (MDD) in Thailand using escitalopram compared to fluoxetine and venlafaxine: A pharmacoeconomic evaluation. Journal of the Medical Association of Thailand 2008; 91(7):1117-28.	Study design (included in economic evaluation SLR)
153	Korte J, Cristina Majo M, Bohlmeijer ET, Westerhof GJ, Smit F. Cost-effectiveness of life-review for older adults with moderate depressive symptomatology: A pragmatic randomized controlled trial. Journal of Aging Studies 2015; 34:146-54.	Patient population
154	Kourlaba G, Maniadakis N, Mougiakos T, Chatzimanolis I. Economic evaluation of agomelatine for major depressive disorders in the Greek setting. Value in Health 2012; 15(4):A87.	Study design (included in economic evaluation SLR)
155	Kozel FA, George MS, Simpson KN. Decision analysis of the cost-effectiveness of repetitive transcranial magnetic stimulation versus electroconvulsive therapy for treatment of nonpsychotic severe depression. CNS Spectrums 2004; 9(6):476-82.	Study design (included in economic evaluation SLR)
156	Kujanpaa T, Ylisaukko-Oja T, Jokelainen J, Linna M, Timonen M. Comparative cost analysis of generalized anxiety disorder and major depressive disorder patients in secondary care from a national hospital registry in Finland. Nordic Journal of Psychiatry 2014; 68(5):306-10.	Country (non-UK)
157	Kulp W, Graf Von Der Schulenburg JM, Greiner W. Cost-effectiveness of outpatient treatment in depressive patients with escitalopram in Germany. European Journal of Health Economics 2005; 6(4):317-21.	Study design (included in economic evaluation SLR)
158	Lachaine J, Beauchemin C, Legault M. Economic evaluation of escitalopram to treat major depressive disorder. Value in Health 2010; 13(3):A114.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
159	Lanati EP, Lidonnici D. Economic evaluation of agomelatine for major depressive disorders relative to other antidepressants in the Italian setting. Value in Health 2014; 17(7):A460.	Study design (included in economic evaluation SLR)
160	Lave JR, Frank RG, Schulberg HC, Kamlet MS. Cost-effectiveness of treatments for major depression in primary care practice. Archives of General Psychiatry 1998; 55(7):645-51.	Study design (included in economic evaluation SLR)
161	Le Pen C, Levy E, Ravily V, Beuzen J, Meurgey F. The cost of treatment dropout in depression: A cost-benefit analysis of fluoxetine vs. tricyclics. Journal of Affective Disorders 1994; 31(1):1-18.	Study design (included in economic evaluation SLR)
162	Le TK, Curtis B, Kahle-Wrobleski K, Johnston J, Haldane D, Melfi C. Treatment patterns and resource use among patients with comorbid diabetes mellitus and major depressive disorder. Journal of Medical Economics 2011; 14(4):440-7.	Country (non-UK)
163	Leelahanaj T. Developing Thai economic model to study cost-effectiveness of switching to bupropion compared to combination with bupropion after the failure of an SSRI for major depressive disorder. Journal of the Medical Association of Thailand 2010; 93(Suppl 6):S35-42.	Study design (included in economic evaluation SLR)
164	Leelahanaj T. Switching to sertraline or venlafaxine after failure of SSRIs treatment in major depressive disorder: an economic evaluation of the STAR D trial. Journal of the Medical Association of Thailand 2012; 95(Suppl 5):S29-37.	Study design (included in economic evaluation SLR)
165	Leelahanaj T. The cost-effectiveness of aripiprazole as adjunctive therapy in major depressive disorder: Thai economic model. Journal of the Medical Association of Thailand 2010; 93(Suppl 6):S43-50.	Study design (included in economic evaluation SLR)
166	Lenox-Smith A, Conway P, Knight C. Cost effectiveness of representatives of three classes of antidepressants used in major depression in the UK. PharmacoEconomics 2004; 22(5):311-9.	Study design (included in economic evaluation SLR)
167	Lenox-Smith A, Greenstreet L, Burslem K, Knight C. Cost effectiveness of venlafaxine compared with generic fluoxetine or generic amitriptyline in major depressive disorder in the UK. Clinical Drug Investigation 2009; 29(3):173-84.	Study design (included in economic evaluation SLR)
168	Leon AC, Walkup JT, Portera L. Assessment and treatment of depression in disability claimants: A cost-benefit simulation study. Journal of Nervous and Mental Disease 2002; 190(1):3-9.	Patient population
169	Lerner D, Adler DA, Rogers WH, Chang H, Greenhill A, et al. A randomized clinical trial of a telephone depression intervention to reduce employee presenteeism and absenteeism.[Erratum appears in Psychiatr Serv. 2015 May 1;66(5):554; PMID: 25930224]. Psychiatric Services 2015; 66(6):570-7.	Study design (included in economic evaluation SLR)
170	Leshno M, Ben-Amnon Y, Brignone M, Marteau F, Hansen K. Cost-utility analysis of escitalopram versus citalopram in major depressive disorder in Israel. Value in Health 2010; 13(7):A453.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
171	Lin HC, Erickson S, Smith D, Balkrishnan R. Antidepressant utilization, adherence and health care spending in the United States: The case of MDD patients 2000-2007. Value in Health 2010; 13(7):A454-A5.	Country (non-UK)
172	Lo Sasso AT, Rost K, Beck A. Modeling the Impact of Enhanced Depression Treatment on Workplace Functioning and Costs: A Cost-Benefit Approach. Medical Care 2006; 44(4):352-8.	Intervention (economic evaluation)
173	Lopez-del-Hoyo Y, Olivan B, Luciano JV, Mayoral F, Roca M, et al. Low intensity vs. self-guided internet-delivered psychotherapy for major depression: a multicenter, controlled, randomized study. BMC Psychiatry 2013; 13:21.	Protocol only
174	Lothgren M, Hemels M, Francois C, Jonsson B. A cost-effectiveness analysis of escitalopram as first line treatment of depression in Sweden. Primary Care Psychiatry 2004; 9(4):153-61.	Study design (included in economic evaluation SLR)
175	Luo Z, Cowell AJ, Musuda YJ, Novak SP, Johnson EO. Course of Major Depressive Disorder and Labor Market Outcome Disruption. Journal of Mental Health Policy and Economics 2010; 13(3):135-49.	Country (non-UK)
176	Lurie IZ, Manheim LM, Dunlop DD. Differences in Medical Care Expenditures for Adults with Depression Compared to Adults with Major Chronic Conditions. Journal of Mental Health Policy and Economics 2009; 12(2):87-95.	Country (non-UK)
177	Lynch FL, Dickerson JF, Clarke G, Vitiello B, Porta G, et al. Incremental cost-effectiveness of combined therapy vs medication only for youth with selective serotonin reuptake inhibitor-resistant depression: treatment of SSRI-resistant depression in adolescents trial findings. Archives of General Psychiatry 2011; 68(3):253-62.	Patient population
178	Machado M, Iskedjian M, Ruiz IA, Einarson TR. The economic impact of introducing serotonin-noradrenaline reuptake inhibitors into the Brazilian national drug formulary: Cost-effectiveness and budget-impact analyses. PharmacoEconomics 2007; 25(11):979-90.	Study design (included in economic evaluation SLR)
179	Machado M, Lopera MM, Diaz-Rojas J, Jaramillo LE, Einarson TR. Pharmacoeconomics of antidepressants in moderate-to-severe depressive disorder in Colombia. Revista Panamericana de Salud Publica/Pan American Journal of Public Health 2008; 24(4):233-9.	Study design (included in economic evaluation SLR)
180	Malone DC. A budget-impact and cost-effectiveness model for second-line treatment of major depression. Journal of Managed Care Pharmacy 2007; 13(6 SUPPL. A):S8-S18.	Study design (included in economic evaluation SLR)
181	Maniadakis N, Kourlaba G, Mougiakos T, Chatzimanolis I, Jonsson L. Economic evaluation of agomelatine relative to other antidepressants for treatment of major depressive disorders in Greece. BMC health services research 2013; 13:173.	Study design (included in economic evaluation SLR)
182	Marynchenko M, Yu AP, Lauzon V, Ramakrishnan K, Wu EQ, et al. Economic outcomes of switching treatment in major depressive disorder patients. American Journal of Pharmacy Benefits 2011; 3(6):e111-e20.	Country (non-UK)

No.	Publication	Exclusion reason
183	McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: A multicentre pragmatic randomised controlled trial and economic analysis. Health Technology Assessment 2007; 11(24):iii-35.	Study design (included in economic evaluation SLR)
184	Melton ST, Kirkwood CK, Farrar TW, Brink DD. Economic evaluation of paroxetine and imipramine in depressed outpatients. Psychopharmacology Bulletin 1997; 33(1):93-100.	Study design (included in economic evaluation SLR)
185	Mencacci C, Aguglia E, Biggio G, Cappellari L, Di Sciascio G, et al. C-QUALITY: Cost and quality-of-life pharmacoeconomic analysis of antidepressants in major depressive disorder in italy. Advances in Therapy 2013; 30(7):697-712.	Study design (included in economic evaluation SLR)
186	Mencacci C, Aguglia E, Biggio G, Cappellari L, Di Sciascio G, Fagiolini A, et al. C-QUALITY: cost and quality-of-life pharmacoeconomic analysis of antidepressants used in major depressive disorder in the regional Italian settings of Veneto and Sardinia. ClinicoEcon. 2013; 5:611-21.	Study design (included in economic evaluation SLR)
187	Mencacci C, Di Sciascio G, Katz P, Ripellino C. Cost-effectiveness evaluation of escitalopram in major depressive disorder in Italy. ClinicoEconomics and Outcomes Research 2013; 5(1):87-99.	Study design (included in economic evaluation SLR)
188	Meuldijk D, Carlier IV, van Vliet IM, van Hemert AM, Zitman FG, van den Akker-van Marle M. Economic evaluation of concise cognitive behavioural therapy and/or pharmacotherapy for depressive and anxiety disorders. Journal of Mental Health Policy and Economics 2015; 18(4):175-83.	Patient population
189	Mihalopoulos C, Vos T, Pirkis J, Carter R. The cost-effectiveness of preventive interventions for mental disorders and suicide. Journal of Mental Health Policy and Economics 2011; (1):S22.	Intervention (economic evaluation)
190	Montgomery SA, Brown RE, Clark M. Economic analysis of treating depression with nefazodone v. imipramine. British Journal of Psychiatry 1996; 168(JUNE):768-71.	Study design (included in economic evaluation SLR)
191	Morey E, Thacher JA, Craighead WE. Patient Preferences for Depression Treatment Programs and Willingness to Pay for Treatment. Journal of Mental Health Policy and Economics 2007; 10(2):73-85.	Country (non-UK)
192	Mukuria C, Brazier J, Barkham M, Connell J, Hardy G, Hutten R, et al. Cost-effectiveness of an Improving Access to Psychological Therapies service. The British Journal of Psychiatry 2013; 202(3):220-7.	Patient population
193	Nguyen KH, Gordon LG. Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation versus Antidepressant Therapy for Treatment-Resistant Depression. Value in Health 2015; 18(5):597-604.	Study design (included in economic evaluation SLR)
194	Nordstrom G, Danchenko N, Despiegel N, Marteau F. Cost-effectiveness evaluation in Sweden of escitalopram compared with venlafaxine extended-release as first-line treatment in major depressive disorder. Value in Health 2012; 15(2):231-9.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
195	Nordstrom G, Despiegel N, Marteau F, Danchenko N, Maman K. Cost effectiveness of escitalopram versus SNRIs in second-step treatment of major depressive disorder in Sweden. Journal of Medical Economics 2010; 13(3):516-26.	Study design (included in economic evaluation SLR)
196	Nuijten MJ, Brignone M, Marteau F, den Boer JA, Hoencamp E. Cost-effectiveness of escitalopram in major depressive disorder in the Dutch health care setting. Clinical Therapeutics 2012; 34(6):1364-78.	Study design (included in economic evaluation SLR)
197	Nuijten MJ, Hardens M, Souetre E. A Markov process analysis comparing the cost effectiveness of maintenance therapy with citalopram versus standard therapy in major depression. Pharmacoeconomics 1995; 8(2):159-68.	Study design (included in economic evaluation SLR)
198	Nuijten MJ. Assessment of clinical guidelines for continuation treatment in major depression. Value in Health 2001; 4(4):281-94.	Study design (included in economic evaluation SLR)
199	O'Connell MM, Kolovos S, Bosmans JE, Forbes JF. Discrete event simulation modelling of long term cost-effectiveness of internet-based blended cognitive behavioural therapy for major depressive disorder: Extrapolation of the e-compared randomised controlled trial. Value in Health 2017; 20(9):A403.	Study design (included in economic evaluation SLR)
200	O'Connor CM, Glassman AH, Harrison DJ. Pharmacoeconomic analysis of sertraline treatment of depression in patients with unstable angina or a recent myocardial infarction. Journal of Clinical Psychiatry 2005; 66(3):346-52.	Patient population
201	O'Leary BA, Hamann GB, Adena MA. Economic evaluation of agomelatine for major depressive disorder in Australia. Value in Health 2011; 14(7):A293-A4.	Study design (included in economic evaluation SLR)
202	Olfson M, Marcus S, Sackeim HA, Thompson J, Pincus HA. Use of ECT for the inpatient treatment of recurrent major depression. American Journal of Psychiatry 1998; 155(1):22-9.	Country (non-UK)
203	Olgiati P, Bajo E, Bigelli M, De Ronchi D, Serretti A. Should pharmacogenetics be incorporated in major depression treatment? Economic evaluation in high- and middle-income European countries. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2012; 36(1):147-54.	Intervention (economic evaluation)
204	Olgiati P, Bajo E, Bigelli M, Montgomery S, Serretti A, group CEAP. Challenging sequential approach to treatment resistant depression: cost-utility analysis based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. European Neuropsychopharmacology 2013; 23(12):1739-46.	Study design (included in economic evaluation SLR)
205	Olgiati P, Bajo E, Serretti A. Benefit of slow titration of paroxetine to treat depression in the elderly. Human Psychopharmacology: Clinical and Experimental 2014; 29(6):544-51.	Study design (included in economic evaluation SLR)
206	Olgiati P, Serretti A, Bigelli M, De Ronchi D, Bajo E. Is pharmacogenetic testing ready for antidepressant treatment? A cost-effectiveness simulation. European Neuropsychopharmacology 2011; (3):S389.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
207	Ostad Haji E, Tadic A, Dragicevic A, Mueller M, Boland K, et al. Costs and cost effectiveness of therapeutic drug monitoring (TDM) for antidepressant treatment with citalopram. Therapeutic Drug Monitoring 2011; 33(4):526.	Intervention (economic evaluation)
208	Pan Y-J, Kuo K-H, Chan H-Y, McCrone P. Cost-effectiveness and cost-utility of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants in depression with comorbid cardiovascular disease. Journal of Psychiatric Research 2014; 54:70-8.	Study design (included in economic evaluation SLR)
209	Pan Y-J, Kuo K-H, Wang S-J. Pharmacological treatment of depression with and without headache disorders: An appraisal of cost effectiveness and cost utility of antidepressants. Journal of Affective Disorders 2015; 170:255-65.	Study design (included in economic evaluation SLR)
210	Parrella A, Mundy L, Hiller J. VNS Therapy(TM) System for the treatment of chronic or recurrent treatment-resistant depression in adults. Health Technology Assessment Database 2016; (4).	Review/editorial
211	Patten SB, Lee RC. Epidemiological theory, decision theory and mental health services research. Social Psychiatry and Psychiatric Epidemiology 2004; 39(11):893-8.	Study design
212	Perlis RH, Patrick A, Smoller JW, Wang PS. When is pharmacogenetic testing for antidepressant response ready for the clinic? A cost-effectiveness analysis based on data from the STAR D study. Neuropsychopharmacology 2009; 34(10):2227-36.	Intervention (economic evaluation)
213	Petrou S, Cooper P, Murray L, Davidson LL. Economic costs of post-natal depression in a high-risk British cohort. The British Journal of Psychiatry 2002; 181(6):505-12.	Patient population
214	Pizzi LT, Jutkowitz E, Frick KD, Suh D-C, Prioli KM, Gitlin LN. Cost-effectiveness of a community-integrated home-based depression intervention in older African Americans. Journal of the American Geriatrics Society 2014; 62(12):2288-95.	Patient population
215	Polanco AC, Ascencio ISI, Salazar A, Gonzalez LA, Pizarro M, Soto H, et al. Cost effectiveness analysis for the use of extended release quetiapine as adjunctive therapy in Mexican adult patients with major depressive disorder non-responders to antidepressant treatment. Value in Health 2013; 16(7):A547.	Study design (included in economic evaluation SLR)
216	Preskorn SH, Fast GA. "Therapeutic drug monitoring for antidepressants: Efficacy, safety, and cost effectiveness": Correction. The Journal of Clinical Psychiatry 1991; 52(8):353.	Review/editorial
217	Prukkanone B, Kongsuk T. Cost-effectiveness of agomelatine in the treatment of major depressive episodes in Thailand. Value in Health 2011; 14(7):A292.	Study design (included in economic evaluation SLR)
218	Prukkanone B, Vos T, Bertram M, Burgess P. Cost-4ffectiveness analysis for pharmacological intervention and cognitive behavioral treatment (CBT) for major depression in Thailand. Value in Health 2010; 13(7):A555.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
219	Prukkanone B, Vos T, Bertram M, Lim S. Cost-effectiveness analysis for antidepressants and cognitive behavioral therapy for major depression in Thailand. Value in Health 2012; 15(1 SUPPL.):S3-S8.	Study design (included in economic evaluation SLR)
220	Pyne JM, Fortney JC, Tripathi SP, Maciejewski ML, Edlund MJ, Williams D. Cost-effectiveness analysis of a rural telemedicine collaborative care intervention for depression. Archives of General Psychiatry 2010; 67(8):812-21.	Intervention (economic evaluation)
221	Pyne JM, Rost KM, Farahati F, Tripathi SP, Smith J, et al. One size fits some: the impact of patient treatment attitudes on the cost-effectiveness of a depression primary-care intervention. Psychological Medicine 2005; 35(6):839-54.	Intervention (economic evaluation)
222	Pyne JM, Rost KM, Zhang M, Williams D, Smith J, Fortney J. Cost-effectiveness of a Primary Care Depression Intervention. Journal of General Internal Medicine 2003; 18(6):432-41.	Intervention (economic evaluation)
223	Pyne JM, Smith J, Fortney J, Zhang M, Williams DK, Rost K. Cost-effectiveness of a primary care intervention for depressed females. Journal of Affective Disorders 2003; 74(1):23-32.	Study design (included in economic evaluation SLR)
224	Ramirez-Gamez J, Duenas-Tentori H. Economic assessment of major depressive disorder treatment under different therapeutic classes at issste. Value in Health 2011; 14(7):A561.	Study design (included in economic evaluation SLR)
225	Rejas Gutierrez J, Blanca Tamayo M, Gascon Barrachina J, Armada Pelaez B. Economic evaluation of desvenlafaxine in the treatment of major depressive disorder in Spain. [Spanish]. Revista de Psiquiatria y Salud Mental 2016; 9(2):87-96.	Copy/duplicate
226	Rejas Gutierrez J, Blanca Tamayo M, Gascon Barrachina J, Armada Pelaez B. [Economic evaluation of desvenlafaxine in the treatment of major depressive disorder in Spain]. Revista de Psiquiatria y Salud Mental 2016; 9(2):87-96.	Study design (included in economic evaluation SLR)
227	Revicki DA, Brown RE, Keller MB, Gonzales J. Cost-effectiveness of newer antidepressants compared with tricyclic antidepressants in managed care settings. The Journal of Clinical Psychiatry 1997; 58(2):47-58.	Study design (included in economic evaluation SLR)
228	Revicki DA, Brown RE, Palmer W, Bakish D, Rosser WW, et al. Modelling the cost effectiveness of antidepressant treatment in primary care. PharmacoEconomics 1995; 8(6):524-40.	Study design (included in economic evaluation SLR)
229	Revicki DA, Siddique J, Frank L, Chung JY, Green BL, et al. Cost-effectiveness of evidence-based pharmacotherapy or cognitive behavior therapy compared with community referral for major depression in predominantly low-income minority women. Archives of General Psychiatry 2005; 62(8):868-75.	Study design (included in economic evaluation SLR)
230	Richards DA, Rhodes S, Ekers D, McMillan D, Taylor RS, et al. Cost and outcome of behavioural activation (COBRA): A randomised controlled trial of behavioural activation versus cognitive-behavioural therapy for depression. Health Technology Assessment 2017; 21(46):i-365.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
231	Ricken R, Wiethoff K, Reinhold T, Stamm TJ, Baghai TC, et al. A standardized stepwise drug treatment algorithm for depression reduces direct treatment costs in depressed inpatients - Results from the German Algorithm Project (GAP3). Journal of Affective Disorders 2018; 228:173-7.	Country (non-UK)
232	Romeo R, Patel A, Knapp M, Thomas C. The cost-effectiveness of mirtazapine versus paroxetine in treating people with depression in primary care. International Clinical Psychopharmacology 2004; 19(3):125-34.	Study design (included in economic evaluation SLR)
233	Romero-Sanchiz P, Nogueira-Arjona R, Garcia-Ruiz A, Luciano JV, Garcia Campayo J, et al. Economic evaluation of a guided and unguided internet-based CBT intervention for major depression: Results from a multi-center, three-armed randomized controlled trial conducted in primary care. PLoS ONE [Electronic Resource] 2017; 12(2):e0172741.	Study design (included in economic evaluation SLR)
234	Rosset N, Andreoli A. Crisis intervention and affective disorders: A comparative cost effectiveness study. Social Psychiatry and Psychiatric Epidemiology 1995; 30(5):231-5.	Study design (included in economic evaluation SLR)
235	Rost K, Pyne JM, Dickinson LM, LoSasso AT. Cost-effectiveness of enhancing primary care depression management on an ongoing basis. Annals of Family Medicine 2005; 3(1):7-14.	Intervention (economic evaluation)
236	Rubio-Valera M, Beneitez I, Penarrubia-Maria MT, Luciano JV, Mendive JM, et al. Cost-effectiveness of active monitoring versus antidepressants for major depression in primary health care: a 12-month non-randomized controlled trial (INFAP study). BMC Psychiatry 2015; 15:63.	Protocol only
237	Russell JM, Hawkins K, Ozminkowski RJ, Orsini L, Crown WH, et al. The cost consequences of treatment-resistant depression. The Journal of clinical psychiatry 2004; 65(3):341-7.	Country (non-UK)
238	Sacristan JA, Gilaberte I, Boto B, Buesching DP, Obenchain RL, et al. Cost-effectiveness of fluoxetine plus pindolol in patients with major depressive disorder: Results from a randomized, double-blind clinical trial. International Clinical Psychopharmacology 2000; 15(2):107-13.	Study design (included in economic evaluation SLR)
239	Sado M, Knapp M, Yamauchi K, Fujisawa D, So M, et al. Cost-effectiveness of combination therapy versus antidepressant therapy for management of depression in Japan. Australian and New Zealand Journal of Psychiatry 2009; 43(6):539-47.	Study design (included in economic evaluation SLR)
240	Sampson CJ, James M. The cost-effectiveness of a specialist depression service for resistant depression: An economic evaluation alongside a clinical trial. Journal of Mental Health Policy and Economics 2015; (1):S35.	Study design (included in economic evaluation SLR)
241	Sava FA, Yates BT, Lupu V, Szentagotai A, David D. Cost-effectiveness and cost-utility of cognitive therapy, rational emotive behavioral therapy, and fluoxetine (Prozac) in treating depression: A randomized clinical trial. Journal of Clinical Psychology 2009; 65(1):36-52.	Study design (included in economic evaluation SLR)
242	Saylan M, Treur MJ, Postema R, Dilbaz N, Savas H, et al. Cost-effectiveness analysis of aripiprazole augmentation treatment of patients with major depressive disorder compared to olanzapine and quetiapine augmentation in Turkey: A microsimulation approach. Value in Health Regional Issues 2013; 2(2):171-80.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
243	Scaccabarozzi L, Takemoto ML, Fernandes RA, Santos PML, Tolentino ACM. Economic evaluation of desvenlafaxine in the acute management of associated major depressive disorder in medically ill inpatients from a Brazilian public general hospital perspective. Value in Health 2011; 14(3):A193.	Study design (included in economic evaluation SLR)
244	Schene AH, Koeter MW, Kikkert MJ, Swinkels JA, McCrone P. Adjuvant occupational therapy for work-related major depression works: randomized trial including economic evaluation. Psychological Medicine 2007; 37(3):351-62.	Study design (included in economic evaluation SLR)
245	Schneider J, Duggan S, Cordingley L, Mozley CG, Hart C. Costs of occupational therapy in residential homes and its impact on service use. Aging Ment Health 2007; 11(1):108-14.	Patient population
246	Scott J, Moon CA, Blacker CV, Thomas JM. A. I. F. Scott & C. P. L. Freeman's "Edinburgh Primary Care Depression Study. British Journal of Psychiatry 1994; 164(3):410-5.	Review/editorial
247	Scott J, Moon CAL, Blacker CVR, Thomas JM. A. I. F. Scott and C. P. I. Freeman's 'Edinburgh primary care depression study'. British Journal of Psychiatry 1994; 164(MAR.):410-5.	Copy/duplicate
248	Scott J, Palmer S, Paykel E, Teasdale J, Hayhurst H. Use of cognitive therapy for relapse prevention in chronic depression: Cost-effectiveness study. British Journal of Psychiatry 2003; 182(MAR.):221-7.	Study design (included in economic evaluation SLR)
249	Seabury SA, Lakdawalla DN, Walter D, Hayes J, Gustafson T, et al. Patient Outcomes and Cost Effects of Medicaid Formulary Restrictions on Antidepressants. Forum for Health Economics and Policy 2014; 17(2):153-68.	Country (non-UK)
250	Serrano-Blanco A, Suarez D, Pinto-Meza A, Penarrubia MT, Haro JM. Fluoxetine and imipramine: Are there differences in cost-utility for depression in primary care? Journal of Evaluation in Clinical Practice 2009; 15(1):195-203.	Study design (included in economic evaluation SLR)
251	Serretti A, Olgiati P, Bajo E, Bigelli M, De Ronchi D. A model to incorporate genetic testing (5-HTTLPR) in pharmacological treatment of major depressive disorders. World Journal of Biological Psychiatry 2011; 12(7):501-15.	Intervention (economic evaluation)
252	Shawyer F, Enticott JC, Ozmen M, Inder B, Meadows GN. Mindfulness-based cognitive therapy for recurrent major depression: A ' best buy ' for health care? Australian and New Zealand Journal of Psychiatry 2016; 50(10):1001-13.	Study design (included in economic evaluation SLR)
253	Shimodera S, Furukawa TA, Mino Y, Shimazu K, Nishida A, Inoue S. Cost-effectiveness of family psychoeducation to prevent relapse in major depression: Results from a randomized controlled trial. BMC Psychiatry 2012; 12(1):40.	Intervention (economic evaluation)
254	Sicras-Mainar A, Navarro-Artieda R, Blanca-Tamayo M, Gimeno-De La Fuente V, Salvatella-Pasant J. Comparison of escitalopram vs. citalopram and venlafaxine in the treatment of major depression in Spain: Clinical and economic consequences. Current Medical Research and Opinion 2010; 26(12):2757-64.	Country (non-UK)

No.	Publication	Exclusion reason
255	Simon GE, Katon WJ, VonKorff M, Unutzer J, Lin EH, et al. Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. American Journal of Psychiatry 2001; 158(10):1638-44.	Patient population
256	Simon J, Pilling S, Burbeck R, Goldberg D. Treatment options in moderate and severe depression: Decision analysis supporting a clinical guideline. The British Journal of Psychiatry 2006; 189(6):494-501.	Patient population
257	Simons CJ, Drukker M, Evers S, van Mastrigt GA, Hohn P, et al. Economic evaluation of an experience sampling method intervention in depression compared with treatment as usual using data from a randomized controlled trial. BMC Psychiatry 2017; 17.	Intervention (economic evaluation)
258	Simpson KN, Welch MJ, Kozel FA, Demitrack MA, Nahas Z. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: A health economics analysis. Advances in Therapy 2009; 26(3):346-68.	Study design (included in economic evaluation SLR)
259	Simpson S, Corney R, Beecham J. A randomized controlled trial to evaluate the effectiveness and cost-effectiveness of psychodynamic counselling for general practice patients with chronic depression. Psychological Medicine 2003; 33(2):229-39.	Study design (included in economic evaluation SLR)
260	Simpson S, Corney R, Fitzgerald P, Beecham J. A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression. Health Technology Assessment Database 2016; (4).	Patient population
261	Singh A, Brooks MM, Voorhees RE, Potter MA, Roberts MS, Luther JF, et al. Cost-effective drug switch options after unsuccessful treatment with an SSRI for depression. Psychiatric Services 2017; 68(1):81-7.	Study design (included in economic evaluation SLR)
262	Siskind D, Araya R, Kim J. Cost-effectiveness of improved primary care treatment of depression in women in Chile. British Journal of Psychiatry 2010; 197(4):291-6.	Intervention (economic evaluation)
263	Siskind D, Baingana F, Kim J. Cost-effectiveness of group psychotherapy for depression in Uganda. Journal of Mental Health Policy and Economics 2008; 11(3):127-33.	Study design (included in economic evaluation SLR)
264	Snedecor SJ, Botteman MF, Schaefer K, Sarocco P, Barry N, et al. Economic Outcomes of Eszopiclone Treatment in Insomnia and Comorbid Major Depressive Disorder. Journal of Mental Health Policy and Economics 2010; 13(1):27-35.	Intervention (economic evaluation)
265	Sobocki P, Ekman M, Ovanfors A, Khandker R, Jonsson B. The cost-utility of maintenance treatment with venlafaxine in patients with recurrent major depressive disorder. International Journal of Clinical Practice 2008; 62(4):623-32.	Study design (included in economic evaluation SLR)
266	Soini E, Hallinen T, Brignone M, Campbell R, Diamand F, et al. Cost-utility analysis of vortioxetine versus agomelatine, bupropion SR, sertraline and venlafaxine XR after treatment switch in major depressive disorder in Finland. Expert Review of Pharmacoeconomics and Outcomes Research 2017; 17(3):293-302.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
267	Soini EJ, Hallinen T, Brignone M, Despiegel N, Aalto-Setala M, Danchenko N, et al. Cost-utility of vortioxetine in the treatment of major depressive disorder: Comparison with agomelatine, bupropion, sertraline and venlafaxine in the Finnish setting. Value in Health 2014; 17(7):A459.	Copy/duplicate
268	Soini EJ, Hallinen TA. Cost-utility of agomelatine, venlafaxine and placebo in the treatment of major depressive disorder (MDD) in Finland - economic modelling study using representative population data. Value in Health 2009; 12(7):A359.	Study design (included in economic evaluation SLR)
269	Solomon D, Proudfoot J, Clarke J, Christensen H. e-CBT (myCompass), antidepressant medication, and face-to-face psychological treatment for depression in Australia: A cost-effectiveness comparison. Journal of Medical Internet Research 2015; 17(11):1-14.	Patient population
270	Sorensen J, Stage K, Damsbo N, Lay AL, Hemels M. A Danish cost-effectiveness model of escitalopram in comparison with citalopram and venlafaxine as first-line treatments for major depressive disorder in primary care. Nordic Journal of Psychiatry 2007; 61(2):100-8.	Study design (included in economic evaluation SLR)
271	Sperling W, Reulbach U, Kornhuber J. Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression. Pharmacopsychiatry 2009; 42(3):85-8.	Country (non-UK)
272	Stant AD, TenVergert EM, Kluiter H, Conradi HJ, Smit A, et al. Cost-Effectiveness of a Psychoeducational Relapse Prevention Program for Depression in Primary Care. Journal of Mental Health Policy and Economics 2009; 12(4):195-204.	Study design (included in economic evaluation SLR)
273	Stikkelbroek Y, Bodden DHM, Dekovic M, van Baar AL. Effectiveness and cost effectiveness of cognitive behavioral therapy (CBT) in clinically depressed adolescents: Individual CBT versus treatment as usual (TAU). BMC Psychiatry 2013; 13(314).	Patient population
274	Subramaniam M, Abdin E, Vaingankar JA, Chong SA. Days out of role due to common mental illnesses: Findings from the Singapore mental health study. Journal of Mental Health Policy and Economics 2011; (1):S34.	Study design
275	Sughondhabirom A, Chamchitchun S. Cost-effectiveness of antidepressant based on discrete event simulation modeling in treatment of major depressive episodes: A comparison of agomelatine versus escitalopram-venlafaxine. Value in Health 2012; 15(7):A670.	Study design (included in economic evaluation SLR)
276	Sussman M, Yu J, Kamat SA, Hartry A, Legacy S, et al. Cost-effectiveness of brexpiprazole adjunctive treatment for major depressive disorder. Journal of Affective Disorders 2017; 207:54-62.	Study design (included in economic evaluation SLR)
277	Svedsater H, Locklear J, Johal S, Stillman IO. Cost-effectiveness and budget impact of adjunct quetiapine fumarate extended-release in patients with major depressive disorder with an inadequate response to previous therapy. Value in Health 2011; 14(3):A192-A3.	Study design (included in economic evaluation SLR)
278	Syeda SS, Wu WK. Economic impact of CYP450 pharmacogenetic testing on depression treatment. Value in Health 2011; 14(3):A193.	Intervention (economic evaluation)

No.	Publication	Exclusion reason
279	Taneja C, Oster G, Jing Y, Baker RA, Forbes RA, et al. Cost-effectiveness of atypical antipsychotics as adjunctive therapy in adult patients with major depressive disorder (MDD). Value in Health 2010; (3):A113.	Study design (included in economic evaluation SLR)
280	Taneja C, Papakostas GI, Jing Y, Baker RA, Forbes RA, et al. Cost-effectiveness of adjunctive therapy with atypical antipsychotics for acute treatment of major depressive disorder. Annals of Pharmacotherapy 2012; 46(5):642-9.	Study design (included in economic evaluation SLR)
281	Tatar M, Dilbaz N, Oral ET, Tan M. Cost-effectiveness of agomelatine in treatment of major depressive disorders in Turkey. Value in Health 2012; 15(4):A88.	Study design (included in economic evaluation SLR)
282	Taylor D, Carlyle J, McPherson S, Rost F, Thomas R, et al. Tavistock Adult Depression Study (TADS): A randomised controlled trial of psychoanalytic psychotherapy for treatment-resistant/treatment-refractory forms of depression. BMC Psychiatry 2012; 12(1):60.	Protocol only
283	Tome MB, Isaac M. Cost effectiveness study of a year follow-up of selective serotonin reuptake inhibitor (SSRI) and augmentor combination compared with SSRI and placebo. International Clinical Psychopharmacology 1998; 13(4):175-82.	Study design (included in economic evaluation SLR)
284	Tome MB, Isaac MT. Cost-benefit & cost-effectiveness analysis of the rapid onset of selective serotonin reuptake inhibitors by augmentation. International Journal of Psychiatry in Medicine 1997; 27(4):377-90.	Study design (included in economic evaluation SLR)
285	Topfer L, Hailey D. Vagus nerve stimulation (VNS) for treatment-resistant depression. Health Technology Assessment Database 2016; (4).	Review/editorial
286	Tosh J, Brennan A. Health economic modelling of the service of care in Sheffield for patients with long-term depression. Journal of Mental Health Policy and Economics 2011; 1:S35.	Protocol only
287	Tosh J, Kearns B, Brennan A, Parry G, Ricketts T, et al. Innovation in health economic modelling of service improvements for longer-term depression: Demonstration in a local health community. Journal of Mental Health Policy and Economics 2013; 1:S34-S5.	Intervention (economic evaluation)
288	Toumi M, Antonanzas F, Hakkaart L, Lam RW, McCrone P, et al. Comprehensive discrete event simulation model for the evaluation of health care technologies in depression. Value in Health 2012; 15(7):A282.	Intervention (economic evaluation)
289	Trivedi MH, Wan GJ, Mallick R, Chen J, Casciano R, et al. Cost and effectiveness of venlafaxine extended-release and selective serotonin reuptake inhibitors in the acute phase of outpatient treatment for major depressive disorder. Journal of Clinical Psychopharmacology 2004; 24(5):497-506.	Study design (included in economic evaluation SLR)
290	Twomey C, Prina AM, Baldwin DS, Das-Munshi J, Kingdon D, et al. Utility of the health of the nation outcome scales (HoNOS) in predicting mental health service costs for patients with common mental health problems: Historical cohort study. PLoS ONE. 2016; 11(11):e0167103.	Study design

No.	Publication	Exclusion reason
291	Vallejo-Torres L, Castilla I, Gonzalez N, Hunter R, Serrano-Perez P, et al. Cost-effectiveness of electroconvulsive therapy compared to repetitive transcranial magnetic stimulation for treatment-resistant severe depression: a decision model. Psychological Medicine 2015; 45(7):1459-70.	Study design (included in economic evaluation SLR)
292	van Baardewijk M, Vis PM, Einarson TR. Cost effectiveness of duloxetine compared with venlafaxine-XR in the treatment of major depressive disorder. Curr Med Res Opin 2005; 21(8):1271-9.	Study design (included in economic evaluation SLR)
293	van den Berg M, Smit F, Vos T, van Baal PH. Cost-effectiveness of opportunistic screening and minimal contact psychotherapy to prevent depression in primary care patients. PLoS ONE [Electronic Resource] 2011; 6(8):e22884.	Patient population
294	Vargas-Valencia JJ, Mould-Quevedo JF, Gutierrez-Ardila MV, Vargas Zea N. Economic evaluation of the use of desvenlafaxine in major depressive disorder in Colombia. Value in Health 2013; 16(3):A61.	Study design (included in economic evaluation SLR)
295	Vasiliadis HM, Dezetter A, Latimer E, Drapeau M, Lesage A. Assessing the costs and benefits of insuring psychological services as part of Medicare for depression in Canada. Psychiatric Services 2017; 68(9):899-906.	Country (non-UK)
296	Vataire AL, Aballea S, Antonanzas F, Roijen LH, Lam RW, et al. Core discrete event simulation model for the evaluation of health care technologies in major depressive disorder. Value in Health 2014; 17(2):183-95.	Study design (included in economic evaluation SLR)
297	Voigt J, Carpenter L, Leuchter A. Cost effectiveness analysis comparing repetitive transcranial magnetic stimulation to antidepressant medications after a first treatment failure for major depressive disorder in newly diagnosed patients - A lifetime analysis. PLoS ONE 2017; 12(10):e0186950.	Study design (included in economic evaluation SLR)
298	Volkl M, Fritze J, Hoffler J, Roth G, Ruther E, et al. Treatment of depression in Germany: An analysis of cost-effectiveness with remission. [German]. Gesundheitsokonomie und Qualitatsmanagement 2007; 12(1):35-43.	Study design (included in economic evaluation SLR)
299	Von Korff M, Katon W, Bush T, Lin EHB, Simon GE, et al. Treatment costs, cost offset, and cost-effectiveness of collaborative management of depression. Psychosomatic Medicine 1998; 60(2):143-9.	Intervention (economic evaluation)
300	Vos T, Corry J, Haby MM, Carter R, Andrews G. Cost-effectiveness of cognitive-behavioural therapy and drug interventions for major depression. The Australian and New Zealand Journal of Psychiatry 2005; 39(8):683-92.	Study design (included in economic evaluation SLR)
301	Wade AG, Fernandez JL, Francois C, Hansen K, Danchenko N, et al. Escitalopram and duloxetine in major depressive disorder: A pharmacoeconomic comparison using UK cost data. PharmacoEconomics 2008; 26(11):969-81.	Study design (included in economic evaluation SLR)
302	Wade AG, Saragoussi D, Despiegel N, Guelfucci F, Francois C. Healthcare cost associated with first-line antidepressant treatments in severe depression in the United Kingdom. European Neuropsychopharmacology 2008; 18(S4):S340.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
303	Wade AG, Toumi I, Hemels ME. A Pharmacoeconomic Evaluation of Escitalopram Versus Citalopram in the Treatment of Severe Depression in the United Kingdom. Clinical Therapeutics: The International Peer-Reviewed Journal of Drug Therapy 2005; 27(4):486-96.	Study design (included in economic evaluation SLR)
304	Wade AG, Toumi I, Hemels MEH. A probabilistic cost-effectiveness analysis of escitalopram, generic citalopram and venlafaxine as a first-line treatment of major depressive disorder in the UK. Current Medical Research and Opinion 2005; 21(4):631-41.	Study design (included in economic evaluation SLR)
305	Walczak J, Nogas G, Garbacka M, Obrzut G, Pieniazek I. Economic analysis of escitalopram (generic drug) in major depressive disorder (MDD). Value in Health 2010; 13(3):A114.	Study design (included in economic evaluation SLR)
306	Walker S, Walker J, Richardson G, Palmer S, Wu Q, et al. Cost-effectiveness of combining systematic identification and treatment of co-morbid major depression for people with chronic diseases: The example of cancer. Psychological Medicine 2014; 44(7):1451-60.	Patient population
307	Walker S, Walker J, Richardson G, Palmer S, Wu Q, et al. Cost-effectiveness of the systematic identification and treatment of comorbid major depression for people with chronic diseases: The example of cancer. Value in Health 2013; 16(7):A414.	Patient population
308	Wang PS, Patrick A, Avorn J, Azocar F, Ludman E, et al. The Costs and Benefits of Enhanced Depression Care to Employers. Archives of General Psychiatry 2006; 63(12):1345-53.	Intervention (economic evaluation)
309	Warmerdam L, Smit F, van Straten A, Riper H, Cuijpers P. Cost-utility and cost-effectiveness of Internet-based treatment for adults with depressive symptoms: Randomized trial. Journal of Medical Internet Research. 2010;12(5):40-50.	Study design (included in economic evaluation SLR)
310	Watkins JB. The role of pharmacoeconomic modeling in depression management by a health plan. Managed Care Interface 2003; 16(SUPPL. B):22-6.	Review/editorial
311	Weobong B, Weiss HA, McDaid D, Singla DR, Hollon SD, et al. Sustained effectiveness and cost-effectiveness of the Healthy Activity Programme, a brief psychological treatment for depression delivered by lay counsellors in primary care: 12-month follow-up of a randomised controlled trial. PLoS Med 2017; 14(9):e1002385.	Intervention (economic evaluation)
312	Wiles N, Thomas L, Abel A, Barnes M, Carroll F, et al. Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: The CoBalT randomised controlled trial. Health Technology Assessment 2014; 18(31):1-167.	Study design (included in economic evaluation SLR)
313	Wiles NJ, Thomas L, Turner N, Garfield K, Kounali D, et al. Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: Follow-up of the CoBalT randomised controlled trial. The Lancet Psychiatry 2016; 3(2):137-44.	Study design (included in economic evaluation SLR)

No.	Publication	Exclusion reason
314	Wilkinson A, Anderson S, Wheeler SB. Screening for and treating postpartum depression and psychosis: A cost-effectiveness analysis. Maternal and Child Health Journal 2017; 21(4):903-14.	Patient population
315	Woo JM, Kim W, Hwang TY, Frick KD, Choi BH, et al. Impact of depression on work productivity and its improvement after outpatient treatment with antidepressants. Value in Health 2011; 14(4):475-82.	Country (non-UK)
316	Wright DR, Haaland WL, Ludman E, McCauley E, Lindenbaum J, et al. The costs and cost-effectiveness of collaborative care for adolescents with depression in primary care settings: A randomized clinical trial. JAMA Pediatrics 2016; 170(11):1048-54.	Patient population
317	Wu EQ, Greenberg PE, ben-Hamadi R, Yu AP, Yang EH, et al. Comparing treatment persistence, healthcare resource utilization, and costs in adult patients with major depressive disorder treated with escitalopram or citalopram. American Health and Drug Benefits 2011; 4(2):78-87.	Country (non-UK)
318	Xie F, Despiegel N, Danchenko N, Hansen K. Cost effectiveness analysis of escitalopram compared to venlafaxine and fluvoxamine in treatment of major depressive disorder. International Journal of Psychiatry in Clinical Practice 2009; 13(1):59-69.	Study design (included in economic evaluation SLR)
319	Young A, Evitt L, Brignone M, Diamand F, Atsou K, et al. Cost-utility evaluation of vortioxetine in patients with major depressive disorder experiencing inadequate response to alternative antidepressants in the United Kingdom. Journal of Affective Disorders 2017; 218:291-8.	Study design (included in economic evaluation SLR)
320	Yu AP, Xie J, Bensimon A, Parikh K, Wu EQ, et al. Economic consequence of switching to citalopram after its generic entry for adult patients with major depressive disorder (MDD) treated with escitalopram: A 6-month retrospective study. Journal of Medical Economics 2010; 13(4):599-609.	Country (non-UK)
321	Zhao YJ, Tor PC, Khoo AL, Teng M, Lim BP, et al. Cost-Effectiveness Modeling of Repetitive Transcranial Magnetic Stimulation Compared to Electroconvulsive Therapy for Treatment-Resistant Depression in Singapore. Neuromodulation 2017.	Study design (included in economic evaluation SLR)
322	Zimmer B. Direct and indirect costs of venlafaxine treatment of depression in the elderly with comorbid medical disorders. Annals of Long-Term Care 1999; 7(11):405-9.	Country (non-UK)
323	Zoun MHH, Koekkoek B, Sinnema H, Muntingh ADT, van Balkom AJLM, et al. Effectiveness and cost-effectiveness of a self-management training for patients with chronic and treatment resistant anxiety or depressive disorders: Design of a multicenter randomized controlled trial. BMC Psychiatry 2016; 16(1):216.	Protocol only
Studies excluded in April 2019 update (n=30)		
324	Abbass A, Kisley S, Town J. Cost-effectiveness of intensive short-term dynamic psychotherapy trial therapy. Psychotherapy and Psychosomatics 2018; 87(4):255-6.	Review/editorial

No.	Publication	Exclusion reason
325	Beiser DG, Ward CE, Vu M, Laiteerapong N, Gibbons RD. Depression in Emergency Department Patients and Association with Healthcare Utilization. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 2019; 18.	Country; non-UK data
326	Biesheuvel-Leliefeld KEM, Bosmans JE, Dijkstra-Kersten SMA, Smit F, Bockting CLH, Van Schaik DJF, et al. A supported self-help for recurrent depression in primary care; An economic evaluation alongside a multi-center randomised controlled trial. PLoS ONE 2018; 13(12):e0208570.	Population
327	Bodden DHM, Stikkelbroek Y, Dirksen CD. Societal burden of adolescent depression, an overview and cost-of-illness study. Journal of Affective Disorders 2018; 241:256-62.	Country; non-UK data
328	Bounthavong M, Pruitt LD, Smolenski DJ, Gahm GA, Bansal A, Hansen RN. Economic evaluation of home-based telebehavioural health care compared to in-person treatment delivery for depression. Journal of Telemedicine and Telecare 2018; 24(2):84-92.	Study design
329	Chatterton ML, Mihalopoulos C, O'Neil A, Itsiopoulos C, Opie R, Castle D, et al. Economic evaluation of a dietary intervention for adults with major depression (the "SMILES" trial). BMC Public Health 2018; 18(1):599.	Study design
330	Christensen MC, Munro V. Cost per successfully treated patient for vortioxetine versus duloxetine in adults with major depressive disorder: an analysis of the complete symptoms of depression and functional outcome. Current Medical Research and Opinion 2018; 34(4):593-600.	Study design
331	Clay E, Vataire A, Cristeau O, Toumi M. Open-Source Discrete Event Simulation Model for Major Depression Disorder (Mdd): An Update Suitable for New Generation Treatment? Value in Health 2018; 21(Supplement 3):S381-S2.	Study design
332	Grochtdreis T, Zimmermann T, Puschmann E, Porzelt S, Dams J, Scherer M, et al. Cost-utility of collaborative nurse-led self-management support for primary care patients with anxiety, depressive or somatic symptoms: A cluster-randomized controlled trial (the SMADS trial). International Journal of Nursing Studies 2018; 80:67-75.	Population
333	Groessl EJ, Tally SR, Hillery N, Maciel A, Garces JA. Cost-effectiveness of a pharmacogenetic test to guide treatment for major depressive disorder. Journal of Managed Care and Specialty Pharmacy 2018; 24(8):726-34.	Study design
334	Harrigan K, Walton SM, Huang SP, Kumar VM, Chapman RH, Atlas SJ, et al. Long-term cost-effectiveness of valbenazine and deutetrabenazine for tardive dyskinesia. Value in Health 2018; 21(Supplement 1):S184.	Population
335	Johnson JE, Stout RL, Miller TR, Zlotnick C, Cerbo LA, Andrade JT, et al. Randomized Cost-Effectiveness Trial of Group Interpersonal Psychotherapy (IPT) for Prisoners With Major Depression. Journal of Consulting and Clinical Psychology 2019.	Study design
336	Johnston KM, Powell LC, Anderson IM, Szabo S, Cline S. The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. Journal of Affective Disorders 2019; 242:195-210.	Review/editorial

No.	Publication	Exclusion reason
337	Kessler D, Burns A, Tallon D, Lewis G, Macneill S, Round J, et al. Combining mirtazapine with ssris or snris for treatment-resistant depression: The MIR RCT. Health Technology Assessment 2018; 22(63):I-136.	Study design
338	Klein NS, Bockting CL, Wijnen B, Kok GD, van Valen E, Riper H, et al. Economic Evaluation of an Internet-Based Preventive Cognitive Therapy With Minimal Therapist Support for Recurrent Depression: Randomized Controlled Trial. Journal of Medical Internet Research 2018; 20(11):e10437.	Population
339	Kolovos S, van Dongen JM, Riper H, Buntrock C, Cuijpers P, Ebert DD, et al. Cost effectiveness of guided Internet-based interventions for depression in comparison with control conditions: An individual-participant data meta-analysis. Depression and Anxiety 2018; 35(3):209-19.	Population
340	Lehnhardt FG, Dohle I, Sartorius A, Grozinger M. Fortschr Neurol Psychiatr 2018; 86(11):680-9.	Unavailable; unable to obtain
341	Lynch TR, Hempel RJ, Whalley B, Byford S, Chamba R, Clarke P, et al. Radically open dialectical behaviour therapy for refractory depression: the RefraMED RCT. NIHR Journals Library 2018; 12:12.	Study design
342	McCrone P, Rost F, Koeser L, Koutoufa I, Stephanou S, Knapp M, et al. The economic cost of treatment-resistant depression in patients referred to a specialist service. Journal of Mental Health 2018; 27(6):567-73.	Included in previous review
343	Meeuwissen JAC, Feenstra TL, Smit F, Blankers M, Spijker J, Bockting CLH, et al. The cost-utility of stepped-care algorithms according to depression guideline recommendations - Results of a state-transition model analysis. Journal of Affective Disorders. 2019;242:244-54.	Study design
344	Nardone C, Russo S, Migliorini R, Trabucco Aurilio M, Mennini FS. Mental Disorders and Major Depression: The Economic Analysis of Social Security Costs in Italy. Value in Health 2018; 21(Supplement 3):S280.	Country; non-UK data
345	Pollutri G, Mattei G, Colombini N, Galeazzi GM. Impact of a day hospital facility on type and length of hospital stay: A cost-effectiveness analysis. Minerva Psichiatrica 2019; 60(1):66-7.	Population
346	Ricken R, Wiethoff K, Reinhold T, Stamm TJ, Baghai TC, Fisher R, et al. A standardized stepwise drug treatment algorithm for depression reduces direct treatment costs in depressed inpatients - Results from the German Algorithm Project (GAP3). Journal of Affective Disorders 2018; 228:173-7.	Country; non-UK data
347	Ross EL, Zivin K, Maixner DF. Cost-effectiveness of electroconvulsive therapy vs pharmacotherapy/psychotherapy for treatment-resistant depression in the United States. JAMA Psychiatry 2018; 75(7):713-22.	Study design

No.	Publication	Exclusion reason
348	Rubio-Valera M, Penarrubia-Maria MT, Iglesias-Gonzalez M, Knapp M, McCrone P, Roig M, et al. Cost-effectiveness of antidepressants versus active monitoring for mild-to-moderate major depressive disorder: a multisite non-randomized-controlled trial in primary care (INFAP study). European Journal of Health Economics 2019.	Study design
349	Sauvaget A, Tostivint A, Etcheverrigaray F, Pichot A, Dert C, Schirr-Bonnais S, et al. Hospital production cost of transcranial direct current stimulation (tDCS) in the treatment of depression. Neurophysiologie Clinique 2019; 49(1):11-8.	Country; non-UK data
350	Segal L, Twizeyemariya A, Zarnowiecki D, Niyonsenga T, Bogomolova S, Wilson A, et al. Cost effectiveness and cost-utility analysis of a group-based diet intervention for treating major depression-the HELFIMED trial. Nutritional Neuroscience 2018.	Study design
351	Sluiter RL, Janzing JGE, van der Wilt GJ, Kievit W, Teichert M. An economic model of the cost-utility of pre-emptive genetic testing to support pharmacotherapy in patients with major depression in primary care. Pharmacogenomics Journal 2019.	Study design
352	Zhang Q, DiBernardo A, Heerlein K, O'Hara M, Benson C, Gonzalez Martin Moro B, et al. Association of treatment resistant depression with healthcare resource utilization and physician satisfaction with disease management. Value in Health 2018; 21(Supplement 1):S188.	Country; non-UK data
353	Zhao YJ, Tor PC, Khoo AL, Teng M, Lim BP, Mok YM. Cost-effectiveness modeling of repetitive transcranial magnetic stimulation compared to electroconvulsive therapy for treatment-resistant depression in Singapore. Brain Stimulation 2018; 11 (6):e9.	Study design
Studies excluded in September 2019 update (n=20)		
354	Anonymous. Internet-delivered cognitive behavioural therapy for major depression and anxiety disorders: A health technology assessment. Ontario Health Technology Assessment Series 2019; 19(6):1-199.	Study design
355	Bozkaya, D. et al. The Implementation of Competing Risks Using Different Modeling Techniques and Structures: The Effect on Incremental Cost-Effectiveness. Value in Health 2019; 22(Suppl 2):S228.	Study design
356	Beiser, D. G. et al. Depression in Emergency Department Patients and Association With Health Care Utilization. Academic Emergency Medicine 2019; 26(8):878-888.	Country (non-UK)
357	Dijkstra-Kersten, S. M. et al. Supported self-help to prevent relapse or recurrence of depression: Who benefits most? Journal of Affective Disorders 2019; 257:180-186.	Country (non-UK)
358	Grochtdreis, T. et al. Cost-effectiveness analysis of collaborative treatment of late-life depression in primary care (GermanIMPACT). European Psychiatry 2019; 57:10-18.	Study design
359	Hernandez, L. G. et al. Cost-Effectiveness Analysis of Esketamine in Treatment-Resistant Depression in the United States. Value in Health 2019; 22 (Suppl 2):S228-S229.	Study design

No.	Publication	Exclusion reason
360	Johnson, J. E. et al. Randomized cost-effectiveness trial of group interpersonal psychotherapy (IPT) for prisoners with major depression. Journal of Consulting and Clinical Psychology 2019; 87(4):392-406.	Identified by previous review
361	Kanters, T. A. et al. Assessing costs using the treatment inventory cost in psychiatric patients (TiC-P), TiC-P mini and TiC-P MIDI. Journal of Mental Health Policy and Economics 2019; 22(1):15-24.	Country (non-UK)
362	Konig, H. et al. The excess costs of depression: A systematic review and meta-analysis. Epidemiology and Psychiatric Sciences 2019;	Review
363	Lin, Y. et al. Cost-effectiveness analysis of prognostic-based depression monitoring. IISE Transactions on Healthcare Systems Engineering 2019; 9(1):41-54.	Study design
364	Meeuwissen, J. A. C. et al. The cost-utility of stepped-care algorithms according to depression guideline recommendations - Results of a state-transition model analysis. Journal of Affective Disorders 2019; 242:244-254.	Identified by previous review
365	Mendlowitz, A. B. et al. Implementation of intermittent theta burst stimulation compared to conventional repetitive transcranial magnetic stimulation in patients with treatment resistant depression: A cost analysis. PLoS ONE 2019; 14(9):e0222546.	Country (non-UK)
366	Pohar, R. and Farrah, K. Repetitive Transcranial Magnetic Stimulation for Patients with Depression: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines – An Update. Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports 2019; 06:28.	Review
367	Rubio-Valera, M. et al. Cost-Effectiveness of Antidepressants versus Active Monitoring for Mild-to-Moderate Major Depressive Disorder: A Multisite Non-Randomized-Controlled Trial in Primary Care (INFAP Study). European Journal of Health Economics 2019; 20(5):703-13.	Identified by previous review
368	Sauvaget, A. et al. Hospital production cost of direct transcranial stimulation (tDCS) in the treatment of depression. Encephale 2019; 45(Suppl 2):S78-S79.	Abstract, superseded
369	Sauvaget, A. et al. Hospital production cost of transcranial direct current stimulation (tDCS) in the treatment of depression. Neurophysiologie Clinique 2019; 49(1):11-18.	Country (non-UK)
370	Sluiter, R. L. et al. An economic model of the cost-utility of pre-emptive genetic testing to support pharmacotherapy in patients with major depression in primary care. Pharmacogenomics Journal 2019;	Identified by previous review
371	Van Bentum, J. S. et al. Treating repetitive suicidal intrusions using eye movements: Study protocol for a multicenter randomized clinical trial. BMC Psychiatry 2019; 19(1):143.	Protocol only
372	Wang, S. T. et al. Cost-effectiveness model for a hypothetical monotherapy vs standard of care in adult patients with treatment-resistant depression. ClinicoEconomics and Outcomes Research 2019; 11:257-270.	Study design

No.	Publication	Exclusion reason
373	Xie, X. et al. A Non-inferiority Framework for Cost-Effectiveness Analysis. International Journal of Technology Assessment in Health Care 2019; 35(4):291-297.	Study design
Studies excluded in September 2019 update (n=16)		
374	Dijkstra-Kersten SM, Biesheuvel-Leliefeld KE, van der Wouden JC, van Schaik DJ, Bosmans JE, van Marwijk HW, et al. Supported self-help to prevent relapse or recurrence of depression: Who benefits most? J Affect Disord. 2019;257:180-6.	Publication date (identified by previous review)
375	Fitzgibbon KP, Plett D, Chan BCF, Hancock-Howard R, Coyte PC, Blumberger DM. Cost-Utility Analysis of Electroconvulsive Therapy and Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Ontario. Canadian Journal of Psychiatry. 2019.	Study design
376	Grochtdreis T, Brettschneider C, Bjerregaard F, Bleich C, Boczor S, Harter M, et al. Cost-effectiveness analysis of collaborative treatment of late-life depression in primary care (GermanIMPACT). European Psychiatry. 2019;57:10-8.	Publication date (identified by previous review)
377	Jaffe DH, Rive B, Denee TR. The humanistic and economic burden of treatment-resistant depression in Europe: A cross-sectional study. BMC Psychiatry Vol 19 2019, ArtID 247. 2019;19.	Publication date (identified by previous review)
378	Leurent B, Gomes M, Cro S, Wiles N, Carpenter J. Reference-based multiple imputation for data missing not-atrandom in cost-effectiveness analysis. Trials Conference: 5th International Clinical Trials Methodology Conference, ICTMC. 2019;20(Supplement 1).	Study design
379	Liu M, Chen W. Pmh30 Cost-Utility Analysis of Vortioxetine for the Treatment of Major Depression Disorders in China. Value in Health. 2019;22 (Supplement 3):S686.	Study design
380	Meeuwissen JA, Feenstra TL, Smit F, Blankers M, Spijker J, Bockting CL, et al. The cost-utility of stepped-care algorithms according to depression guideline recommendations-Results of a state-transition model analysis. J Affect Disord. 2019;242:244-54.	Publication date (identified by previous review)
381	Richard B, Kovacs S, Vincze G, Fittler A, Botz L, Zemplenyi A. Pmh26 Model Development for Assessing Cost-Effectiveness and Prepare Reimbursement Dossier of Rtms in Patient Population with Treatment-Resistant Depression in Hungary. Value in Health. 2019;22 (Supplement 3):S685.	Review/editorial
382	Ross EL, Zivin K, Maixner DF. Cost-effectiveness of Electroconvulsive Therapy vs Pharmacotherapy/Psychotherapy for Treatment-Resistant Depression in the United States. JAMA Psychiatry. 2018;75(7):713-22.	Publication date (identified by previous review)
383	Rubio-Valera M, Penarrubia-Maria MT, Iglesias-Gonzalez M, Knapp M, McCrone P, Roig M. Cost-Effectiveness of Antidepressants versus Active Monitoring for Mild-to-Moderate Major Depressive Disorder: A Multisite Non-Randomized-Controlled Trial in Primary Care (INFAP Study). European Journal of Health Economics. 2019;20(5):703-13.	Publication date (identified by previous review)

No.	Publication	Exclusion reason
384	Shearer J, Lynch TR, Chamba R, Clarke S, Hempel RJ, Kingdon DG, et al. Refractory depression - cost-effectiveness of radically open dialectical behaviour therapy: findings of economic evaluation of RefraMED trial. BJPsych Open. 2019;5(5):e64.	Publication date (identified by previous review)
385	Touchette D, Boyer N, Atlas SJ, Agboola FO, Talon B, Schultz B, et al. Pmh16 Long-Term Cost-Effectiveness of Esketamine for the Treatment of Treatment-Resistant Depression. Value in Health. 2019;22 (Supplement 3):S683.	Study design
386	Wang G, Zhao K, Reynaud-Mougin C, Loft H, Ren H, Eriksen HF, et al. Successfully treated patients with vortioxetine versus venlafaxine: a simplified cost-effectiveness analysis based on a head-to-head study in Asian patients with major depressive disorder. Curr Med Res Opin. 2020:1.	Abstract; superseded by Wang_2020 (included in economic evaluation review)
387	Wang G, Zhao K, Reynaud-Mougin C, Loft H, Ren H, Eriksen HL, et al. Pmh27 Successfully Treated Patients with Vortioxetine Versus Venlafaxine: A Simplified Cost-Effectiveness Analysis in Asian Patients with Major Depressive Disorder. Value in Health. 2019;22 (Supplement 3):S685.	Study design
388	Yan C, Rittenbach K, Souri S, Silverstone PH. Cost-effectiveness analysis of a randomized study of depression treatment options in primary care suggests stepped-care treatment may have economic benefits. BMC Psychiatry Vol 19 2019, ArtID 240. 2019;19.	Study design
389	Yoon J, Zisook S, Park A, Johnson GR, Scrymgeour A, Mohamed S. Comparing Cost-Effectiveness of Aripiprazole Augmentation With Other "Next-Step" Depression Treatment Strategies: A Randomized Clinical Trial. J Clin Psychiatry. 2018;80(1):18.	Study design

J.1.6 Local adaptation

To support this submission for ESK NS for the treatment of TRD in Denmark, the global SLR was adapted by excluding all studies not relevant to a Danish setting. The objective of the global SLR was to identify economic evaluations of relevant interventions and resource/cost data associated with TRD and MDD. As no sources were identified that aligned with the Danish setting, all sources from the global SLR were excluded as inputs for the health economic model.

Targeted literature review – economic studies

In addition to the SLR, a TLR was conducted to identify and collect relevant inputs for the health economic model. Apart from the data from the ESCAPE-TRD trial[65], 8 references were identified to provide input for the health economic model. The TLR was conducted pragmatically, focusing solely on inputs not informed by SmPC, cost sources, etc.

Table 116 List of studies included to identify cost/resource use, TLR

Source name/database	Location/source	Search strategy	Date of search
Daly et al. [94]	Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial	Key trial data	N/A
Janssen. 2019 [80]	Data on File. Statistical Analysis of Patient Level Data from Esketamine Trials	Key trial data	N/A
Rush AJ, Trivedi MH, Wisniewski SR, et al. [20]	Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report.	Hand search	N/A
Edwards SJ, Hamilton V, Nherera L, Trevor N. [81]	Lithium or an atypical antipsychotic drug in the management of treatment-resistant depression: a systematic review and economic evaluation.	Hand search	N/A
Bergfeld IO, Mantione M, Figee M, Schuurman PR, Lok A, Denys D. [24]	Treatment-resistant depression and suicidality.	Hand search	N/A
Ekman M, Granström O, Omérov S, Jacob J, Landén M [82]	The societal cost of depression: evidence from 10,000 Swedish patients in psychiatric care	Hand search	N/A
Petersen J, Gronemann FH, Ankarfeldt MZ, Solem EJ, Jørgensen MB, Osler M. [83]	Treatment Resistant Depression in Denmark (TRIDEN): Healthcare resource utilization in relation to treatment resistance in patients with major	Hand search	N/A

	depression in a nation-wide Danish cohort.		
Starr L. WA, Dale E. [84]	Phase 3 Amendment 4: A Randomized, Double-blind, Multicenter, Active-controlled Study of Intranasal ESK Plus an Oral Antidepressant for relapse prevention in treatment-resistant depression	Hand search	N/A

J.1.7 Quality assessment

N/A

J.1.8 Unpublished data

N/A

Appendix K. Transition probabilities

Transition probabilities

An overview of all transition probabilities used in the base case analysis for the base case analysis is summarised in Table 117, below.

Table 117 Transitions in the health economic model; base case analysis

	Health state (from)	Health state (to)	28- day probability, % (SE %)	Description of method	Reference
First treatment line					
Discontinuation in MDE	MDE cycle 1	MDE2	[redacted]	Observed approach	ESCAPE-TRD, post-hoc analysis[65]
	MDE cycle 2	MDE2		Observed approach	
	MDE cycle 3	MDE2		Observed approach	
	MDE cycle 4	MDE2		Observed approach	
	MDE cycle 5	MDE2		Observed approach	
Response	MDE cycle 1	Response		Observed approach	
	MDE cycle 2	Response		Observed approach	
	MDE cycle 3	Response		Observed approach	
	MDE cycle 4	Response		Observed approach	

	MDE cycle 5	Response	[redacted]	Observed approach	
Remission	MDE cycle 1	Remission		Observed approach	
	MDE cycle 2	Remission		Observed approach	
	MDE cycle 3	Remission		Observed approach	
	MDE cycle 4	Remission		Observed approach	
	MDE cycle 5	Remission		Observed approach	
	Response	Remission		Transition rate turned into probability	
Loss of response	Response (on or off treatment)	MDE2		Transition rate turned into probability	Assumed to be the same as the ITT population from the ESCAPE-TRD, post-hoc analysis[65]
Relapse	Remission (on or off treatment)	MDE2		Transition rate turned into probability	
Discontinuation in response or remission	Response or remission on treatment	Response or remission off treatment		Transition rate turned into probability	ESCAPE-TRD, post-hoc analysis[65]
Discontinuation	Remission on	Recovery off treatment		Observed approach	Assumption based on ESKINTRD3003[94]. Assumption

upon recovery	treatment				adapted in the QTP XR arm, following a conservative approach.
Discontinuation during recovery	Remission on treatment	Recovery off treatment	[redacted]	Transition rate turned into probability	Assumption (99% discontinuation within two years of recovery). Assumption adapted in the QTP XR arm, following a conservative approach.
Recurrence	Recovery on or off treatment	MDE2		Transition rate turned into probability	Assumed equal to relapse ESK. Assumption adapted in the QTP XR arm, following a conservative approach.
Subsequent treatment lines (2nd, 3rd, and 4th)					
Response	MDE	Response	[redacted]	Transition rate turned into probability	ESCAPE-TRD, post-hoc analysis[65]
Remission	MDE	Response	[redacted]	Transition rate turned into probability	ESCAPE-TRD, post-hoc analysis[65]
	Response	Remission	[redacted]	Transition rate turned into probability	ESCAPE-TRD, post-hoc analysis[65]
Loss of response	Response	MDE	ESK NS: 22.81 (5.70) QTP XR: 22.81 (5.70)	Transition rate turned into probability	Step 4. Rush et al.[20] Exponential function. Refer to Step 4.
Relapse	Remission	MDE	ESK NS: 12.79 (3.20) QTP XR: 12.79 (3.20)	Transition rate turned into probability	Step 4. Rush et al.[20] Exponential function. Refer to Step 4.
Recurrence	Recovery	MDE	ESK NS: 12.79 (3.20) QTP XR: 12.79 (3.20)	Transition rate turned into probability	Assumed same as relapse

Later lines after the subsequent treatment (non-specific treatment lines)					
Response	MDE	Response	ESK NS: 0.83 (0.21) QTP XR: 0.83 (0.21)	Reported risk. Standard methodology was used to convert 2-month risks to 4-week risks.	Edward et al., 2013[81]; assumed SE
Remission	MDE	Remis-sion	ESK NS: 0.41 (0.10) QTP XR: 0.41 (0.10)	Reported risk. Standard methodology was used to convert 2-month risks to 4-week risks.	Edward et al., 2013[81]; assumed SE
Loss of re-sponse	Response	MDE	ESK NS: 10.38 (2.59) QTP XR: 10.38 (2.59)	Reported risk. Standard methodology was used to convert 2-month risks to 4-week risks.	Edward et al., 2013[81]; assumed SE
Relapse	Remis-sion	MDE	ESK NS: 4.20 (1.05) QTP XR: 4.20 (1.05)	Reported risk. Standard methodology was used to convert 2-month risks to 4-week risks.	Edward et al., 2013[81]; assumed SE

Abbreviations: ESK, esketamine; ITT, intention-to-treat; MDE, major depressive episode; NS, nasal spray; QTP, quetiapine; SE, standard error ; XR, extended-release.

Illustrations of the transition probability matrices are shown in Figure 16 and Figure 17, for patients on initial or subsequent TRD treatment and on non-specific treatment (OADs from two classes: a SSRI or a SNRI), respectively. The blue boxes highlight the transitions that are possible from any given health state into the same or other health states.

Patients on Initial or Subsequent Treatment		Transitions To			
		MDE	Response	Remission	Recovery
Transitions From	MDE				
	Response				
	Remission				
	Recovery				

Figure 16 Transition Probability Matrix: Patients On Initial or Subsequent Treatment

Note: Light blue cells indicate permissible transitions.
Abbreviations: MDE = Major depressive episode

Patients on Non-specific Treatment		Transitions To		
		MDE	Response	Remission
Transitions From	MDE			
	Response			
	Remission			

Figure 17 Transition Probability Matrix: Patients Off-Active-Treatment

Note: Light blue cells indicate permissible transitions.
Abbreviations: MDE = Major depressive episode

Transition probabilities derived from STAR*D

To estimate the transition probabilities in the subsequent treatment lines, the STAR*D trial is used. STAR*D is the largest study to examine the durability of OAD (monotherapy, combination and augmentation) response in patients with MDD and TRD and represents the best source to inform relapse risk for OAD, given the re-randomised design of SUSTAIN-1 and especially when compared to a trial setting where additional clinic visits and a placebo nasal spray was added to the OAD to ensure blinding.

No modifications were made to the loss of response (relapse among responders) rates obtained from STAR*D. Although different scales were used between STAR*D and the ESK NS trials to measure depressive symptoms, in order to use the published results from STAR*D (survival curves) it was assumed that the response and remission health states defined if each source (ESK NS trials and STAR*D) were equivalent, e.g., a 50% reduction from baseline in the scale used in STAR*D (QIDS-SR_{16}) is assumed equivalent to a 50% reduction from baseline in MADRS (used in the ESK NS trials).

Loss of response

Loss of response data was used to inform the model on the transition from response to the MDE health state in subsequent treatment lines. Figure 4 in the STAR*D publication[1] was used for the extrapolation of loss of response. Specifically, the Kaplan Meier (KM) curves provided in Figure 4 of the STAR*D publication, in particular for Step 4 (the latest treatment line included in STAR*D), were digitised and an exponential model was fit to the digitised data. This process is outlined below.

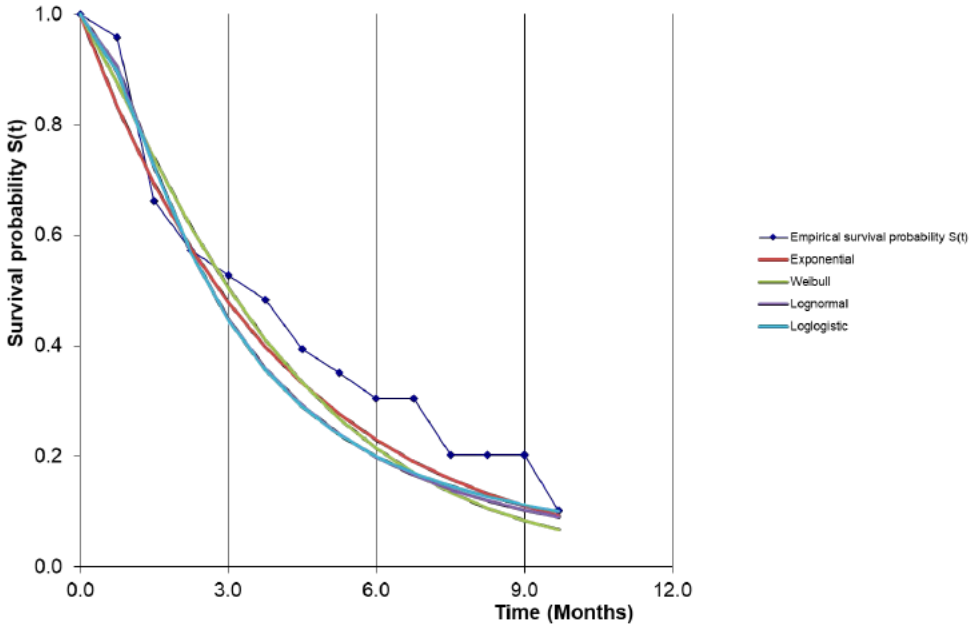
Table 118. Step 4 – Model fitting

	Exponential	Weibull	Lognormal	Loglogistic
AIC	126.26	127.36	125.91	127.36
BIC	127.72	130.29	128.84	130.29
Parameters				
Intercept	1.4051	1.4229	0.9754	0.9727
Log(scale)	0.0000	-0.1607	-0.0368	-0.5282
Lambda	0.245339601415447	0.1881		0.1921
Gamma	1.0000	1.1743		1.6958

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Figure 18 Step 4 – Model fit versus observed data

[1] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17.



4-week loss of response rate of step 4 was estimated to be 22.8% for OADs.

Relapse

Relapse data was used to inform the model on the transition from remission or recovery to the MDE health state in subsequent treatment lines. Figure 3 in the STAR*D publication was used to derive relapse rates. As was the case for loss of response, no modifications were made to relapse (relapse among remitters) rates obtained from STAR*D.

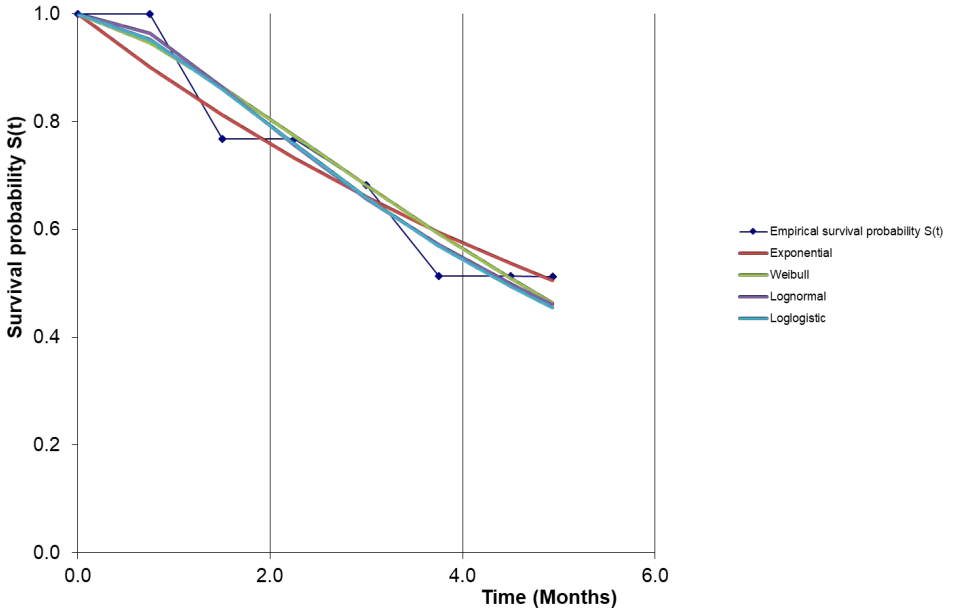
The KM curves provided in Figure 3 of the STAR*D publication, in particular for Step 4, were digitised and an exponential model was fit to the digitised data. This process is outlined below.

Table 119 Step 4 – Model fitting

	Exponential	Weibull	Lognormal	Loglogistic
AIC	41.20	42.42	41.35	41.90
BIC	41.91	43.84	42.77	43.31
Parameters				
Intercept	1.9785	1.7856	1.5011	1.4888
Log(scale)	0.0000	-0.3329	-0.0054	-0.5219
Lambda	0.13827317797635	0.0828		0.0814
Gamma	1.0000	1.3950		1.6852

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Figure 19 Step 4 – Model fit versus observed data



4-week relapse risks for step 4 were estimated to be 12.8%.

Appendix L. Retreatment model

As a retreatment model was requested by the DMC for the previous assessment, a scenario is provided to show the impact of retreatment on the incremental cost and cost-effectiveness of ESK NS. The model structure is shown in Figure 20.

Figure 20

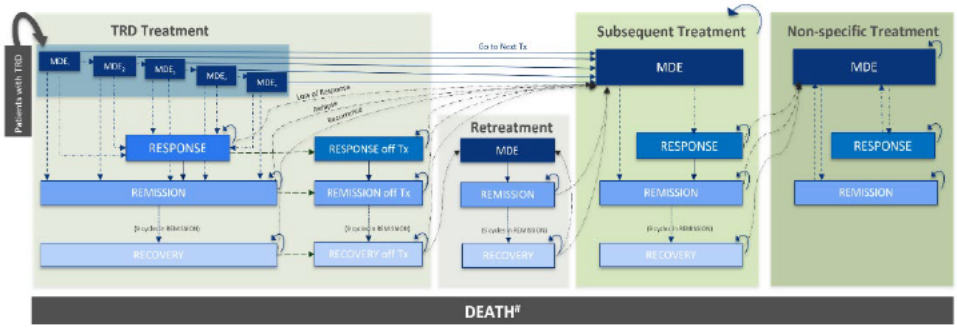


Figure 20 Model structure with re-treatment scenario

Abbreviations: AD, antidepressant; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, Major depressive disorder; MDE, Major depressive episode; TRD, treatment resistant depression; Tx, treatment

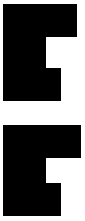
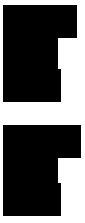
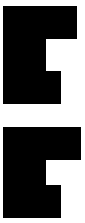
L.1 Modelling approach

The modelling approach is informed by clinical opinion and the Expert Committee's request, according to which retreatment will only be used in clinical practice if the active treatment was successful before, and the patient is no longer on that treatment. Patients who have been in stable remission for at least 9 months and have discontinued ESK NS are assumed to be eligible for ESK NS retreatment.

An overview of all transition probabilities used in the health economic model for the ESK NS retreatment scenario is summarised in Table 120 below.

Table 120 Transitions in the health economic model; retreatment scenario

Health state (from)	Health state (to)	28- day probability, % (SE %)	Description of method	Reference	Rationale
Retreatment					
Remission	MDE	Remission	ESK NS: 100.00 (0.00)	N/A*	Assumption

			QTP XR: 100.00 (0.00)		
Relapse	Remission	MDE		N/A*	Assumed equal to relapse in first line
Discontinuation in remission	Remission on treatment	Remission off treatment		N/A*	Assumed equal to discontinuation during remission in first line
Discontinuation upon recovery	Remission on treatment	Recovery off treatment		N/A*	Assumed equal to discontinuation upon recovery in first line. Assumption adapted in the QTP XR arm, following a conservative approach.
Discontinuation during recovery	Recovery on treatment	Recovery off treatment		N/A*	Assumed equal to discontinuation during recovery in first line. Assumption adapted in the QTP XR arm, following a conservative approach.
Recurrence	Recovery on or off treatment	MDE2		N/A*	Assumed equal to recurrence in first line

Abbreviations: ESK, esketamine; MDE, major depressive episode; N/A, not applicable; NS, nasal spray; QTP, quetiapine; SE, standard error ; XR, extended-release.

* Transition probabilities are based on assumptions rather than sourced data. Assumptions are informed by data obtained from the ESCAPE-TRD trial[65].* Transition probabilities are based on assumptions rather than sourced data. Assumptions are informed by data obtained from the ESCAPE-TRD trial[65].

L.2 Limitations of the retreatment model

Including retreatment in the model is associated with substantial limitations, most of which relate to lack of data to inform the retreatment scenario analysis:

- In the retreatment model scenario, retreatment is only for patients treated with ESK NS + OAD who had previously been in stable remission for at least 9 months, then discontinued ESK NS, and subsequently experienced a recurrence while in the recovery health state.
- The positioning and sequencing of ESK NS during retreatment of the new episode is uncertain and based on assumptions
- The data to inform the effectiveness of ESK NS during retreatment are based on the assumptions taken from initial treatment of the first episode with ESK NS.
- It is assumed similar health states (MDE, remission and recovery (but no response)) also apply to ESK NS in retreatment of the new episode.
- The dosage and frequency of ESK NS (and hence treatment costs) are based upon initial ESK NS treatment.
- The safety profile of ESK NS retreatment is assumed to be consistent with initial treatment with ESK NS.

Overall, the retreatment scenario significantly increases the uncertainty in the incremental cost and cost effectiveness of ESK NS. The above limitations show that the retreatment model should not be considered more than a scenario and should be interpreted with caution.

Appendix M. Results from long-term TRD cohorts

Table 121 Results from long-term TRD cohorts

Study	Outcome time point	Definition of remission	Remission on current treatment	Response on current treatment
Rush et al, 2006 - STAR*D20	1 year	A QIDS-SR score of ≤5 (equivalent to ≤7 on the HRSD) defined remission	4.85%	Not reported
Dunner et al, 2006[176]	2 years	IDS-SR-30 score of ≤14	8%	18.4% (including remission; ≥50% decrease in total baseline score, hence including remission)
Aaronson et al, 2017[177]	1 year	MADRS total score ≤ 9 at any post-baseline visit	12%	25% (including remission; ≥50% reduction from baseline MADRS score at any postbaseline visit)

Abbreviations: HRDS, Hamilton Rating Scale for Depression; IDS-SR-30, Self-rated Inventory of Depressive Symptomatology; MADRS, Montgomery & Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology

Appendix N. Frequency of healthcare utilisation

Table 122 shows the average number of visits or hospital days for TRD during MDE sourced from Petersen et al. (TRIDEN)[83]. Table 122 shows the average number of visits or hospital days for TRD during MDE sourced from Petersen et al. (TRIDEN)[83].

Table 122 Average healthcare utilisation in the first year after TRD for patients treated with SSRI or SNRI as first line antidepressant treatment after TRD

Type of health care utilisation	SSRI Mean (SD)	SNRI Mean (SD)
Psychiatric contracts		
Acute hosp. days	4.7 (19.7)	5.3 (20.4)
Elective hosp. days	1.0 (8.5)	1.1 (10.5)
ED visits	0.2 (0.9)	0.2 (1.3)
Somatic contacts		
Acute hosp. days	2.6 (8.8)	2.0 (8.2)
Elective hosp. days	0.7 (4.0)	0.6 (4.4)
ED visits	0.4 (1.1)	0.3 (0.9)
Outpatient visits	3.2 (7.3)	3.0 (7.0)
GP	9.2 (9.5)	9.6 (9.4)

Abbreviations: ED, emergency department visits; hosp, hospital; GP, general practioner; SD, standard deviations; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors, SNRI

Appendix O. Esketamine NS TRD reimbursement

Spravato TRD Positive Reimbursement Decisions 2020-23

#	Country	Reimbursement Date	Type of restriction
1	**Israel**	30 Jan 2020	After 2 treatment failures with 2 ADs of different classes
2	**Luxemburg**	1 Jul 2020	Full label
3	**Sweden**	15 Aug 2020	After 4 treatment failures (2 ADs of different classes, augmentation treatment with lithium or an antipsychotic, ECT/TMS considered/tested)
4	**Scotland**	7 Sept 2020	Full label
5	**France**	1 Oct 2020	After 2 treatments failures with ADs, <65 years, severe episode
6	**Kuwait**	21 May 2021	After 3 treatment failures (2 ADs and 1 augmentation/combination treatment)
7	**Belgium**	1 Jun 2021	After 2 treatment failures (of which 1 must be augmentation/combination treatment)
8	**UAE**	1 Jun 2021	Full label
9	**Netherlands**	1 Sept 2021	After 3 treatment failures (2 ADs and 1 augmentation treatment)
10	**KSA**	1 Oct 2021	Full label
11	**Croatia**	25 Dec 2021	Severe depression
12	**Ireland**	1 Jan 2022	Full label
13	**Estonia**	1 Jan 2022	After 3 treatment failures (3 drugs with different MoAs and 1 augmentation/combination treatment). After ECT or failed to it due to side effects or contraindication to it
14	**Italy**	19 May 2022	Full label
15	**Finland**	1 Jun 2022	After 3 treatment failures (2 ADs and 1 augmentation with lithium or an antipsychotic), Severe depression
16	**Switzerland**	1 Oct 2022	After 2 ADs and 1 augmentation, Severe depression (CGI-S ≥5). Max 10 months duration (case by case if patients show continued response (CGI-S ≥2 reduction from baseline)
17	**Egypt**	1 Oct 2022	Full label
18	**Spain**	1 Nov 2022	After at least 3 different treatment strategies, of which at least one is combination or augmentation, Adults (18-74 years), severe depressive episode
19	**Bulgaria**	2 Jan 2023	Full label
20	**Lithuania**	April 2023	Age restriction (18-64 years)
21	**Greece**	24 April 2023	Full label
22	**Poland**	1 Jul 2023	18-75 yrs, ≥2 episodes, current episode lasting ≥6 months, contraindicated has not benefitted from or refuses ECT
23	**Romania**	Jul 2023	Full label
24	**Germany**	Sep 2023	Full label
25	**Slovakia**	1 Oct 2023	After 3 treatment failures, 18-64 years, moderate to severe episode, inpatient and outpatient

Spravato TRD Positive Reimbursement Decisions 2024-

#	Country	Reimbursement Date	Type of restriction
26	**Hungary**	Jan 2024	Full label
27	**Slovenia**	29 Feb 2024	Full label
28	**Oman**	Jul 2024	Full label
29	**Austria**	1 Aug 2024	< 75 yrs, after failing at least 2 AD classes incl. 1 augmentation, baseline MADRS ≥30, after 4 wk induction in hospital setting & ≥50% reduction in MADRS
30	**Iceland**	1 Oct 2024	Full label
31	**Latvia**	1 Oct 2024	MADRS ≥ 28, current episode lasting at least 2 years, at one of seven designated centers across the country. Treatment to be discontinued without ≥50% reduction in MADRS after 8 weeks
32	**Czech Republic**	1 Feb 2025	≤ 65 yrs, inadequate treatment response (0%-25% symptom reduction) on at least 2 ADs. Treatment to be discontinued without ≥50% reduction in MADRS after 8 weeks. Regular re-assessment at least every 3 months

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