ThemenCheck Medizin

Extract of HTA report

Depression in children and adolescents:

Does psychotherapy lead to better results when compared with other therapies?[1]

Health technology assessment commissioned by IQWiG

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[1] Translation of Chapters 1 to 9 of the HTA report HT19-04 *Depressionen bei Kindern und Jugendlichen: Führt Psychotherapie im Vergleich zu anderen Therapien zu besseren Ergebnissen?* (Version 1.0; Status: 14 January 2022 [German original], 12 August 2022 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers.

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IQWiG coordinated the project, conducted the literature search for the domains “Benefit assessment“ and “Health economic evaluation”, and prepared “HTA kompakt” the easily understandable short version.

Keywords: Psychotherapy, Depressive Disorder, Child, Adolescent, Benefit Assessment, Systematic Review, Technology Assessment – Biomedical

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A12 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the HTA report?

Insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies through "ThemenCheck Medizin" (Topic Check Medicine) to the Institute for Quality and Efficiency in Health Care (IQWiG). The assessment is done in the form of a health technology assessment (HTA) report. HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-step selection procedure, which also involves the public, up to 5 new topics are selected each year from among all submitted proposals. According to the legal mandate, these topics should be of particular relevance to patients [1]. IQWiG then commissions external teams of scientists to investigate the topics in accordance with IQWiG methods, and it publishes the HTA reports.

In December 2019, IQWiG commissioned a team of scientists from the University for Continuing Education Krems to investigate the selected topic "HT19-04: Depression in children and adolescents: Does psychotherapy lead to better results when compared with other therapies?". The team consisted of methodologists experienced in generating HTA reports, experts with knowledge and experience in health economic, ethical, social, legal, and organizational topics as well as a physician specializing in paediatric and adolescent psychiatry and a psychological psychotherapist.

Why is the HTA report important?

Like adults, children and adolescents with depression exhibit typical symptoms such as deep sadness and avolition. However, the disorder may also manifest differently and, e.g. in primary school children, be associated with irritability and outbursts of rage, physical symptoms such as headache or stomachache, or pronounced parental separation anxiety. In adolescents, symptoms including weight fluctuations, drug and alcohol use, extreme sleepiness, and suicidal ideation may suggest depression. Varied symptoms can make it difficult to recognize and diagnose depression at an early stage – particularly since symptoms often overlap with behavioural problems such as aggression and hyperactivity or coincide with other problems such as anxiety or eating disorders.

Up to 1 in 100 children and about 5 in 100 adolescents suffer from depressive disorder [2]. Up to 90% of patients recover from a depressive episode within 1 to 2 years, but more than half of them experience a relapse within 5 years [3,4].

Against this background, a member of the public asked, among other things, whether in children and adolescents, psychotherapy should be started as soon as the first depressive symptoms occur or whether specific therapy should be initially foregone.

Therefore, this HTA report investigates the effects of psychotherapy compared to inactive controls (e.g. waiting list, psychological placebo) with regard to patient-relevant outcomes such as changes in depressive symptoms, suicide risk, or health-related quality of life. Additionally, a comparison with antidepressant therapy or non-drug interventions such as exercise or relaxation exercises was of interest.

Which questions are answered – and which are not?

For this HTA report, medical benefit and harm were assessed on the basis of systematic reviews. In its investigation, the group of authors from the University for Continuing Education Krems included a total of 13 systematic reviews with data from 150 studies of informative value. Studies were found on 3 types of psychotherapy: cognitive behavioural therapy, interpersonal psychotherapy, and psychodynamic psychotherapy. Systemic therapy was excluded a priori since IQWiG has been commissioned by the Federal Joint Committee (G-BA) to assess this therapy [5]. The psychotherapy types were investigated in comparison with inactive controls or with antidepressant therapy and as add-ons to antidepressant therapy. No studies were available for a comparison with non-drug interventions such as exercise and relaxation exercises, which are typically recommended only for mild depression.

The systematic reviews included children and adolescents 4 to 18 years of age. Their analyses typically did not differentiate by age or severity of depression. Therefore, the question about the best approach in children and adolescents with initial mild depressive symptoms cannot be answered on the basis of the included publications. Only general conclusions were drawn:

There were indications of cognitive behavioural therapy and interpersonal psychotherapy alleviating symptoms of depression. An indication was also found for interpersonal psychotherapy effectively helping children and adolescents better manage family, school, and social activities. For psychodynamic psychotherapy, in contrast, there was no hint of alleviation of depressive symptoms. However, limited results are available on psychodynamic psychotherapy because they are based on network metaanalyses which also included studies where fewer than 80% of participants met the inclusion criteria of this HTA report. In addition, the effects of psychotherapies on suicide risk (suicidal ideation and behaviour) were impossible to be reliably assessed even on the basis of these aggregated data since confidence intervals were too wide.

For virtually all investigated outcomes, no hints were found for psychotherapy being more effective than antidepressant therapy nor for antidepressants with add-on psychotherapy being more effective than antidepressant monotherapy. Only for cognitive behavioural

therapy administered as an add-on to an antidepressant was there a hint of a long-term advantage in the management of family, school, and social activities.

No systematic review reported any results on all-cause and suicide mortality or health-related quality of life. In addition, no adverse events were investigated, rendering a complete weighing of benefits versus harm impossible.

While the statutory health insurance (SHI) pays for cognitive behavioural therapy and psychodynamic psychotherapy, it does not regularly do so for interpersonal psychotherapy since the SHI catalogue of services currently does not list the latter as an outpatient service. The cost of antidepressants, mental health education, or relaxation therapy are covered for patients with a corresponding diagnosis.

For comparing benefit and cost, 5 health economic studies from the United States and the United Kingdom were found which investigated cognitive behavioural therapy. According to the authors commissioned by IQWiG for this report, however, excessively large differences in healthcare structures made it impossible to adapt these results to the German healthcare context.

On the basis of scoping literature searches and expert interviews, some ethical, social, legal, and organizational aspects related to the disease and the investigated interventions were additionally identified.

The early diagnosis of depression in children and adolescents presents a challenge because its symptoms are often overlapped by other symptoms and comorbidities, or initial symptoms are misinterpreted as typical adolescent or pubescent behaviour. When depression is first suspected, affected people and their family members are often uncertain about how to proceed. Family members do not know whether the situation is hazardous enough to require professional help, and if so, whom to contact. Additionally, concerns about stigmatization can impede early consultation and diagnostic clarification of depressive symptoms. Initial contacts may be general practitioners, paediatricians, and family counselling centres, which refer affected people to psychotherapists, for instance. Additionally, outpatient psychotherapy consultation hours have become available some time ago for seeking advice. If a treatment slot is needed, however, affected people can often expect long waits – particularly if they live in rural areas.

Qualitative research suggests that most patients largely accept psychotherapy and view it as a causative treatment option for depression. According to the commissioned team of scientists, antidepressants, in contrast, tend to be perceived as symptomatic treatment and as associated with potential risks, e.g. dependency or loss of autonomy.

What was discussed in the commenting procedure?

Several comments received by IQWiG regarding the preliminary HTA report noted that current studies on psychodynamic psychotherapy were excluded from the HTA report because the "review of reviews" method was chosen. According to the commentators, a search for primary studies might have resulted in more evidence on the effectiveness of this type of psychotherapy. They added that it was impossible to draw differentiated conclusions by age or severity of depression. In the oral discussion, the group of authors from the University for Continuing Education Krems reiterated that limiting the study analysis largely to systematic reviews is a particularly suitable approach for HTA reports, which are to cover a broad research question on various treatment options and for which many current reviews are available. The authors reviewed the primary studies on psychodynamic psychotherapy which the commentators mentioned as missing from the report. However, these studies did not meet the report's inclusion criteria. The check of 2 reviews on psychodynamic psychotherapy which were published after completion of the systematic search for the HTA report likewise failed to identify any additional relevant studies.

Furthermore, some commentators suggested answering the member of the public's initial question more clearly, taking into account the recommendations for action from the S3 guideline "Treatment of depressive disorders in children and adolescents" [6]. In the oral discussion, the authors explained that the objectives of HTA reports differ from those of guidelines. In addition, conclusions were to be drawn only on the basis of the available evidence, rather than adopting recommendations for action from guidelines which are based in part or in full on the opinions of clinical experts.

What's the next step?

Due to the high disease burden for individuals and their families and the psychological consequences of untreated depression, initial depressive symptoms in children and adolescents should be diagnostically evaluated and, where a diagnosis is established, treated at an early time. Therefore, it seems all the more important for low-threshold services to be available as initial contact points as well as for sufficient therapy slots to exist for patients in this age group.

The HTA report shows that cognitive behavioural therapy and interpersonal psychotherapy can alleviate depressive symptoms in children and adolescents. On the basis of the available literature, however, no conclusion can be drawn as to their effectiveness in patients with various severities of depression or patients of different age groups. The available evidence on psychodynamic psychotherapy is insufficient for drawing a definitive conclusion on effectiveness. When comparing psychotherapy versus antidepressants, there is no evidence of one of the therapies being more effective than the other. However, patients' individual preferences play an important role in the choice of therapies.

Overall, there is a need for studies of informative value in the German healthcare context. In particular, studies are lacking in psychodynamic psychotherapy as well as in the population of preschool children. Generally, studies should investigate health-related quality of life and adverse events as well as analyse and present results separately by age and severity of depression. Furthermore, longer-term follow-up periods are needed, particularly to more reliably assess the risk of relapse.

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HTA key statements

Research question of the HTA report

The aims of this investigation are to

assess the benefit of psychotherapy (behavioural therapy, psychodynamic psychotherapy [depth psychology-based therapy, analytical psychotherapy], interpersonal psychotherapy) in comparison with active monitoring, antidepressant treatment, treatment with other non-drug interventions (e.g. relaxation exercises), or no treatment (e.g. waiting list) in children and adolescents with depression with regard to patient-relevant outcomes,

determine (intervention) costs arising in psychotherapy in comparison with active monitoring, antidepressant treatment, treatment with other non-drug interventions (e.g. relaxation exercises), or no treatment (e.g. waiting list) in children and adolescents with depression,

assess the cost effectiveness of psychotherapy in comparison with active monitoring, antidepressant treatment, treatment with other non-drug interventions (e.g. relaxation exercises), or no treatment (e.g. waiting list) in children and adolescents with depression as well as

review ethical, social, legal, and organizational aspects associated with the medical intervention.

Conclusion of the HTA report

Regarding the effectiveness and safety of psychotherapy in children and adolescents with depression, 13 systematic reviews with data from 150 primary studies were included in the present report. Six systematic reviews investigated cognitive behavioural therapy, 2 focused on interpersonal psychotherapy, 3 investigated both types of psychotherapy, and 2 focused on cognitive behavioural therapy, interpersonal psychotherapy as well as psychodynamic psychotherapy (short-term psychoanalytical psychotherapy and focused psychodynamic psychotherapy). Systematic reviews on systemic therapy were disregarded in this health technology assessment (HTA) report because it is covered by another project by the Institute for Quality and Efficiency in Health Care (IQWiG), which will be commissioned shortly. Nine systematic reviews looked at the evidence available for children and adolescents jointly. Two systematic reviews focused only on children (7–13 years) and 2 only on adolescents (13–18 years). The psychotherapies included in the systematic reviews varied in duration between 4 and 54 weeks, and the number of sessions ranged from 4 to 36 units. The investigated psychotherapies took place in outpatient settings, in schools, communities, or primary care.

The psychotherapy types were analysed for effectiveness compared to inactive controls or antidepressants, or as add-ons to antidepressants. Inactive control was defined as an approach without standardized treatment (e.g. waiting list or "usual care" in which the control group is, for ethical reasons, free to utilize services from routine care) or the use of sham treatment (psychological placebo). No ongoing systematic reviews were identified. No data were found on the outcomes of all-cause or suicide mortality, health-related quality of life, or adverse events. Likewise, no evidence was found for a comparison with other non-drug therapies (e.g. exercise, relaxation exercises) or active monitoring (e.g. mental health education). In this HTA report, benefit was assessed on the basis of systematic reviews, whose reporting quality heavily impacts the result. For instance, the publications typically did not carry out subgroup analyses by patient age or depression severity. No conclusions can consequently be drawn on the benefit or harm of psychotherapy for certain subgroups (e.g. children or adolescents with mild depression).

Below, the results on the reported outcomes are summarized for each comparison. To the extent reported in the systematic reviews, the time when the outcome was surveyed is provided by categorizing the follow-up as 12 to 16 weeks (short term), about 6 months (medium term), and 12 months or more (long term).

Cognitive behavioural therapy versus inactive controls: There is an indication of cognitive behavioural therapy reducing depressive symptoms more effectively than inactive controls. The comparison shows no hint of cognitive behavioural therapy increasing or reducing suicide risk. The systematic reviews did not show whether these effects are short-term, medium-term, or long-term effects. For this comparison, no data are available regarding the outcomes of response, remission, or functioning.

Cognitive behavioural therapy versus antidepressants: When compared with antidepressant treatment, there is no hint of cognitive behavioural therapy reducing suicide risk. Likewise, the comparison shows no hint of cognitive behavioural therapy or antidepressant therapy more commonly leading to short-term or medium-term remission, reduction of depressive symptoms, or better functioning. For this comparison, no data are available on the outcome of response.

Cognitive behavioural therapy + antidepressants versus antidepressants: No hint of greater benefit was found regarding short-term or long-term treatment response for the combination of cognitive behavioural therapy and antidepressants in comparison with antidepressant monotherapy. Likewise, there is no hint of greater benefit with regard to short-term, medium-term, or long-term remission, changes in depressive symptoms, or short-term or long-term suicide risk. With regard to functioning, a hint of greater benefit of add-on behavioural therapy was found in the long term, but not in the short or medium term.

Interpersonal psychotherapy versus inactive controls: In comparison with inactive controls, there is a hint of short-term, medium-term, and long-term benefit with regard to the reduction of depressive symptoms as well as a short-term benefit with regard to functioning. However, there is no hint of interpersonal psychotherapy increasing or decreasing suicide risk in the short term. The data on treatment response were disregarded in the derivation of added benefit since all studies were also included in the "changes in depressive symptoms" study pool, and response was surveyed using the same scales. Regarding the outcome of remission, no data are available for this comparison.

Interpersonal psychotherapy versus antidepressants: Compared with antidepressant treatment, there is no hint of greater or lesser benefit with regard to changes in depressive symptoms. No data were available on the time the outcome was surveyed. Likewise, this comparison lacks data on the outcomes of suicide risk, response, remission, and functioning.

Interpersonal psychotherapy + antidepressants versus antidepressants: No data are available on the combination of interpersonal psychotherapy plus antidepressants versus antidepressant monotherapy.

Psychodynamic psychotherapy versus inactive controls: In comparison with inactive controls, there is no hint of greater or lesser benefit with regard to reduction in depressive symptoms. There is also no hint of psychodynamic psychotherapy increasing or reducing suicide risk when compared with inactive controls. For this comparison, data were available neither on the time of outcome measurement nor on the outcomes of response, remission, and functioning.

Psychodynamic psychotherapy versus antidepressants: In comparison with antidepressant treatment, there is no hint of greater or lesser benefit with regard to reduction in depressive symptoms. No data were available on the time the outcome was surveyed. For this comparison, there is a lack of data regarding the outcomes of suicide risk, response, remission, and functioning.

Psychodynamic psychotherapy + antidepressants versus antidepressants: No data are available for a comparison of psychodynamic psychotherapy in combination with antidepressants versus antidepressant monotherapy.

Psychotherapy in general versus inactive controls: One systematic review analysed different types of psychotherapy together, comparing them with inactive controls. For the outcome of changes in depressive symptoms, it showed an indication of short-term benefit, but no medium-term or long-term benefit, of psychotherapy in general. For this comparison, no data are available regarding the outcomes of suicide risk, response, remission, or functioning.

The calculation of intervention costs for the German healthcare context shows that psychotherapy incurs higher direct costs than do treatment alternatives. Short-term one-on-

one psychotherapy costs between € 1793 and € 2105 for a time period of 12 weeks. While the cost of cognitive behavioural therapy and psychodynamic psychotherapy (short-term psychoanalytical psychotherapy and focused psychodynamic psychotherapy) is covered by health insurance funds, interpersonal therapy is not governed by clear legal provisions. According to service providers, however, qualified professionals have been able to bill interpersonal psychotherapy practised thus far as a behavioural therapeutic method (in some cases also as psychodynamic therapy). In addition, some large health insurance funds have included interpersonal psychotherapy in their selective contracts. Treatment with the antidepressant fluoxetine – the only antidepressant approved in Germany for children 8 years and above – costs between € 311 and € 319 for 8 weeks of therapy. Mental health education – a form of active monitoring – costs € 305 to € 660. Six to 8 weeks of relaxation therapy costs € 349 to € 411. However, these figures do not include the diverse (long-term) consequential costs of untreated depression (e.g. lower income in adulthood).

Regarding cost effectiveness, 5 studies from the United States and the United Kingdom were found, all of which investigated cognitive behavioural therapy. Due to excessive differences between the systems, the results cannot be directly adapted to the German healthcare context.

Diagnosing depression in children and adolescents represents a social, ethical, and organizational challenge because other symptoms and comorbidities often overlap with the symptoms of the disorder, and depressive symptoms are frequently misinterpreted as typical adolescent behaviour. Further reasons for people with mental health issues not utilizing professional help include uncertainty whether the health problem is serious enough, worries about potential stigmatization, lack of knowledge about contact points and treatment options as well as a lack of services. In Germany, more services for children and adolescents with depression are available in urban than in rural areas, and the service networks are denser in the west than in the east.

Many children, adolescents, and parents accept psychotherapy as a treatment option and perceive it as being associated with fewer side effects than antidepressants. The objective of psychotherapy is to strengthen the child’s or adolescent’s autonomy and self-esteem. Therefore, obtaining the minor’s consent already at the start of therapy is an ethical and legal necessity. Voluntary participation and a good, trusting patient-therapist relationship are important for long-term therapy. From an ethical and legal perspective, healthcare professionals’ duty of confidentiality can lead to conflicts between the obligation of secrecy and duties to inform parents or guardians.

Overall conclusion across domains

The general question of whether psychotherapy leads to better results than other therapies in children and adolescents with depression can be answered to some degree. Both for cognitive behavioural therapy and interpersonal psychotherapy, indications of benefit were found in comparison with no active treatment. Due to limited available evidence, no conclusion can currently be drawn on the question of whether psychodynamic psychotherapy is associated with any benefit or harm. This is due to the fact that the results concerning this question are from individual studies from network metaanalyses and are available only for the outcomes of suicide risk and change in depressive symptoms. In future, further research on this type of psychotherapy in children and adolescents would be needed to draw valid conclusions on effectiveness and safety. Concerning the comparison between cognitive behavioural therapy or interpersonal psychotherapy versus antidepressants, no hint of greater or lesser benefit was derived. However, patients perceive psychotherapy as being associated with fewer side effects than antidepressants. Only cognitive behavioural therapy was investigated as an add-on to antidepressant treatment; while it led to better functioning in the long term, it was not associated with any other added benefit. None of the included systematic reviews reported on the effects of psychotherapy on mortality, health-related quality of life, and adverse events, making it virtually impossible to weigh the benefit versus harm of psychotherapy in children and adolescents with depression. Since the systematic reviews did not distinguish between mild, moderate, and severe forms of depression, the chosen method, umbrella review, does not allow drawing separate conclusions on the treatment, broken down by severity of depression.

The calculation of short-term intervention costs for the German healthcare context shows that higher direct costs result from psychotherapy than from treatment alternatives. From a patient perspective, this is a less relevant issue, however, since the costs – at least for guideline therapies – are covered by the SHI funds. While health economic analyses which include the treatments' long-term costs as well as short-term and long-term benefit and harm were found for English-speaking countries, their results cannot be adapted to the framework conditions in Germany due to the difference in healthcare systems.

In addition, it should be noted that most systematic reviews analyse children and adolescents together. A separate analysis would have been desirable because children and adolescents differ in their neurobiology and risk factors. Evidence regarding the effectiveness of cognitive, interpersonal, and psychodynamic psychotherapy is completely lacking, particularly for children up to 8 years of age and is insufficient up to age 12 years. For this age group, additional studies with a sufficiently sized sample would be desirable to examine the effectiveness of the different types of psychotherapy in comparison with a waiting list control group. For adolescents as well as children, it would be desirable for studies to increasingly focus on the outcomes of health-related quality of life, functioning, and adverse events as

well. Likewise, it would be helpful to carry out randomized controlled trials in Germany since this study design is best suited for identifying cause-effect relationships, and data of this type are currently lacking for the Germany healthcare context. Long-term follow-up would be important as well. The establishment of a national registry could provide relevant data for this purpose in the long term.

Particularly in view of the limited evidence available on severity of depression and insufficient reporting on adverse events, it is all the more important to select therapies taking into account the expertise of treating psychotherapists or physicians as well as the needs and preferences of affected children and adolescents regarding the available treatment options. Since untreated depressive disorders can have substantial long-term consequences for the affected people, their environment, and society, even mild depressive symptoms persisting for a longer period should be diagnostically clarified by professionals who are adequately qualified to correctly diagnose and treat depression. Because the general public's awareness of treatment options is often limited, contacts within the healthcare system (e.g. general practitioners) as well as in children's and adolescents' social environment (e.g. teachers) should assist patients and their families in contacting qualified professionals.

Options for increasing the availability of services, e.g. in often underserved rural areas, include expanding locally available psychotherapeutic services and increasing the use of online psychotherapy services by psychotherapists. In addition, it is important to improve the image of mental disorders and the utilization of treatment options, e.g. through image campaigns in (social) media.

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List of abbreviations

Abbreviation	Meaning
AD	antidepressant
ADAPT	Adolescent Depression Antidepressant and Psychotherapy Trial
APT	analytical psychotherapy
BGH	Bundesgerichtshof (Federal Court of Justice)
BT	behavioural therapy
CBT	cognitive behavioural therapy
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	confidence interval
DGKJP	Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie e.V. (German Association for Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy)
DP	depth psychology-based psychotherapy
DYN	psychodynamic psychotherapy
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	health technology assessment
ICD	International Classification of Diseases
IPT	interpersonal psychotherapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (German Health Interview and Examination Survey for Children and Adolescents)
MD	mean difference
MPC	Model Professional Code of Conduct
NMA	network metaanalysis
OR	odds ratio
QALY	quality-adjusted life years
RCT	randomized controlled trial
RX	drug switch
SHI	statutory health insurance
SMD	standardized mean difference

Abbreviation	Meaning
SSRI	selective serotonin reuptake inhibitor
TADS	Treatment for Adolescents with Depression Study

HTA overview

1 Background

1.1 Health policy background and commission

According to § 139b (5) Social Code Book V, Statutory Health Insurance, statutory health insurance members and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these health technology assessment (HTA) reports can be submitted on the ThemenCheck Medizin ("topic check medicine") website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and answer questions which are particularly relevant in patient care.

Once yearly, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which HTA reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts and a publisher's comment by IQWiG are then published in the form of an HTA report.

IQWiG disseminates HTA reports to German institutions, for instance, those deciding about healthcare services and structures. The HTA report will be made available to the professional community through the IQWiG website (www.iqwig.de). In addition, a lay summary of the results of the HTA report will be published under the title "HTA compact: The most important points clearly explained". This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

1.2.1 Definition and epidemiology

The diagnostic criteria for a depressive episode are met when patients exhibit at least 2 of the 3 following core symptoms for at least 2 weeks: marked, persistent depressed mood, loss of joy, desire, and interests (anhedonia) as well as avolition. (according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification; ICD-10-GM, version 2020 [1]). Further, the following secondary criteria characterize the clinical image of depression: low self-confidence, low self-esteem, self-blame, guilt, suicidal ideation and behaviour, difficulties concentrating and making decisions, psychomotor agitation or inhibition, sleep problems as well as reduced or increased appetite [2]. With regard to severity, the ICD-10 classification distinguishes between mild, moderate, and severe depressive episodes with(out) symptoms. In mild depressive episodes (F32.0), at least 2 of the above 3 core symptoms and at least 2 secondary criteria are observed.

However, the child or adolescent is able to continue everyday activities. In moderate depressive episodes (F32.1), the patient exhibits at least 2 core symptoms and at least 3 (or better 4) of the above-mentioned secondary criteria. The patient's daily life is already substantially impacted. For diagnosing a severe depressive episode without psychotic symptoms (F32.2), all 3 core symptoms and at least 8 secondary criteria should be met. Patients with a severe depressive episode typically experience a substantial reduction in self-esteem and strong feelings of guilt as well as suicidal ideation accompanied by somatic symptoms. If patients additionally exhibit hallucinations, delusions, pronounced psychomotor retardation, or stupor (complete loss of activity in an awake, conscious state), they are in a severe depressive episode with psychotic symptoms (F32.3). Recurrent depressive disorder (F33) is characterized by repeated episodes of depression, where the first episode may occur at any age and the episode duration varies from a few weeks to several months. The current episode can be classified by severity as mild (F33.1), moderate (F33.2), severe without psychotic syndromes (F33.2), or severe with psychotic symptoms (F33.3) [3].

Depressive disorder must be distinguished, among others, from 2 other disorders: if manic episodes are observed between the episodes of depression, the patient suffers from bipolar affective disorder (F31). Dysthymia (F34.1) is characterized by chronic depression of mood lasting at least several years which is not sufficiently severe, or in which individual episodes are not sufficiently prolonged, to justify a diagnosis of mild recurrent depressive disorder (F33.1) [1].

The manifestation of depressive disorder in adolescence has already been well researched; its symptoms are the same as those listed for depression in general. Children, on the other hand, predominantly exhibit somatic symptoms such as headache and stomach aches. Often, symptoms overlap with anxiety and social insecurity [4].

In adults, alongside headache, neck pain, and lower back pain, depressive disorders represent the most common contributor to impaired health and quality of life worldwide [5]. According to estimates by the 2017 Global Burden of Disease Study, about 264 million persons 15 years or older worldwide are affected by depressive disorders [5,6]. The 2015 Global Burden of Disease Study shows that, worldwide, 4.4% of the population age 15 or above suffer from depressive disorder [7]. Women are affected more commonly than men (5.1% versus 3.6%). Children and adolescents under the age of 15 years exhibit depressive disorders less commonly than people in other age groups. The international prevalence equals 2.6% for children and adolescents (95% confidence interval [CI]: [1.7; 3.9]); these figures are based on a systematic review of 23 studies with 59 492 children and adolescents worldwide whose psychological health was examined in representative population surveys [8]. The prevalence of depressive disorder is lower in children (< 1% in most studies) than in adolescents (4% to 5%) [9]. During childhood, no differences are found between sexes, but after puberty,

depressive disorders are diagnosed twice as often in girls as in boys [9]. Based on data from a survey on mental health, behaviour, and health-related quality of life carried out in Germany (BELLA study), 11.2% of children and adolescents exhibited clinically relevant signs of depression according to the parental survey (7 to 11 year olds) and 16.1% in the self-report (11 to 19 year olds) [10]. The higher prevalence found in the German study when compared to the systematic review is likely due to depressive symptoms not being equivalent to a diagnosed depressive disorder and the evaluation not being performed by qualified professionals.

1.2.2 Causes and course of disease

Since individual, familial, social, and biological risk factors are interrelated and influence one another, the specific contribution of individual risk factors to the development of depression cannot be determined [4,9]. Compared with children of nondepressed parents, children whose parents have a depressive disorder are at 3 to 4 times higher risk of developing depression. In addition to genetic predisposition, however, vulnerable attachment to the child as a result of depression plays an essential role [2]. Critical life events such as the death of a close relative, environmental catastrophes, longer-term burdens such as physical disorders or psychosocial aspects such as neglect, maltreatment, or abuse likewise increase the risk of developing a depressive disorder [9].

Up to 90% of children and adolescents who are treated for a depressive episode recover within 1 to 2 years [4]. However, 45% to 75% of children and adolescents who recover from a depressive episode experience a relapse within 5 years [4,11]. Adolescents who suffer from a depressive disorder are at higher risk of developing anxiety, substance abuse, and bipolar affective disorder as adults [9].

1.2.3 Diagnostics and treatment

The diagnostic workup typically includes a medical history as reported by the patient, including the topics of family, development, and school experiences, a medical history on the basis of information provided by relatives, a family history, an analysis of the social environment, a clinical interview as well as a self-assessment and a third-party assessment, often obtained with the aid of standardized written questionnaires. For purposes of a differential diagnosis, both a physical examination and a survey of drug and medication use are recommended [3]. As part of the diagnostic workup, anxiety, attention deficit hyperactivity disorders, eating disorders, and obsessive-compulsive disorder should additionally be ruled out. The diagnostic workup should be performed only by trained professionals [12].

For the treatment of depressive disorders in children and adolescents between the ages of 3 and 18 years, an S3 guideline has been issued in 2013 by the German Association for Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy (DGKJP) [12]. However, this

S3 guideline expired on 1 July 2018 and is currently being revised. Given the current lack of more recent German recommendations, the contents of this S3 guideline are nevertheless used below.

The treatment strategy should be chosen based on episode severity, the extent of preserved functioning in daily life as well as family and individual resources [3]. In case of mild depressive episodes, the DGKJP S3 guideline [12] recommends active monitoring as well as measures to promote mental health, i.e. active support, consultation, or mental health education for a time period of 6 to 8 weeks. Only if symptoms persist should further interventions be planned. Active monitoring is recommended only in the absence of any relevant burden or signs of deterioration. The child or adolescent must be fully capable of managing daily life in an age-appropriate way.

For children under 8 years of age, no recommendation can be made due to a lack of evidence. As the first-choice treatment in older children and adolescents with mild depressive episodes and additional burdens as well as those with moderate or severe depressive episodes, the S3 guideline recommends psychotherapy (cognitive behavioural therapy or interpersonal psychotherapy), the drug fluoxetine, or a combination of both. Psychotherapy is to be preferred over psychopharmacotherapy since the latter can be associated with a risk of intensified suicidal thoughts and other adverse effects. A separate opinion states that adolescents with depressive disorder should receive psychotherapy and that pharmacotherapy is recommended as the second-choice therapy. In severe depressive episodes, the advantages and disadvantages of combination therapy versus psychotherapy alone must be weighed. In cases where the 2 above-mentioned types of psychotherapy cannot be used, the S3 guideline alternatively recommends psychodynamic or systemic psychotherapy as the first-choice treatment. According to the S3 guideline, alternatives to fluoxetine are the drugs escitalopram, citalopram, or sertraline, albeit in “off-label use” since they are not approved for children and adolescents in Germany. Treatment can typically be provided on an outpatient basis. Semi-inpatient or inpatient care should be initiated under the following conditions: suicidality without support by relevant attachment figures, substantial psychosocial burdens, or impaired functioning [12].

Psychotherapy

All psychotherapy types listed as first-choice therapies in the DGKJP S3 guideline [12] are briefly described below. **Cognitive behavioural therapy** (CBT) is based on empirical psychology and integrates diverse treatment elements: patient information about the symptoms and causes of depressive disorder, promotion of social competencies, enhancement of positive activities, and cognitive restructuring. CBT aims to change patterns of behaviour and thought and to enable children and adolescents to control negative

feelings [4]. According to the Guidelines for Psychotherapy published by the Federal Joint Committee (G-BA), the German health insurance funds cover the cost of CBT [13].

Interpersonal psychotherapy (IPT), a short-term therapy, is based on the assumption that dysfunctional relationships and interpersonal problems contribute to the development and persistence of depressive disorders in adolescents. Therefore, IPT focuses on social isolation as well as role conflicts and promotes positive social behaviours [4]. The DGKJP S3 guideline recommends IPT since international studies confirm its effectiveness, but it points out that IPT has not been approved as guideline procedure by the G-BA and no qualification standards have been established [12].

Psychodynamic psychotherapy types (DYN) include depth psychology-based psychotherapy (DP) as well as analytical psychotherapy (APT). DYN emphasizes the importance of the unconscious and instincts in individual behaviour and uses the concept of transference: past experiences are projected onto the therapist so that the experienced conflicts can be processed during therapy [14]. This intervention is recognized in Germany, and its cost is covered by the health insurance funds [13].

Systemic therapy, which includes family therapy, focuses on the social context of mental illnesses. The therapeutic work includes not only the affected children and adolescents, but also important individuals in the relevant social system. Therapy focuses on cognitive emotional, physical as well as interpersonal problems and available resources [12]. This HTA report disregards systemic therapy because it is the topic of a different IQWiG report which is about to be commissioned [15].

The DGKJP S3 guideline [12] does not state the recommended session frequency or duration for the various psychotherapy types. Treatment can be terminated after children and adolescents have not exhibited any clinically relevant symptoms for at least 2 months. According to an open recommendation, however, follow-up appointments should be offered for a period of 12 months. Another relevant aspect in this context is that different psychotherapy session allotments require specific approval steps from the health insurance funds [16].

Antidepressants

In Germany, fluoxetine is currently the only drug approved for the treatment of depressive disorders in children 8 years and older [17]. It is a selective serotonin reuptake inhibitor (SSRI). SSRIs block serotonin transport proteins in the brain and prevent the reuptake of serotonin from the synaptic gap, thereby increasing the concentration of serotonin in the brain. At the start of treatment, the DGKJP guideline [12] recommends a dosage of 10 mg/day; after 1 week, it can be increased to 20 mg/day if clinically necessary. Since the drug's energizing effect also increases the risk of self-harm behaviours and suicidal thoughts, it should be taken

in the morning and the dosage increased slowly. Often, children and adolescents respond to this treatment only after about 2 to 4 weeks. The side effects prevailing during this period often prompt a patient's wish to discontinue treatment. During this phase, it is critical to advise patients to continue therapy [17]. Based on 10 studies, a network metaanalysis (NMA) [18] showed that fluoxetine more effectively reduces depressive symptoms than a placebo (standardized mean difference [SMD] - 0.51; 95% CI: [- 0.99; - 0.03]). In comparison with placebo, patients taking fluoxetine more commonly exhibited side effects such as headache, diarrhoea, somnolence, sleeplessness, emotional instability, mania, and hypomania [19].

Children or adolescents who have been free from clinically relevant symptoms for at least 2 months should continue to receive treatment for at least 6 more months according to the DGKJP S3 guideline [12]. Thereafter, discontinuation of the psychopharmacological treatment can be considered.

In Germany, no other second-generation SSRIs (escitalopram, citalopram, sertraline) are approved for the treatment of children and adolescents. Due to their shorter half-life and hence easier control, however, these drugs are in off-label use in clinical practice [17].

Active monitoring and measures for promoting mental health

Active monitoring includes **consultation and information** (mental health education) about the depressive disorder to help patients and their family members understand information about the disorder and treatment measures. Its objective is for patients to adopt potential self-help strategies and utilize treatment where necessary. Mental health education is not an "independent" treatment method such as psychotherapy but a component of the overall psychological intervention. Mental health education can also be viewed as an active monitoring measure. Mental health education is based on behavioural therapy (BT), with several modern variations also including elements of talk therapy. Objectives of mental health education include improving the understanding and management of the disorder and hence achieving emotional relief for patients and their relatives. In addition, mental health education is intended to contribute to better adherence to any administered therapies [20].

According to the DGKJP S3 guideline [12], in mild depressive disorder without additional burdens, active monitoring for a period of 6 to 8 weeks can be sufficient – provided that patients are able to manage their daily lives in an age-appropriate manner. In addition, **measures to improve mental health** should be offered, such as mindfulness exercises, participation in structured exercise such as running, aerobic, or strength training, and relaxation exercises such as Jacobson's Relaxation Technique [21]. The health economic part of this HTA report uses progressive muscle relaxation as an example to calculate intervention costs for non-drug interventions. Muscle relaxation is based on the observation that experiencing stress and anxiety is associated with increased muscle tone, while relaxation is

associated with lower muscle tone. In this treatment, patients first briefly tense individual muscle groups and then relax them in a stepwise (progressive) manner. Attention remains on the respective muscle group before the next muscle group is tensed.

1.3 Health services situation

In Germany, children and adolescents with mental health issues rarely seek help. Data from the baseline study of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) show that only 11.8% of children and adolescents classified as borderline symptomatic and 18.6% of those classified as symptomatic seek help for their mental health (from psychiatrists, psychologists, youth welfare services) [22]. Even among minors whose parents explicitly reported them to have been diagnosed with a mental disorder, only about half received psychological, psychotherapeutic, or psychiatric treatment [23]. In the second KiGGS survey round from 2014 through 2017, a total of 3.8% of parents of children between 0 and 17 years of age in the overall population reported visiting a practice for psychiatry or child and adolescent psychiatry, while 2.5% reported utilizing psychotherapy for their children. Persons of low sociooeconomic status were 2 times more likely to seek help from a psychiatrist than those of higher sociooeconomic status [24]. Children and adolescents from western German states are less commonly treated than those from eastern German states. In addition, individuals residing in towns with higher populations were more likely to utilize psychosocial services [25].

For insured children and adolescents with depressive episodes and recurrent depressive disorder, statutory health insurance (SHI) funds cover the cost of psychotherapy – the types being defined in the G-BA's Guidelines for Psychotherapy [13]. For instance, costs are reimbursed for behavioural therapy as well as psychodynamic psychotherapy services such as DP and APT. For DP or APT, up to 150 hours of one-on-one therapy for children or up to 180 hours for adolescents or 90 double-hour sessions of group therapy can be approved; for behavioural therapy, the maximum is 80 hours of one-on-one or group therapy for children and adolescents. SHI funds cover the cost of systemic therapy only for adults. Regarding IPT, G-BA guideline procedures do not provide for cost reimbursement by SHI funds [13]. According to the agreement on psychotherapy provided in contractual care (Psychotherapy Agreement [26]), these types of therapy can be performed by the following professionals: physicians specializing in psychiatry and psychotherapy, physicians specializing in child and adolescent psychiatry and psychotherapy, psychological psychotherapists as well as child and adolescent psychotherapists and therapists with appropriate qualifications.

1.4 Concerns of those proposing the topic

A member of the public asked whether, in children and adolescents with initial depressive symptoms, a wait-and-see approach is preferable to psychotherapy or pharmacological therapy. Particularly since increasing numbers of depressive episodes are diagnosed in

children and adolescents and these symptoms are difficult to differentiate from (pre)pubescent symptoms, the member of the public was interested in the comparison of psychotherapy versus no therapy.

The *ThemenCheck Medizin* staff at IQWiG developed the following HTA research question on the basis of this suggestion. The focus was not on the comparison of pharmacological therapy versus no therapy because *ThemenCheck Medizin* does not cover the safety and effectiveness of drug therapies. Nevertheless, drug therapy was included as a comparator intervention for psychotherapy.

2 Research questions

The aims of this investigation are to

- assess the benefit of psychotherapy (behavioural therapy, psychodynamic psychotherapy [depth psychology-based therapy, analytical psychotherapy], interpersonal psychotherapy) in comparison with active monitoring, antidepressant treatment, treatment with other non-drug interventions (e.g. relaxation exercises), or no treatment (e.g. waiting list) in children and adolescents with depression with regard to patient-relevant outcomes,
- determine (intervention) costs arising in psychotherapy in comparison with active monitoring, antidepressant treatment, treatment with other non-drug interventions (e.g. relaxation exercises), or no treatment (e.g. waiting list) in children and adolescents with depression,
- assess the cost effectiveness of psychotherapy in comparison with active monitoring, antidepressant treatment, treatment with other non-drug interventions (e.g. relaxation exercises), or no treatment (e.g. waiting list) in children and adolescents with depression as well as
- review ethical, social, legal, and organizational aspects associated with the medical intervention.

3 Methods

3.1 Methods – benefit assessment

The target population of the benefit assessment was children and adolescents (≤ 18 years) with diagnosed depression. This report does not focus on children and adolescents suffering from dysthymia or other affective disorders (e.g. bipolar affective disorder) or mental disorders. Likewise excluded were children and adolescents who, according to the authors of the systematic review, suffered from treatment-resistant depression or in whom depression was a comorbidity of an underlying somatic disorder (e.g. thyroid dysfunction, cancer) or those with a special form of depression (perinatal/postnatal depression in adolescent girls). The experimental intervention was psychotherapy either as monotherapy or as an add-on to antidepressant treatment. The focus was on cognitive behavioural therapy, interpersonal psychotherapy, and psychodynamic psychotherapy, which includes depth psychology-based therapy and analytical psychotherapy. Computerized cognitive behavioural therapy (cCBT) was included as well, provided it involved qualified professionals. Inactive control interventions included sham treatment (psychological placebo), no treatment, waiting list, or usual care.

Patients on the waiting list or on usual care typically receive no interventions during the study, but for ethical reasons, they are not prevented from utilizing routine healthcare services. For psychological placebo, sham therapy is performed, e.g. in the form of conversations. This does not correspond to any recognized type of psychotherapy, however, and can therefore not be deemed active therapy. Other possible comparator interventions were treatment with antidepressants (AD), with other non-drug interventions (e.g. relaxation exercises or exercise) as well as active monitoring (mental health education).

The following patient-relevant outcomes were included in the assessment:

- Mortality (all-cause mortality, suicide mortality)
- Morbidity
  - suicidal ideation and behaviour
  - Response
  - Remission of depression
  - Change in depressive symptoms
  - Functioning (social, cognitive, mental, physical)
- Health-related quality of life
- Adverse events

Due to their major importance, suicidal ideation and behaviour were defined as a separate outcome despite these aspects also being surveyed as an item on many scales for depressive symptoms.

In addition to the above-mentioned patient-relevant outcomes, treatment acceptance was analysed using the outcome of patient satisfaction.

The benefit assessment was informed by systematic reviews of randomized controlled trials in German or English language, provided that the systematic reviews were published in 2010 or later and used adequate methodologies (Oxman-Guyatt index ≥ 5). No restrictions were in place regarding study duration of the included randomized controlled trials (RCTs).

A systematic literature search for systematic reviews was carried out in the databases MEDLINE (which includes the Cochrane Database of Systematic Reviews), Embase, and HTA Database. The following sources of information and search techniques were additionally used: search in PROSPERO (registry for systematic reviews), contacting of authors of relevant systematic reviews registered in PROSPERO but not published; viewing of reference lists of identified systematic reviews and overviews of reviews; search on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ). Any additional relevant documents identified during the commenting procedure for the preliminary HTA were to be taken into account before the finalization of the report.

Relevant systematic reviews were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. One person extracted the data into standardized tables, and another person reviewed them. The qualitative certainty of results was assessed based on the risk of bias of the primary studies as reported in the systematic reviews. Additionally, the methodological quality of the systematic reviews was assessed by 2 persons independently from each other by means of the Oxman-Guyatt index. Rather than metaanalyses, a narrative summary was generated because the systematic reviews were insufficiently comparable with regard to their research question and relevant characteristics. The results description of the systematic reviews was organized by outcomes and type of psychotherapy. In cases where systematic reviews used several depression scales to report results on the same outcome, the data from the scale most commonly used across all systematic reviews were chosen. If data were available on both third-party and self-assessment, both were extracted. Based on the systematic reviews' presentation of results, subgroup results were reported for children and adolescents, for psychotherapy with and without parental involvement, and for follow-up durations. A 12-to-16-week follow-up (short term) was distinguished from follow-ups of about 6 months (medium term) and 12 months or more (long term). It was not possible to analyse subgroups by severity of depression, patient sex, or psychosocial aspects.

The assessment of the primary studies' risk of bias was adopted from the systematic reviews. Where the same study was rated differently by different systematic reviews, a cautious approach was taken, using the assessment with the highest risk of bias in this HTA.

Pooled effect estimators from metaanalyses were adopted if 80% of included patients met the above inclusion criteria. Otherwise, the results from the appropriate individual studies were narratively extracted. However, exceptions applied to NMAs and large metaanalyses, from which pooled effect estimators were extracted even if fewer than 80% of patients taken into account met the inclusion criteria since similarity was assumed and deviations were minimal.

For each outcome, a conclusion was drawn regarding evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or none of the above. The latter was the case if no data were available, or the available data did not permit classification into one of the other categories. In that case, no hint of (greater) benefit or (greater) harm was derived. Where results of a systematic review or results from individual studies were available for a comparison and outcome, evidence was derived based on the standardized IQWiG guidelines. Where multiple systematic reviews reported on the same outcome and comparison, it was first checked whether the results are in the same direction. If so, the data were synthesized into a narrative summary. Otherwise, priority was given to results from systematic reviews with higher quality ratings. Whenever the ratings were equal, priority was given to the results which were based on the most RCTs, reported direct comparisons or results from pairwise metaanalyses from the NMAs, and had a current search date. Since the individual studies in all systematic reviews tended to have a high risk of bias, no prioritization was possible on this basis.

3.2 Methods – health economic assessment

3.2.1 Intervention costs

To calculate intervention costs, the average resources used when performing the experimental and comparator interventions were determined. Services directly associated with performing the interventions were taken into account as well. Wherever possible and available, the relevant regulated or negotiated prices of these services were used. For any services not subject to clear regulations or price negotiations whose costs were impossible to determine via database searches, queries were sent to service providers. Potential individual circumstances and their associated costs were presented only in a rudimentary fashion, e.g. in the form of different drug dosages. The costs of the initial diagnosis of depression (F32 or F33 according to ICD-10) were disregarded, and reimbursable and non-reimbursable costs listed separately.

3.2.2 Cost effectiveness

To assess health economic aspects, a systematic search was carried out for comparative studies – i.e. cost-effectiveness/efficacy analyses, cost-utility analyses, or cost-benefit analyses – in English and German [27]. Cost effectiveness studies were restricted to studies from Germany, high-income countries as defined by the World Bank [28] (gross national income per capita of USD 12 376 or about €11 255 or more) as well as to countries whose healthcare system is similar to the one in Germany. Results of health economic studies from these countries are expected to be more adaptable to Germany.

As part of the focused information retrieval, the databases Embase, HTA database, and MEDLINE were searched. Two persons viewed relevant articles on the cost effectiveness of psychotherapy in children and adolescents. Systematic reviews and HTAs were used as supplementary sources. Any other relevant documents identified during the commenting procedure for the preliminary HTA report were to also be taken into account before the report was finalized.

One person extracted the data from the included studies into standardized tables, and another person reviewed them. For all included health economic studies, an assessment was conducted of reporting quality and methodical quality on the basis of the criteria of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [29], and the adaptation of results was assessed based on the criteria of the HTA Adaptation Toolkit from the European network for Health Technology Assessment (EUnetHTA) [30] (see 5.2.4). The HTA report comparatively describes the results regarding cost effectiveness as reported in the studies as well as the authors' conclusions.

3.3 Methods – ethical aspects

Based on the overarching questions from the simplified questionnaire according to Hofmann et al. 2014 [31], the information on ethical aspects was analysed in terms of social and moral norms and values related to psychotherapy and depression in children and adolescents. In addition, the authors of the report applied the reflective thoughts method, i.e. they reflected on potential ethical aspects based on their own knowledge [32].

The scoping search was performed using the information sources of Belit, CINAHL, EthxWeb, ETHICSWEB, MEDLINE, PsycINFO, and Scopus. In addition, the studies included for the benefit and economic assessment as well as websites of interest groups and the documented expert interviews were consulted.

One person viewed information from all sources identified in the searches for conclusions on ethical arguments and aspects of the intervention to be investigated, extracted them into standardized tables, and also provided a narrative. A 2nd person assured the quality of the result.

3.4 Methods – social, legal, and organizational aspects

For the analysis of **social and organizational aspects**, scoping searches were carried out in MEDLINE, the Association of the Scientific Medical Societies in Germany (AMWF) guideline database, and websites of relevant institutes (Robert Koch Institute [RKI], G-BA, Gesundheitsinformation.de). The systematic reviews and the studies included for the health economic assessment were likewise searched for social aspects. In addition, the documented expert interviews were reviewed. As supplementary information, the reflective-thoughts method was applied in accordance with INTEGRATE-HTA instructions [32].

The information processing on social aspects followed the conceptional framework proposed by Mozygemba et al. 2016 [33], while the information processing on organizational aspects was based on the grid template proposed by Perleth 2014 [34] for the assessment of organizational consequences of treatment methods.

One reviewer screened information from all sources found in the scoping searches for conclusions on social and/or organizational arguments and aspects of the treatment options to be investigated. The result was scrutinized for quality by a 2nd person. All arguments and aspects necessary for information processing were extracted into tables and summarized as a narrative.

For the literature search regarding the analysis of **legal aspects**, the databases of the German Federal Court of Justice (BGH), the Federal Information System for Law, and the legislative databases by Manz and Lexis Nexis were used. Additional searches were conducted at the

library of the University for Continuing Education Krems and on the Internet (Google), and relevant comments and handbooks were consulted.

Information processing on legal aspects was based on the guideline developed by Brönneke 2016 [35].

One person screened information for conclusions regarding legal aspects of the treatment options to be investigated. Comments were selected by recency, relevance, and availability. A 2nd person critically read the arguments and comments to assure quality.

3.5 Incorporation of the patient perspective

The original plan provided for 8 interviews with affected children, adolescents, and parents. However, the ethics committee of the University of Continuing Education Krems did not approve these interviews because it deemed the target group to be too vulnerable. To obtain indirect information on the situation of affected people, guide-based expert interviews with a child and adolescent psychiatrist and a child and adolescent psychotherapist who led a self-help group for adolescents were therefore conducted alternatively. The interviews aimed to verify the patient relevance of this HTA report's outcomes as well as to examine additional ethical, social, and organizational aspects of the implementation of psychotherapy in children and adolescents with depression. The experts were informed about the goals of the interview and the HTA as well as the approach used in conducting the interview. They were informed in advance about the interviews being analysed in an anonymized fashion and that their name would be mentioned in the HTA report, if desired. The interviews were conducted online due to the COVID pandemic, took 45 to 70 minutes, and were recorded using the Zoom software. While the audio track was stored for later analysis, the video track was erased immediately after the interview. After the interviews were transcribed, the recordings were erased. A 2nd person checked the interview transcripts for comprehensibility. Insights gained from these interviews informed the assessment of ethical, social, and organizational aspects.

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

The information retrieval identified 13 systematic reviews as relevant for the research question of the benefit assessment [36-48]. No planned or ongoing systematic reviews were found via PROSPERO. Further, 2 completed systematic reviews were found [49,50] for which no results had been reported by November 2020.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 8 April 2020. A supplementary focused or scoping search for RCTs in accordance with the HTA report protocol was foregone because all psychotherapy types relevant for this HTA report have been discussed in systematic reviews which are currently sufficient and of adequate quality.

Table 1: Exclusions due to a quality assessment by Oxman-Guyatt score

Author, year	**Consensus Oxman-Guyatt score**
Arnberg, 2014 [51]	4
Babowitch, 2016 [52]	3
Briggs, 2019 [53]	4
Bunge, 2016 [54]	2
Calati, 2011 [55]	2
Cossu, 2015 [56]	2
Dardas, 2018 [57]	2
Devenish, 2016 [58]	4
Duffy, 2019 [59]	4
Ebert, 2015 [60]	4
Eckshtain, 2020 [61]	4
Forman-Hoffman, 2016 [62]	4
Francis, 2012 [63]	2
Garber, 2016 [64]	3
Garrido, 2019 [65]	3
Keles, 2018 [66]	4
Ma, 2014 [67]	4
Mychailyszyn, 2018 [68]	2
Nocon, 2017 [69]	3
Rice, 2014 [70]	3
Spinhoven, 2018 [71]	4

Table 1: Exclusions due to a quality assessment by Oxman-Guyatt score

Author, year	**Consensus Oxman-Guyatt score**
Stiles-Shields, 2016 [72]	3
Sun, 2019 [73]	4
Tuerk, 2018 [74]	4
Weersing, 2017 [75]	3
Weisz, 2013 [76]	3
Weisz, 2017 [77]	4
NICE guideline [78]	4

Table 2: Study pool for the health economic assessment

Study	**Available documents [reference]**	**Clinical study**
Byford	2007, British Journal of Psychiatry, 191:521-527 [79]	ADAPT trial [80,81]
Dickerson	2018, Pediatrics, 141(2):e20171969 [82]	STAND trial [83]
Domino08	2008, Am J Psychiatry 165:588-596 [84] ***(Follow-up: 12 weeks)***	TADS trial [85-87]
Domino09	2009, J Am Acad Adolesc Psychiatry, 48:7 [88] ***(Follow-up: 36 weeks)***	
Goodyer	2017, Health Technol Assess, 21(12) [89]	IMPACT trial [89,90]
Lynch	2011, Arch Gen Psychiatry, 68(3):253-262 [91]	TORDIA trial [92,93]

4.2 Characteristics of the systematic reviews included in the assessment

The 13 systematic reviews included in the HTA report covered a total of 150 nonoverlapping RCTs. For the systematic reviews, the last search for primary studies was carried out between March 2009 and January 2019. Six systematic reviews investigated CBT (monotherapy or, in some cases, in combination with antidepressants) [36,37,40,41,45,46], 2 systematic reviews focused on IPT [43,44], 3 systematic reviews investigated CBT and IPT [38,39,42], and 2 systematic reviews focused on all 3 psychotherapy types relevant for this HTA report: CBT, IPT, and DYN [47,48]. The therapy format and duration and frequency of interventions differed widely between the systematic reviews. Two systematic reviews investigated only one-on-one therapy [37,43], 2 systematic reviews analysed only group therapy [36,46], while the remaining systematic reviews included studies on one-on-one as well as on group therapy or provided no specific information on the form of therapy. The psychotherapy durations in the systematic reviews varied between 4 and 54 weeks, and the number of sessions ranged from 4 to 36. Only in rare cases did the included systematic reviews report on whether the psychotherapy took place in an outpatient or inpatient setting. Where information on this topic was provided,

the treatment was performed on an inpatient basis. The systematic reviews investigated the psychotherapy types for effectiveness in comparison with inactive controls (psychological placebo, waiting list, no intervention, usual care) or with antidepressants. “Psychological placebo” and “usual care” were not defined in detail in the systematic reviews.

Forti-Buratti 2016 [41] and Yang 2017 [46] focused on children (7–13 years), while Chi 2018 [36] and Dubicka 2010 [40] investigated only adolescents (13–18years). All other systematic reviews included studies on both children and adolescents and analysed them jointly. None of the systematic reviews included studies on children under 7 years of age. The results sections of the included systematic reviews which focused on the treatment of unipolar depression did not distinguish by severity of depression.

Where studies irrelevant for this HTA report – e.g. studies on depression in adults – were included in a systematic review, the HTA report disregarded these studies. For this HTA report, we examined only the results of the relevant primary studies. The only systematic reviews which were included in their entirety were the ones by Pu 2017 [44] and Yang 2017 [46]. In addition, 3 NMAs by Liang 2020 [42], Zhou 2020 [47], and Zhou 2015 [48] were included: In these cases, the extracted data are based on the entire NMA; while not all included studies met the inclusion criteria defined a priori, they were nevertheless used in the network. The NMA results were extracted because the comparisons relevant for this HTA report were carried out at least indirectly. In the derivation of evidence, these results were used only if no direct comparisons were available from individual studies or pairwise metaanalyses. Studies which were part of the network but failed to meet the inclusion criteria of this HTA report deviated primarily with regard to the intervention to be investigated since the network also comprised studies on other types of psychotherapy or comparisons between types of psychotherapy or antidepressants and placebo [42,47,48]. This approach was necessary to identify indirect comparisons. In Zhou 2020 [47], 15% of the NMA studies (11 of 71) deviated from the inclusion criteria of this HTA report with regard to their population since they included not only children and adolescents with depression, but also those with dysthymia, but the authors did not report the percentage of these participants in the individual studies. From a clinical perspective, this deviation is deemed minor since it concerns only 15% of the studies, of which only some actually enrolled persons with dysthymia.

All 3 NMAs reported that the similarity assumptions (similar study and patient characteristics) were adequate for combining the studies in an NMA [42,47,48].

4.3 Overview of patient-relevant outcomes

From 13 systematic reviews, data were extracted on the patient-relevant outcomes of suicide risk (suicidal ideation and behaviour), treatment response, remission, change in depressive symptoms, and functioning. The systematic reviews did not report any data on mortality (all-

cause mortality, suicide mortality), health-related quality of life, or adverse events. Regarding the outcome of patient satisfaction, the included systematic reviews likewise provided no results. Table 3 presents an overview of the available data on patient-relevant outcomes from the included reviews.

Table 3: Matrix of patient-relevant outcomes

Systematic review	Outcomes							
	Mortality	Morbidity					Health-related quality of life and psychosocial aspects	
	All-cause mortality / suicide mortality	Suicide risk (suicidal ideation and behaviour)	Treatment response	Remission	Change in depressive symptoms	Adverse events	Functioning	Health-related quality of life
Chi 2018	-	-	-	-	●	-	-	-
Cox 2014	-	●	-	●	●	-	●	-
Cuijpers 2020	-	-	-	-	●	-	-	-
Davaasambuu 2020	-	-	-	-	●	-	-	-
Dubicka 2010	-	●	●	-	●	-	-	-
Forti-Buratti 2016	-	-	-	-	●	-	-	-
Liang 2020	-	-	-	-	●	-	-	-
O'Connor 2013	-	○	-	-	○	-	-	-
Pu 2017	-	●	-*	-	●	-	●	-
Tindall 2017	-	-	-	-	●	-	-	-
Yang 2017	-	-	-	-	●	-	-	-
Zhou 2020	-	●	-	-	●	-	-	-
Zhou 2015	-	-	-	-	●	-	-	-

● Data were reported and were usable.
○ Data were reported but not extracted for the benefit assessment, because all studies had already been reported in other systematic reviews.
- No data were reported.
* The data largely overlapped with the data on the outcome of change in depressive symptoms and therefore were not used once again for the outcome of treatment response.

4.4 Assessment of the quality of systematic reviews and the risk of bias of the results

Quality was rated very high for 9 systematic reviews (7 of 7 points) [37,38,42-48], while 3 systematic reviews received 6 of 7 points [39,40] and 1 systematic review, 5 of 7 points [41]. All systematic reviews which technically met the inclusion criteria but scored fewer than 5 points in the quality assessment were disregarded in this HTA report (see A3.2.2, Table 8 of the full HTA report).

The risk of bias of the primary studies had been assessed by the authors of the systematic reviews. If they assessed only the bias domains but provided no overall assessment of the primary studies, the authors of this HTA report determined an overall rating of the risk of bias. One person performed the assessment and a 2nd person reviewed it. In 18 out of 152 primary studies reported in the systematic reviews, the risk of bias across outcomes was rated as low by at least 1 systematic review, but as unclear or high by the remaining ones. Some of the primary studies which were included in multiple systematic reviews received different ratings of their risk of bias. In case of different ratings, the authors of this HTA report adopted the stricter rating (see A3.2.2).

The risk of bias on the outcome level was not analysed separately because the systematic reviews did not provide this information in the required detail.

4.5 Results on patient-relevant outcomes

Below, results are briefly presented by patient-relevant outcome. First CBT, followed by IPT and then DYN are discussed. It comes down to first comparing psychotherapy with inactive control interventions (placebo, waiting list, no treatment, typical treatment) and then with antidepressant treatment. Afterwards, the evidence on the use of psychotherapy as an add-on to antidepressant treatment is presented. Where for 1 or more of these comparisons, no evidence is available on an outcome, this is stated.

No evidence was found regarding any outcome for comparisons with other active therapies such as exercise or relaxation exercises. Likewise, no evidence was found on the additional outcome of patient satisfaction (acceptance). Detailed results are presented in the tables in Section A3.3.

4.5.1 Results on mortality

The relevant systematic reviews did not report any results on this outcome.

4.5.2 Results on suicide risk

4.5.2.1 Cognitive behavioural therapy

CBT versus inactive controls

The reported evidence does not allow drawing any conclusions as to whether CBT in comparison with an inactive control intervention (placebo or usual care) increases or reduces the risk of suicide. While 1 direct comparison and 1 associated NMA showed no statistically significant difference with regard to suicide risk between CBT and inactive control, the confidence interval was too wide in each case to allow drawing valid conclusions (CBT versus psychological placebo [PP]: NMA: odds ratio [OR] 11.31; 95% CI: [0.01; 46.11]; RCT: OR 1.02; 95% CI: [0.06; 16.45]; CBT versus usual care: OR 276.9; 95% CI: [0.02; 1163]) [47]. Furthermore, no information was available as to whether these results referred to short-term, medium-term, or long-term suicide risk.

Hence, there is no hint of benefit of CBT.

CBT versus antidepressants

While a direct comparison from a systematic review published in 2020 with data on 220 children and adolescents showed a numerically lower suicide risk in the CBT group, the difference was not statistically significant (OR 0.52; 95% CI: [0.17; 1.62]) [47]. One systematic review from 2014 [37] showed in a direct comparison that children and adolescents treated with CBT exhibited a statistically significantly reduced frequency of suicidal thoughts and behaviour than those on antidepressant therapy (CBT versus AD after 12 weeks: OR 0.26; 95% CI: [0.09; 0.72]; 1 RCT with data on 188 children and adolescents; after 18 weeks: OR 0.26; 95% CI: [0.07; 0.98]; 1 RCT with data on 149 children and adolescents). In absolute terms, after 12 weeks, 6% of patients receiving CBT and 19% of patients on antidepressants had an elevated suicide risk [37].

Based on the most current systematic review [47], no hint of greater benefit of CBT versus antidepressants can be derived.

CBT + antidepressants versus antidepressants

Where CBT was used as an add-on to antidepressant treatment in comparison with antidepressant monotherapy, no statistically significant difference regarding the frequency of suicidal thoughts or suicidal behaviour in children and adolescents was found in either the short term or the long term [37,40,47]. One metaanalysis investigating this topic based on 2 individual studies with 388 children and adolescents arrived at the following results after 12 weeks: CBT + AD: OR 0.75; 95% CI: [0.26; 2.16] [37]. Another metaanalysis of 2 studies with data on 424 children arrived at a similar result: OR: 0.75, 95% CI: [0.35; 1.59] [47]. One metaanalysis of 2 studies with data from 344 children and adolescents showed no statistically

significant difference even after 40–50 weeks of follow-up: OR 0.53; 95% CI: [0,06; 4,58] [37]. Only 1 older systematic review, which was disregarded in the derivation of evidence based on the methods described in Section 3.1, reported on a study with 157 enrolled adolescents in which after 36 weeks, suicidal behaviour was more commonly observed in those on antidepressant monotherapy than in those receiving a combination of antidepressants and CBT [40].

Based on 2 systematic reviews (each with an Oxman-Guyatt index of 7 of 7) [37,47], no hint of greater benefit of antidepressant therapy with add-on CBT can be derived in comparison with antidepressant monotherapy.

4.5.2.2 Interpersonal psychotherapy

IPT versus inactive controls

One systematic review including studies where children and adolescents received 10 to 16 sessions of IPT over a period of 6 to 16 weeks showed no statistically significant difference in suicide risk between children and adolescents who received IPT versus those who received psychological placebo or usual care. The confidence interval was too wide to allow deriving valid conclusions: OR 0.70; 95% CI: [0.17; 2.93]; 2 RCTs with data on 112 children and adolescents [44]. These findings were confirmed by 1 NMA and 2 individual studies with direct comparisons from the NMA [47].

This results in no hint of benefit of IPT.

IPT versus antidepressants

No evidence was found on this comparison.

IPT + antidepressants versus antidepressants

No evidence was found on this comparison.

4.5.2.3 Psychodynamic psychotherapy

DYN versus inactive controls

In direct comparison, no statistically significant difference in suicide risk was found between children and adolescents after DYN therapy versus psychological placebo: OR 1.01; 95% CI: [0.06; 16.23]; 1 RCT with data on 315 children and adolescents. Information is missing on the time the outcome was surveyed [47]. One of the NMAs calculated in this systematic review arrived at the same result, likewise with no information being available on the time the outcome was surveyed. In addition, the confidence interval was very wide, making it impossible to draw valid conclusions: OR 8.64; 95% CI: [0.01; 40.05] [47].

There is no hint of benefit of DYN.

DYN versus antidepressants

No evidence was found on this comparison.

DYN + antidepressants versus antidepressants

No evidence was found on this comparison.

4.5.3 Results on treatment response

Treatment response was reported by 2 systematic reviews. Dubicka 2010 defined treatment response as "much improved" or "very much improved" according to the Clinical Global Impression of Improvement Scale (CGI-i scale) [40]. Pu 2017 defined response as a 50% improvement on a depression scale [44].

4.5.3.1 Cognitive behavioural therapy

CBT versus inactive controls

No evidence was found on this comparison.

CBT versus antidepressants

No evidence was found on this comparison.

CBT + antidepressants versus antidepressants

In adolescents, after 12 weeks and after 28 to 36 weeks, the combination of CBT and antidepressants resulted in no statistically significant difference in comparison with antidepressant monotherapy (12 weeks: Treatment for Adolescents with Depression Study [TADS] based on data from 193 adolescents: OR 0.61; 95% CI: [0,33; 1,14]; Adolescent Depression Antidepressant and Psychotherapy Trial [ADAPT] based on data from 202 adolescents: OR 1.09; 95% CI: [0.62; 1.89]; 28–36 weeks (TADS, ADAPT): OR 1.09; 95% CI: [0.68; 1.78]; 2 RCTs with data on 349 adolescents) [40].

Hence, there is no hint of greater benefit of the combination of CBT with antidepressants in comparison with antidepressant monotherapy.

4.5.3.2 Interpersonal psychotherapy

IPT versus inactive controls

After 12 to 16 weeks, nearly twice as many children and adolescents who received IPT achieved response compared with those without psychotherapy (placebo, usual care, waiting list) (OR 1.87; 95% CI: [1.40; 2.51]; 4 RCTs with data on 366 children and adolescents) [44].

Since all studies used for the response analysis were also used for the outcome of "change in depressive symptoms", employing the same survey instruments, the option of taking this evidence into account once more for the outcome of response was foregone.

IPT versus antidepressants

No evidence was found on this comparison.

IPT + antidepressants versus antidepressants

No evidence was found on this comparison.

4.5.3.3 Psychodynamic psychotherapy

None of the included systematic reviews reported on response in comparison with DYN.

4.5.4 Results on remission

Remission was reported in 1 systematic review, where it was defined as 8 weeks of freedom from symptoms [37].

4.5.4.1 Cognitive behavioural therapy

CBT versus inactive controls

No evidence was found on this comparison.

CBT versus antidepressants

The comparison of CBT versus antidepressants showed no statistically significant difference in remission among children and adolescents after 12 weeks nor after 6 months; the confidence intervals were very wide (CBT versus AD: 12 weeks: OR 0.62; 95% CI: [0.28; 1.35]; 2 RCTs with data on 186 children and adolescents; CBT versus AD: 6 months: OR 0.83; 95% CI: [0.27; 2.60]; 1 RCT with data on 48 children and adolescents) [37].

There is no hint of greater or lesser benefit of CBT.

CBT + antidepressants versus antidepressants

After 12 weeks, the combination of CBT and antidepressants led to remission more frequently than antidepressant monotherapy, but the difference was not statistically significant (OR 1.50; 95% CI: [0.99; 2.27]; 3 RCTs with data on 317 children and adolescents). Even after 6 months and after about 1 year, no statistically significant difference was found, and confidence intervals were wide [37].

Hence, there is no hint of greater benefit of CBT.

4.5.4.2 Interpersonal psychotherapy

No evidence for a comparison with IPT was found on this outcome.

4.5.4.3 Psychodynamic psychotherapy

No evidence for a comparison with DYN was found on this outcome.

4.5.5 Results on the change in depressive symptoms

4.5.5.1 Cognitive behavioural therapy

CBT versus inactive controls

In comparison with inactive control interventions (psychological placebo, waiting list, usual care), most systematic reviews found CBT to lead to a statistically significant improvement in depressive symptoms in children and adolescents [36,38,39,42,46-48]. The same was found in the metaanalysis, which took into account 28 RCTs (but did not report the number of included children and adolescents): Hedges' g: 0.44; 95% CI: [0.23; 0.65] [38]. In 2 systematic reviews, the relevant RCTs also revealed advantages of CBT, but the difference to the control group was not statistically significant. However, these systematic reviews contained few studies, which were also included in the other systematic reviews [41,45]. The use of computer-based CBT was more effective than psychological placebo or waiting list at reducing depressive symptoms [42]. Mindfulness-based therapy (a subtype of CBT) likewise showed a statistically significant improvement in depressive symptoms in direct comparison with usual care [36]. In NMAs, mindfulness-based therapy, like problem-solving therapy, was not statistically significantly more effective than psychological placebo or usual care at reducing depressive symptoms [42,47,48].

One systematic review analysed children and adolescents separately. It showed that CBT was more effective than the control both in children and in adolescents [38]. Subgroup analyses showed that CBT reduced depressive symptoms in children without comorbidities, but not in children with comorbidities [46]. A subgroup analysis also found CBT to be more effective without parental involvement than with parental involvement [46]. For subgroup analyses which showed no statistically significant result, however, it must be noted that some subgroups contained a very small number of studies, and consequently, the absence of a statistically significant effect might also be due to lack of statistical power [46].

Based on the results of the most current systematic review containing the most RCTs (Oxman-Guyatt index of 7 of 7) [38], there is an indication of benefit for CBT.

CBT versus antidepressants

The most recent systematic review showed, based on 1 study with 220 participants, a statistically significant advantage of antidepressants versus CBT in direct comparison (SMD 0.67; 95% CI: [0.40; 0.97]). No information was available on the survey time [47]. One older systemic review based on 2 RCTs showed no statistically significant difference in reduction of depressive symptoms after 12 weeks nor after about 6 months when patients self-rated their symptoms [37]. When assessed by a physician, an advantage was found for antidepressant therapy after 12 weeks, based on 1 RCT [37]. In the indirect network comparison, the difference was not statistically significant [47].

Based on the systematic review containing the most RCTs [37], no hint of greater or lesser benefit of CBT versus antidepressant treatment was found.

CBT + antidepressants versus antidepressants

Compared with antidepressant monotherapy, the combination of CBT plus antidepressants showed no statistically significant difference in the short term or medium term [37,40,47]. The metaanalysis which took into account the most RCTs showed the following result after 12 weeks: SMD - 0.14; 95% CI: [- 0.36; 0.09]; 5 RCTs with data on 383 children and adolescents [37]. Only for the 1-year follow-up were the depressive symptoms in the group receiving additional CBT statistically significantly lower (SMD - 0.26, 95% CI: [- 0.46; - 0.05]; 2 RCTs with data on 268 children and adolescents) [37]. However, the CI includes the irrelevance threshold of 0.2 according to IQWiG methods; therefore, it is not certain whether the statistically significant difference is in fact patient relevant.

No hint of greater or lesser benefit of CBT as an add-on to antidepressant therapy in comparison with antidepressant monotherapy can be derived from this.

4.5.5.2 Interpersonal psychotherapy

IPT versus inactive controls

IPT is statistically significantly more effective than inactive controls (psychological placebo, waiting list, usual care) at reducing depressive symptoms in both the short term and the long term [42,44,47,48]. The systematic review which, in the metaanalysis, took into account most RCTs showed an SMD of -0.74 (95% CI: [- 0.91; - 0.56], 7 RCTs with data on 527 children and adolescents) after 6 to 16 weeks, and after 6 to 18 months, an SMD of - 0.75; 95% CI: [- 1.21; - 0,29], 2 RCTs with data on 89 children and adolescents [44]. A subgroup analysis showed that IPT, both in one-on-one and in group therapy, was more effective than no active therapy [44].

Based on the systematic review containing the most RCTs (Oxman-Guyatt index of 7 of 7) [44], there is an indication of benefit for IPT.

IPT versus antidepressants

In 1 NMA, IPT was compared indirectly with the antidepressant fluoxetine; this comparison showed no statistically significant difference in the reduction of depressive symptoms (SMD 0.13; 95% CI: [- 0.74; 1]) [47].

There is no hint of greater or lesser benefit of IPT in comparison with antidepressant treatment.

IPT + antidepressants versus antidepressants

No evidence was found on this comparison.

4.5.5.3 Psychodynamic psychotherapy

DYN versus inactive controls

Evidence on DYN is available from a direct comparison in a pairwise metaanalysis, which showed no statistically significant difference in comparison with psychological placebo [47]. Indirect comparisons from 2 NMAs likewise showed no statistically significant advantage of DYN versus psychological placebo, waiting list, usual care, or no treatment [47,48].

There is no hint of benefit of DYN.

DYN versus antidepressants

In an indirect comparison from 1 NMA, the comparison of DYN versus the antidepressant fluoxetine revealed no statistically significant difference [47].

There is no hint of greater or lesser benefit of DYN in comparison with antidepressant treatment.

DYN + antidepressants versus antidepressants

No evidence was found on this comparison.

4.5.5.4 Psychotherapy in general

One systematic review with 43 RCTs combined various types of psychotherapy and analysed their effectiveness in comparison with usual care, waiting list, or other treatment. In the subgroup of children as well as in the subgroup of adolescents, psychotherapy was statistically significantly more effective than the control intervention at reducing depressive symptoms. However, 6 to 24 months after the intervention, these differences were no longer statistically significant [38].

This results in an indication of short-term benefit for psychotherapy in general in comparison with inactive controls, but not a medium-term or long-term benefit.

4.5.6 Results on functioning

This outcome comprises the mental, social, and school functioning of children and adolescents.

4.5.6.1 Cognitive behavioural therapy

CBT versus inactive controls

No evidence was found on this comparison.

CBT versus antidepressants

The comparison of CBT versus antidepressants showed no statistically significant difference in experienced functioning of children and adolescents after 12 weeks or after 6 months (based on 1 study with 42 participants) [37].

This results in no hint of greater or lesser short-term or medium-term benefit of CBT in comparison with antidepressant treatment.

CBT + antidepressants versus antidepressants

The comparison of CBT + antidepressants versus antidepressant monotherapy likewise showed no statistically significant difference in experienced functioning in children and adolescents after 12 weeks or after 6 months [37,40]. One-year follow-up results from 1 RCT with 152 participants show statistically significantly better functioning in children and adolescents with add-on CBT than in those with antidepressant monotherapy (MD 3.00, 95% CI: [0.40; 5.60] [37].

This results in no hint of greater or lesser short-term or medium-term benefit of add-on CBT in comparison with antidepressant monotherapy [37,40]. In the long term, however, a hint of greater benefit was found for add-on CBT compared with antidepressant monotherapy [37].

4.5.6.2 Interpersonal psychotherapy

IPT versus inactive controls

In children and adolescents, IPT led to a statistically significant improvement in functioning in comparison with no active intervention (waiting list, psychological placebo, or usual care) 10 to 16 weeks after the intervention (SMD 0.53, 95% CI: [0.21; 0.85]; 5 RCTs with data on 407 children and adolescents) [44].

There is a hint of greater short-term benefit of IPT.

IPT versus antidepressants

No evidence was found on this comparison.

IPT + antidepressants versus antidepressants

No evidence was found on this comparison.

4.5.6.3 Psychodynamic psychotherapy

No evidence for a comparison with DYN was found on this outcome.

4.5.7 Results on health-related quality of life

The relevant systematic reviews did not report any results on this outcome.

4.5.8 Results on adverse events

The relevant systematic reviews did not report any results on this outcome.

4.6 Evidence map

Table 4 below shows the evidence map regarding patient-relevant outcomes.

Table 4: Evidence map regarding patient-relevant outcomes

	Mortality	**Morbidity**					**Health-related quality of life and psychosocial aspects**	
	All-cause mortality / suicide mortality	**Suicide risk (suicidal ideation and behaviour)**	**Treatment response**	**Remission**	**Change in depressive symptoms**	**Adverse events**	**Functioning**	**Health-related quality of life**
CBT vs. inactive controls	-	(⇔) (ND)	-	-	⇧ (ND)	-	-	-
CBT vs. AD	-	⇔ (ND)	-	(⇔) (st, mt)	⇔ (st, mt)	-	⇔ (st, mt)	-
CBT + AD vs. AD	-	⇔ (st, lt)	⇔ (st, mt)	⇔ (st, mt, lt)	⇔ (st, mt, lt)	-	⇔ (st, mt) ⇗ (lt)	-
IPT vs. inactive controls	-	(⇔) (st)	-*	-	⇧ (st, mt, lt)	-	⇧ (st)	-
IPT vs. AD	-	-	-	-	⇔ (ND)	-	-	-
IPT + AD vs. AD	-	-	-	-	-	-	-	-
DYN vs. inactive controls	-	(⇔) (ND)	-	-	⇔ (ND)	-	-	-
DYN vs. AD	-	-	-	-	⇔ (ND)	-	-	-
DYN + AD vs. AD	-	-	-	-	-	-	-	-
Psychotherapy in general	-	-	-	-	⇧ (st) ⇔ (mt, lt)	-	-	-

⇧: indication of (greater) benefit or indication of lesser harm
⇗: hint of (greater) benefit or hint of lesser harm
⇔: no hint, indication, or proof; homogeneous result
(⇔): no hint, indication, or proof; homogeneous result. The 95% confidence interval for relative effect is so imprecise that neither an effect being cut in half, nor one being doubled can be ruled out.
-: no data reported
* The data largely overlapped with the data on the outcome of change in depressive symptoms and therefore were not additionally used for the outcome of treatment response.
Abbreviations: AD: antidepressant treatment; CBT: cognitive behavioural therapy; DYN: psychodynamic psychotherapy; IPT: interpersonal psychotherapy; lt: long term; mt: medium term; ND: no data on follow-up; st: short-term

4.7 Outcomes from the perspectives of patient representatives

The interviewed experts confirmed the outcomes used in this HTA report to be relevant. They explained that adolescents predominantly suffer from symptoms such as difficulty concentrating, avolition, low self-esteem, and low regulation of negative emotions such as sadness, anxiety, and (auto)aggressiveness as well as from loneliness. Parents reportedly

experience the children's and adolescents' social withdrawal, avolition, and listlessness as particularly dramatic. These described changes in experiences (thoughts and feelings) as well as in behaviour are reflected by the scales used for recording depressive symptoms.

The experts deemed improvement in depressive symptoms, quality of life, and functioning to be the most relevant outcomes. With regard to the children's and adolescents' quality of life, they also highlighted the quality of relationships with relevant attachment figures and with peers. One expert added cognitive performance, inpatient stays as well as daily media consumption and drug use as further relevant outcomes. In qualitative interviews with adolescents, the alleviation of depressive symptoms and improved functioning were likewise found to be important outcomes of psychotherapeutic treatment of depressive disorders. From the perspective of this study's adolescent participants, however, personal growth, the improvement of relationships, coping behaviours, and self-management as well as of their own well-being played important roles as well [94]. While adolescents aimed to achieve, in particular, changes in coping behaviours such as behavioural activation and resilience, parents as well as therapists placed greater value on school and work-related functioning [94]. An international expert committee has developed a consensus-based standard set of outcomes for the measurement of treatment results in depressive and other mental disorders. It defined the measurement of symptoms of disease, suicidal thoughts and behaviours as well as functioning [95].

5 Results: Health economic assessment

5.1 Intervention costs

The extent and intensity of the treatment of a depressive episode or recurring depressive disorder depend on the individual circumstances and any comorbidities, which often affect children and adolescents in particular. The costs identified herein take these individual circumstances into account only to some extent, e.g. in the form of different drug dosages. Further, the exclusive analysis of intervention costs disregards various potential (long-term) consequential costs of depression (e.g. lower income during adulthood) or costs arising in other sectors (e.g. in school). Few studies are available on this economic disease burden, which exceeds intervention costs, and while these studies primarily focus on adults, they show that said burdens can be substantial [96].

In the following cost calculations, 7 treatment alternatives and their characteristics are analysed on the basis of an S3 guideline on the treatment of depressive disorders in children and adolescents ("S3 guideline") [6]. The alternatives comprise CBT, the 2 types of DYN (DP and APT), IPT, antidepressant treatment (fluoxetine), mental health education, and Jacobson's Relaxation Technique. The direct costs of applying an intervention are presented in the form of average costs from the perspective of the public payers (SHI community). Costs were calculated for a period of 6 to 12 weeks, depending on the treatment alternative, and for an outpatient setting. The costs of initial diagnosis were disregarded, but the estimated intervention costs include diagnostics during treatment. They include initial consultations and trial sessions to determine which therapy is appropriate in the individual case and to define target criteria. Interim consultations, closing consultations, and response checks serve to regularly verify treatment success. Further, particularly in children, an attachment figure should be involved in the treatment steps [6]. A detailed breakdown of the cost items and treatment services is found in the full report (see A4.2.2.3).

5.1.1 Cognitive behavioural therapy, depth psychology-based and analytical psychotherapy

CBT, DP, and APT can be billed to the health insurance funds in accordance with the G-BA Guidelines for Psychotherapy and therefore constitute guideline-recommended therapy in accordance with Section 15 [13]. Costs are calculated on the basis of short-term therapy in accordance with the National Association of Statutory Health Insurance Physicians. In the calculations, all 3 types of therapy therefore share the same treatment and cost structures (treatment duration, number of sessions, required talk therapy units, reimbursable amount, etc.). The therapies differ in nothing but the applied treatment approach. CBT combines cognitive techniques and elements with behavioural treatment approaches. In older children and adolescents with mild to moderate depressive disorder, CBT, alongside interpersonal psychotherapy, is the treatment of first choice [6]. In severe cases, CBT is combined with

pharmacotherapy. The application of DP, which is a type of psychodynamic psychotherapy, is recommended by the S3 guideline in cases where CBT is impossible or not desired [6]. Alongside CBT, DP is the most commonly rendered service in outpatient psychotherapeutic care [97]. Like DP, APT is a type of psychodynamic psychotherapy and represents the third procedure recognized in Germany. According to the S3 guideline, APT may be used if CBT is impossible or not desired [6].

For all 3 treatment types, the total costs of 12 weeks of one-on-one therapy with twelve 50-minute sessions or twelve 2 x 25-minute sessions, including all component services, equal € 1793.08 to € 2104.68. The exact figure depends largely on the trial sessions needed in the individual case. It also provides for involvement of the relevant attachment figure [13]. The total cost is composed of the cost for the individual sessions, the required (2 to 6) trial sessions, and the determination of the insurance coverage. In addition, 11 follow-up visits at 20 minutes each take place throughout the treatment period. A 10-minute closing consultation is held to determine the further procedure.

5.1.2 Interpersonal psychotherapy

On the basis of the evidence on children and adolescents cited therein, the S3 guideline strongly recommends IPT as first-line therapy [6]. To date, IPT is not included in the SHI catalogue of services or the Uniform Value Scale and is de jure unbillable. However, IPT has been included in selective contracts of large health insurance funds and can be billed and reimbursed through them as well as through private health insurers. According to service providers, qualified professionals have so far been able to bill IPT as a behavioural therapeutic method (in some cases also as psychodynamic therapy [98]) in routine (outpatient) practice. According to the German Society for Interpersonal Psychotherapy (DG-IPT), a corresponding application for inclusion in the catalogue of services has been submitted to the G-BA.

Since therapy in routine outpatient care is billed using the CBT fee schedule item, the planned costs must also include at least 2 obligatory trial sessions at 50 minutes each. As is the case for the other 3 types of psychotherapy, CBT, APT, and DPT, the cost substantially depends on the trial sessions needed for the individual patient, including involvement of the attachment figure. The total costs are composed, firstly, of the 12 sessions, the (2 to 6) obligatory trial sessions, and the determination of the insurance coverage. The treatment period further includes 11 follow-up visits at 20 minutes each and a 10-minute consultation to determine the next steps. Assuming that 12 weeks of one-on-one IPT with 12 sessions at either 50 minutes or 2 x 25 minutes each, including all component services, can be billed as behavioural therapy, the total costs of IPT for children and adolescent range from € 1793.08 to € 2104.68.

5.1.3 Pharmacotherapy

In Germany, fluoxetine is currently the only drug approved for pharmacotherapy of depressive children and adolescents 8 years or older. According to the S3 guideline on the treatment of depressive disorders in children and adolescents, psychotherapy is to be preferred, particularly in mild to moderate depression, because antidepressant therapy might lead to higher suicidality and additional adverse events [6]. Antidepressant monotherapy is deemed only a second-choice treatment for adolescents with depression. In severe depression, combination therapy – typically with CBT – can additionally be weighed as a treatment option. However, patients under either form of treatment should be examined for adverse drug effects in the recommended follow-up visits. In addition to cost of the drug itself, the overall costs include 1 initial consultation, 4 follow-up visits, and 2 complete blood counts. In addition, response checks should be carried out after 4 weeks and after 8 weeks to document effectiveness and symptoms. After the last consultation, a decision should be made on potential continuation (≥ 6 months) or a switch in treatment strategy. In case of nonresponse to an antidepressant, measuring the serum (plasma) level, with consecutive dose adaptation (therapeutic drug monitoring, TDM), may be an option. In clinical practice, however, this is done only in exceptional cases [99].

In total, 8 weeks of therapy costs between € 311.23 and € 318.47 depending on the required dose (minimum of 10 mg, maximum of 20 mg) and drug product.

5.1.4 Active monitoring and measures for promoting mental health

Active monitoring alone is recommended only in case of mild depressive disorder. It includes health-promoting measures such as relaxation or movement therapies as well as informative interventions such as mental health education [6]. In clinical routine, some of these therapies are typically combined with other therapy types, such as psychotherapy or pharmacotherapy.

Active monitoring / mental health education

As part of mental health education, complicated medical and scientific topics are conveyed in a simple and generally understandable manner. According to the Guidelines for Psychotherapy, each patient is entitled to one psychotherapeutic consultation [6]. Said consultation provides rapid, low-threshold access to outpatient psychotherapeutic care.

Six units of mental health education, not including an additional one-on-one consultation for the accompanying person, cost a total of € 304.56. For 9 units including 4 units of psychotherapeutic consultation for the accompanying person, the cost amounts to € 659.88.

Relaxation therapy (Jacobson's Relaxation Technique)

As a non-drug treatment option, the S3 guideline lists relaxation therapy for a period of 6 to 8 weeks, which is likewise recommended only for mild depressive disorders [6]. Hence, the

costs are calculated based on 6 to 8 weeks of treatment with 8 to 10 sessions at 60 minutes each on the basis of the German Association of Psychologists (BDP) “psychological expert group – relaxation techniques” [100].

In total, relaxation therapy in the recommended group setting results in total costs ranging from € 349.36 to € 411.32.

5.2 Systematic review of health economic evaluations

From the outset, it must be noted that the results of the health economic systematic reviews cannot be directly adapted to the German healthcare context because the studies were embedded in the US and British healthcare systems. Nevertheless, the results are presented below to provide an overview of the current evidence on this research question.

5.2.1 Results of the information retrieval

To examine the efficiency of the compared treatment types, a total of 5 studies [80,81,83,85-87,89,90,92,93] published in 6 relevant health economic publications [79,82,84,88,89,91] (390 hits in total) are relevant for this part of the report in accordance with the predefined inclusion and exclusion criteria. The studies’ literature lists did not contain any other relevant studies. Where information was missing in the health economic publications, the associated clinical studies were consulted.

5.2.2 Characteristics of the studies included in the assessment

Study characteristics

All of the 6 identified and included health economic publications were generated as additions to a clinical trial in the form of a so-called piggy-back analysis. Two studies [79,89] were conducted in the United Kingdom, and 3 in the United States [82,84,88,91], with the studies ranging in dates from 2007 [79] to 2018 [82]. Each of the studies was embedded in an outpatient and inpatient setting. All publications report the funding source. In 4 of 6 publications, a potential conflict of interest existed due to activities related to the industry [84,88,89,91].

All included studies focused on one-on-one CBT for children and adolescents, either as CBT monotherapy [84,89] or in combination with another type of therapy [79,82,84,88,91]. Three studies compared the experimental intervention with a pharmacological comparator intervention (fluoxetine or drug switch [RX]) [79,84,88,91]. Two studies compared the experimental intervention with non-drug interventions (standard therapy [91] or short-term psychoanalytical psychotherapy and psychosocial intervention [89]). One publication [84] listed placebo treatment as an additional comparator therapy.

The smallest study [79] included a total of 208 children and adolescents in 2 active arms, while the largest study [84] enrolled 369 children and adolescents in 3 active arms with a placebo arm. The mean age of the adolescents ranged from 14.6 years [91] to 15.9 years [84]. The minimum age was 11 years [79] and the maximum 18 years [82,84]. Among the children and adolescents with severe depression who were included in the respective studies, 47.8% [88] to 88.5% [79] had a comorbidity.

Four studies, or 5 publications [79,82,84,88,91], carried out a cost-effectiveness analysis with clinical outcomes and additionally performed a cost-utility analysis with a general measure concerning quality of life. One study [89] carried out a cost-utility analysis only. All studies reported on incremental cost-effectiveness ratios (ICERs) or incremental cost-benefit ratios (ICBRs).

As mentioned above, the health economic studies are each based on clinical data from an RCT. The oldest clinical study was published in 2004 [85] and the most current one in 2017 [90]. Follow-up periods ranged from 12 weeks [84] to 24 months[97].

All health economic studies analysed the uncertainty of assumptions and results and conducted univariate sensitivity analyses. The latter were most frequently conducted on various cost parameters, such as reimbursement rates (e.g. cost of therapist's services), drug costs, and the exclusive consideration of outpatient costs. However, depression/preference weighting for the quality-adjusted life years (QALY) calculation was also varied.

Outcome parameters

The studies used a total of 3 different clinical assessment instruments [89,101,102] and an additional 3 clinical outcomes [91,103] for assessing depression as part of follow-up. In addition to the primary clinical outcomes, all studies calculated utility parameters in the form of QALYs. Either EQ-5D utility values were converted into QALYs [104-108], or clinical outcomes were indirectly transformed into QALYs via depression-free days [82,84,88,89,91]. One study [89] adjusted QALYs for the length of follow-up (discontinuation).

Cost parameters and quantities

In all studies, costs and quantities were calculated from a societal perspective using the respective national currencies – pound sterling [79,89] or United States dollar [82,84,88,91] – and adjusted to 1 index year, where necessary. The individual studies attempted, to different extents, to include direct medical costs (costs for staff, treatment unit, medications, other clinical costs due to hospital contacts and general practitioner services) as well as direct nonmedical costs (parents' travel cost, cost for staff housing). Furthermore, some of the studies listed indirect costs in the form of productivity losses and lost income due to travel and waiting times for the person accompanying the child or adolescent. Costs and quantities were calculated on the basis of clinical records, accounting documents, professionals'

estimates, individual costs from databases such as the British National Formulary (BNF), or other health economic studies.

5.2.3 Results of health economic evaluations

All studies calculated incremental cost-effectiveness or cost-utility relationships on the basis of the input data listed above (cost and outcomes). Only some of the studies used explicit threshold values for assessing whether a treatment is cost effective.

Cognitive behavioural therapy and combination therapy (CBT + fluoxetine, CBT + UC, CBT + RX)

Using a reported threshold for the public's willingness to pay (WTP) of $100 000 to $125 000 per QALY, CBT compared with placebo and CBT + fluoxetine compared with fluoxetine for a 12-week follow-up period were not cost effective [84]. However, CBT was cost effective compared to short-term psychotherapeutic intervention with a total follow-up of 86 weeks and at WTP values of £20 000 or £30 000 [89].

According to 1 study [79], at thresholds of £50 000 or £150 000, the probability of CBT + fluoxetine combination therapy compared to fluoxetine monotherapy being cost effective is under 4%. Another study reported in 1 publication [84] with a follow-up period of 12 weeks that combination therapy is not cost effective when compared with fluoxetine. The 2nd publication on this study with a follow-up period of 36 weeks [88], in contrast, showed that combination therapy, compared with fluoxetine monotherapy, was cost effective at a probability of over 90%. In the study with the drug switch and a follow-up duration of 24 weeks, CBT + RX therapy compared with RX alone has a moderate probability (61%) of being cost effective at a threshold of $100 000. In the comparison of CBT+UC versus UC in one 24-month study, CBT+UC was cost effective at all WTPs.

One study reports that the combination of CBT and fluoxetine in comparison with placebo is cost-effective after a follow-up period of 12 weeks [84].

Short-term psychoanalytical psychotherapy

Compared to brief psychotherapeutic intervention (BPI), short-term psychoanalytical psychotherapy (STPP) was not cost effective at the given thresholds [109] after an 86-week follow-up [89].

5.2.4 Assessment of reporting quality, methodological quality, and adaptability to a given healthcare system

The critical assessment of the underlying studies attempted to illustrate the limitations of the methods, statistical procedures, (clinical) benefit parameters, resource consumption, cost, presentation of results, and discussion using the standardized CHEERS checklist [29]. The

assessed items comprise, for instance, the included interventions, their comparison, the cost calculation perspective, the included costs, clinical measuring instruments, threshold values for assessing cost effectiveness, and other study-related items. The adaptability of studies and their results to Germany was assessed based on the criteria of the EUnetHTA HTA Adaptation Toolkit [30] by determining whether the available studies can be applied to the German healthcare context.

The studies exhibited the following key limitations (for a detailed description, see A4.2.4 of the full report):

- They failed to mention optional independent psychotherapy options or optional add-on therapies such as interpersonal psychotherapy, psychodynamic psychotherapy types, systemic therapy, movement therapy, relaxation training, mental health education, art therapies, or occupational therapies.
- Not all health economic studies reported all inclusion and exclusion criteria for study participation.
- The majority of the studies typically analysed a time horizon of a few weeks, but for the clinical picture of depression, a longer-term perspective is relevant.
- Not all studies justified the choice of the reported thresholds for public WTP. Some of the analyses used arbitrary thresholds.
- The studies employed only utility value survey methods for adults. In some cases, no preference-based approaches were used for utility values.
- Mortality rates, interpersonal and social functioning, or the number of AEs were not explicitly reported.
- Most studies used cost data which were 4 to 5 years old. It is unclear whether treatment standards and price relationships have remained unchanged over this relatively long time period. Additionally, no long-term costs were reported.
- Adaptability was discussed only in part, with regard to adaptability to another country.
- Due to structural differences between systems, it is unclear whether the health services rendered in the studies correspond to the realities of care in Germany.
- While the cost categories in the US and UK studies can be generally adapted to the German context, it is difficult to convert specific prices, particularly from the US healthcare system.

5.2.5 Discussion

A critical assessment of methodological and reporting quality shows that while the studies do not suffer from any substantial methodological limitations, direct adaptation of the studies to

the German healthcare context is impossible due to excessive differences between the systems and other factors. Using the studies as a basis for making health economic decisions in Germany is therefore recommended only to a limited extent or not at all. Consequently, conducting independent health economic analyses particularly for the German healthcare context is recommended for the future. Future health economic analyses specific to Germany in the form of cost effectiveness/utility analyses or economic modelling studies should illuminate not only long-term costs, long-term benefits, and adverse effects, but also the effects of various treatment pathways across sectors and for society as a whole.

6 Results: Ethical, social, legal, and organizational aspects

6.1 Results on ethical aspects

On the basis of the Socratic approach checklist by Hofmann [31], we identified ethically relevant aspects with regard to the target group, disorder, interest groups, and the intervention in question. Where applicable, aspects relating to children (0–12) versus adolescents (13–18) were distinguished because depressive symptoms can manifest differently in different age groups. The analysis of ethical aspects is based on 78 publications.

6.1.1 Ethical aspects related to the target population

The ethical imperative for the treatment of depression is based on the principle of beneficence, which states that individuals in health professions are obligated to act in the patient's best interest. The risk of depression persisting into adulthood is one reason why treatment for the purpose of preventing future impairment is needed. Depression can also cause changes in thinking, motivation, mood, or behaviour, and, if untreated, present a risk of suicide [110].

Since depression additionally has an unfavourable effect on the child's or adolescent's healthy development, the concept of vulnerability is of particular ethical relevance [110-113]. Depression reduces the quality of life, and in combination with shyness and low self-esteem, it can increase loneliness [114,115]. In the context of vulnerability, another relevant aspect is that depression can also manifest alongside long-term clinical symptoms and disorders [116]. Family-related vulnerability represents a major ethical problem [117]. Unfavourable factors contributing to depression include physical and sexual abuse, poor support in case of homosexual orientation [118], neglect, attachment disorder, parental depressive disorders [119,120], family conflicts, stress and breakdown, insecure relationships between parents and adolescents [117] as well as childhood trauma [121].

6.1.2 Ethical questions related to the disorder

The diagnosis of depression in children and adolescents represents a challenge because the manifestation of symptoms in children and adolescents differs from that in adults [110]. In addition, clearly differentiating pathological from normal behaviours can be difficult.

The above challenges are associated with underdiagnosis. Since the prevalence of depression increases between late childhood and early adulthood [115], many argue that depressive disorders in children and adults are still detected and treated at insufficient rates [122]. According to a US study, only one-third of children with depression receive professional support, reportedly due to poor detection of depressive symptoms, health insurance problems, stigmatization of mental disorders, and poor availability of services [111]. Treatment may also be delayed because adolescents prefer to seek help only once the

situation becomes very serious [123]. Furthermore, parents may refuse to initiate diagnostics and treatment for the depressive children [124].

However, the concept of underdiagnosis should be contrasted with the concept of medicalization to avoid human (emotional) states being defined and treated as medical conditions. According to some US voices opposing the medicalization of children and adolescents, numerous investigations indicate a dramatic rise in prescriptions for psychoactive drugs (particularly SSRIs) for children and adolescents [125]. The average duration of psychotherapy, in contrast, has dropped considerably [126]. Several authors additionally propose rejecting the treatment imperative – treating simply because treatment is possible – and foregoing the treatment of human emotional states [127]. The term medicalization is also relevant in the context of religious views of depressive disorders, according to which depression can be seen as a form of spiritual ritual [128]. Furthermore, a Canadian study shows a relationship between participation in religious events (worship services, etc.) and lower severity of depression in adolescents with depressive disorder [129].

Pathologicalization of depression may impair autonomy – the right or ability to lead a self-determined life – by reducing concentration, enthusiasm, energy, or hope [128,130]. However, particularly in young people, the idea of a stable self is problematic because children and adolescents undergo “rapid changes in development in the mental, cognitive, affective, communicative, and interpersonal areas” [113].

6.1.3 Ethical aspects concerning the intervention, comparator interventions, and stakeholders

A relevant objective of psychotherapy is to promote patient autonomy [131] in an effort to improve their independence and self-esteem [132]. Even at the start of treatment, autonomy is a prerequisite for granting a clear informed consent. Therefore, the start of (psycho)therapy without an initial informed consent discussion seems somewhat contradictory in terms of autonomy since therapy is typically not sought by the children and adolescents themselves but initiated by their parents or guardians [133]. All nonemancipated adolescents are required to participate in treatment once their parents/guardians provide consent [133]. It helps to view agreement and informed consent as a continuum. As children get older, this decision becomes more self-determined [134]. From an expert perspective as well, it is very important to explain in detail the objectives and process of psychotherapy in order to obtain the children’s and adolescents’ consent to therapy. The invitation to discuss topics of their choice during therapy promotes patient autonomy. Due to their often high level of suffering, most are reportedly very open to treatment (interviews with child and adolescent psychiatrist/psychotherapist).

Confidentiality or privacy of information can present a conflict in the assessment of what is in the best interest and presents a challenge for healthcare professionals. If the qualified professional obtains information about suspected mistreatment (e.g. abuse or neglect), self-harm or suicidal intent, the promise of confidentiality can be suspended in order to act in the patient's best interest. Preventing acute risks to self or others can take priority over confidentiality [133], but it can also represent a breach of trust and induce the young person to discontinue treatment [135]. Additional tension can result from excessive involvement of parents/guardians.

In the special situations outlined above as well as in routine work with depressive children and adults, qualified professionals must make well-reasoned clinical and moral decisions, with moral principles being weighed against one another (best interest versus confidentiality and trust [136], individual autonomy of children and adolescents versus relational autonomy [137]). They must inform children and adolescents about unrealistic expectations (informed consent) [136] while simultaneously maximizing favourable effects of treatment and minimizing harm (in line with the Hippocratic Oath) [111]. For therapists, the challenge lies in recognizing the key problem to be solved by therapy, understanding that the interests of all involved parties may not necessarily be congruent [112].

As mentioned above, while there is evidence of psychotherapy being effective in depressed adolescents, only a limited number of research projects exist on children under 12 years of age [41]. For this reason, psychotherapy is argued to be easiest to administer in situations where depression is mild, or stressors can be eliminated [138]. Antidepressants constitute the treatment alternative to psychotherapy. Regarding antidepressants, qualitative studies report that adolescents whose "self-image is someone who is independent and free from external control" experienced medication as threatening to their autonomy. Key topics were "fear of dependency" and "the desire for autonomy" [139]. The expert interviews also emphasized that add-on pharmacotherapy requires intensively informing the affected people (interviews with child and adolescent psychiatrist/psychotherapist). It should also be noted that in 2004, the U.S. Food and Drug Administration (FDA) issued a black box warning against the use of any antidepressants in children [119] because antidepressants (particularly selective serotonin reuptake inhibitors) can increase the risk of suicide in children [140]. In the benefit assessment portion of this HTA report, however, no hint was found for greater or lesser suicide risk on antidepressants in comparison with psychotherapy. None of the systematic reviews surveyed adverse events, which made it impossible to definitively weigh benefits versus harm.

6.2 Results on social aspects

The analysis of information on social aspects was guided by the comprehensive conceptional framework suggested by Mozygemba et al. 2016 [87] and was based on 17 publications (studies, website of interest groups).

6.2.1 Social construct / perception of depression in children and adolescents

Depression in children and adolescents is an established disorder with clearly defined diagnostic criteria in accordance with ICD-10. Children and adolescents often experience it as very burdensome and hopeless. Nevertheless, depression in the early years of life is often detected very late or not at all, because other symptoms (e.g. aggressiveness, hyperactivity) and comorbidities frequently overlap the disorder, or depressive symptoms are misinterpreted as typical adolescent behaviour [108,141,142]. Adolescents also report not sharing their feelings of depression for a long time for fear of stigmatization, loss of autonomy, or burdening their social environment [108].

6.2.2 Social image / perception of the intervention

Adolescents view psychotherapy as a causative therapy option for their disorder, while antidepressants are perceived as symptomatic treatment [139]. Children and adolescents hope that psychotherapy will provide them with instructions and support for better handling their daily lives and reintegrating at school and with their families and friends, and ultimately to becoming healthy [137,143]. However, parents as well as children and adolescents themselves are often unaware of the services available in Germany [144].

Psychotherapy is a widely accepted treatment option [143,145]. Nevertheless, about one-fourth of parents do not seek professional help for their child for fear of what other people might think [144]. Cultural backgrounds may influence the acceptance of psychotherapy as well [146]. Whether adolescents accept psychotherapy depends, firstly, on whether they undergo it voluntarily. Being forced into therapy is associated with a negative attitude and low acceptance, which can promote treatment discontinuation. Secondly, a good, trustful patient-therapist relationship is essential for accepting therapy and continuing it in the long term. Dissatisfaction with the relationship, the treatment approach, or the achieved improvements can lead to treatment discontinuation [135].

Both parents and adolescents view psychotherapy as being associated with few risks, while they consider antidepressant treatment to be associated with risks such as dependency, loss of autonomy, and self-harming behaviours [139,147]. Some parents worry about psychotherapy potentially reawakening trauma and worsening the child's health [148]. According to the experts, parents also worry about the child having excessive autonomy. Some children and adolescents fear being rejected by their social environment because of their participation in psychotherapy [56].

6.2.3 Sociocultural aspects of the use of the intervention

In Germany, the prevalence of mental disorders is unevenly distributed in terms of sociooeconomic status. Children from families of low sociooeconomic status suffer from mental problems more frequently (26%) than children from families of high (9.7%) or

moderate (16.1%) sociooeconomic status [149]. In Germany, girls are slightly more commonly affected by depression than boys (3.7% versus 2.5%). Regional differences (Eastern/Western Germany) have not been observed [150]. However, the availability of psychotherapy treatment slots differs between German regions. Care provision for children and adolescents with depression is better in urban than in rural areas, and more services are available in the west than in the east [151].

Collaboration between different healthcare professions is necessary to guide children and adolescents through the healthcare system in a goal-oriented manner from the outset. This means that initial patient contacts such as general practitioners and paediatricians should refer children and adolescents with suspected depression to qualified professionals. Likewise, it must be noted that child and adolescent psychiatrists may also prescribe medications, while child and adolescent psychotherapists may offer only psychotherapy. Should combination therapy be required, psychologists must work with psychiatrists. The expert interviews show that there is a particular need for low-threshold services in the children's and adolescents' living environments, such as school social workers.

6.3 Results on legal aspects

Information processing on legal aspects was based on the guideline developed by Brönneke et al. 2016 [35] for the identification of legal aspects and drew upon 14 documents.

6.3.1 Patient autonomy I – informed consent

According to German Civil Code (BGB) Section 630d (1) clause 1, prior to implementing medical treatment, particularly a procedure affecting the body or health, the treating party is obliged to acquire the consent of the patient.

The emphasis lies on the patient's self-determination, who, as an autonomous subject, should be able to decide on the implementation of the treatment. This, in turn, requires that the patient has been properly informed in a comprehensible manner and asked explicitly and unambiguously whether he or she agrees to the procedure [152].

According to BGB Section 630e (1) and settled case law, the treating physician is obliged to inform the patient of relevant treatment options with materially different risks or materially different chances of success. As the subject of treatment, the patient must be allowed to choose between treatment methods which are equally medically indicated (BGH 15.03.2005, VI ZR 313/03, page 6 with further evidence) [153].

The respective professional codes and the Model Professional Code of Conduct (MPC) for psychological psychotherapists and child and adolescent psychotherapists [154] likewise specify that any treatment requires the patient's informed consent (MPC Section 7) [154].

6.3.2 Patient autonomy II – child/adolescent consent

A prerequisite for valid consent is the patient's capacity to grant consent [155]. This requires the person in question to have the natural capacity to form one's own will and to possess sufficient comprehension and judgement to weigh the benefits and risks of treatment and then come to an autonomous decision (Laufs/Kern, Handbook of Medical Law [Handbuch des Arztrechts], Section 137(7)) [156]. A minor's consent to an intervention affecting physical integrity is legally valid if the person has the mental and moral maturity to understand the meaning and scope of the procedure and of granting consent (BGH 5 December 1958, VI ZR 266/57 = NJW 1959,811) [157]. The MPC [154] likewise refers to the required natural ability to understand the treatment (e.g. Section 12(2) MPC).

Children and adolescents do not always have this capacity to grant consent. According to the German Civil Code Section 630d(1) clause 2 BGB [158], if the patient lacks the capacity to give consent, the consent of a party entitled to do so is to be obtained. Whether minors capable to grant consent can in fact consent without involving their legal representatives is a subject of controversy. As far as can be ascertained, the prevailing opinion is that minors capable of granting consent may decide independently (Spickhoff A. in Spickhoff, Medical Law [Medizinrecht] Sections 630d(8)) [155]. The BGH, as far as can be ascertained, holds that minors have veto rights (BGH 10 October 2006, AZ VI ZR 74/05) [159]. Where patients lack the capacity to give consent, consent must be obtained of a party entitled to do so, who must take into account the abilities and needs of the minor while exercising custody. This is specified in the MPC as well (Section 12(2) MPC) [154].

Minors under the age of 14 years will not have the capacity to grant consent; minors between 14 and 17 years of age may have the capacity to grant consent, but this must be determined for each individual case.

6.3.3 Data protection

In terms of data protection, Section 10 MPC requires psychotherapists to ensure that any collected data and personal records be stored securely and fully protected from access by unauthorized third persons.

Health data are particularly worthy of protection and are subject to even stricter rules. Health data are considered "sensitive data" (GDPR Art. 9) [160] and therefore represent a special category of personal data. "Data concerning health" are defined as "personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status" (General Data Protection Regulation Art. 4(15)) [160]. Such data must be processed only for the purposes listed or in the context of exhaustive justification, e.g. for the defence of legal claims (Art. 9(2f)) [160]. In addition to providing for explicit patient consent, which is retractable at any time, GDPR

Art. 9(2) allows processing when, e.g. it is necessary for the purposes of preventive medicine, medical diagnosis, the provision of health or social care or treatment or the management of health or social care systems and services on the basis of law or pursuant to contract with a health professional (Art. 9 (2h))[160].

6.3.4 Duty of confidentiality

The relevant MPC provides for a comprehensive duty of confidentiality, which may lead to conflicts between the duty of confidentiality and the duty to inform parents/guardians. For instance, MPC Section 8(1) specifies that psychotherapists have a duty of confidentiality regarding treatment relationships and information they have learned from and about patients or third parties in the context of their professional activities.

According to MPC Section 12(6), psychotherapists have a duty of confidentiality vis-à-vis patients capable of insight as well as any attachment figures participating in the therapeutic process. To the extent that minors possess the natural capacity to comprehend the treatment, any viewing of the patient records by parents/guardians requires the minor's consent. In cases where the child does not possess sufficient understanding and judgement, the parents' right to exercise custody (BGB Section 1626f) results in a duty to inform parents (also MPC Section 8(2)) [154]. However, where patients put themselves or others at risk or are being put at risk, treatment providers must weigh confidentiality versus the protection of the patient, third parties, and public welfare. If necessary, they must take measures to protect the patient or third parties (MPC Section 8(4)) [154].

6.3.5 Licensure / professional practice

Psychotherapist training has been revised by the Psychotherapist Training Reform Act from 19 November 2019 (PsychThGAusbRefG, Federal Law Gazette 2019, Part I No. 40, issued on 22 November 2019 in Bonn, in force since 1 September 2020) [161]. However, the Psychotherapist Training Reform Act also provides for transitional provisions with regard to the continued use of old professional titles (Section 26), the completion of commenced training programmes (Section 27), and the continued validity of state recognition of training facilities (Section 28). The training of psychotherapists involves 5 years of university studies. These studies consist of a bachelor's followed by a master's degree and may be offered only at universities or at higher education institutions which are equivalent to universities. After successful completion of studies and meeting of prerequisites as well as completion of a psychotherapist exam (board examination at state level), licensure, and several years of continued education (specialization in a method), specialist knowledge (specialist training as "psychotherapist in training" in one of the guideline procedures such as depth-based psychology or child and adolescent psychotherapy, etc.) can be demonstrated, thereby obtaining access to the SHI system.

Psychological psychotherapists, child and adolescent psychotherapists as well as physicians are allowed to use the title “psychotherapist”. Physicians can add the term “medical”, with the prerequisites being a university degree in medicine, that is, successful completion of studies of medicine, and additional training in psychotherapy (e.g. specialist training in child and adolescent psychotherapy). In addition to performing psychotherapy, physicians may also prescribe drugs, etc.

6.3.6 Reimbursement of costs in the healthcare system

Under certain conditions, such as the presence of a pathology and suitability of psychotherapy for alleviating or curing the disorder, the cost of psychotherapy is covered by SHI (see SGB V Section 92(6a)) [162]. However, this applies only to therapies carried out in accordance with the G-BA Guidelines for Psychotherapy [13]. The Guidelines for Psychotherapy specify in more detail the psychotherapy types and forms which can be billed to the SHI as well as their scope of application as well as the consultation, application and expert opinion procedure, the scope of services, and requirements regarding basic psychosomatic care. Furthermore, the Guidelines for Psychotherapy (Sections 34, 35) and the psychotherapy agreement (Section 12) contain provisions on the so-called expert opinion procedure (see [16] regarding numbers of sessions). In an expert opinion procedure which forms part of the patient’s application for payment of psychotherapy, the therapist’s report is submitted, and experts commissioned by the National Association of SHI Physicians in agreement with the National Association of SHI Funds then come to a decision [163]. In this context, however, it must be noted that psychotherapist training has been reformed (Psychotherapist Training Reform Act), with implications for the expert opinion procedure in that – as far as can be ascertained – new forms of quality assurance are to be developed for outpatient psychotherapy (see [164] and reports on the project, including by the Federal Chamber of Psychotherapists [165]).

Outside the SHI system, cost assumption depends on the private health insurer, particularly the private health insurer’s general policy conditions.

6.4 Results on organizational aspects

The information processing on organizational aspects followed the grid template proposed by Perleth et al. 2014 [34] for the assessment of organizational consequences of treatment methods. The evaluation of organizational aspects was based on 15 publications (studies, guideline, stakeholder websites).

6.4.1 Influence on the prerequisites of service provision

If depression is suspected, the first contact for the affected person can be a general practitioner, paediatrician, psychosocial counselling centre, or sociopsychiatric services. These providers can recognize a need for psychotherapy, but they neither diagnose depression nor offer psychotherapy. Only qualified healthcare providers should diagnose depression in

children and adolescents, with preference given to healthcare providers possessing special knowledge of the developmental psychology-related variations in clinical manifestations of depressive syndromes during childhood and adolescence [6]. First contacts can also be psychotherapy or medical specialist practices. Since 2017, SHI-authorized psychotherapists as well as psychological psychotherapists also offer psychotherapeutic consultations. This low-threshold service, which patients can use directly, without a referral, allows clarifying any treatment needs in a timely manner and guiding patients to the proper care in a coordinated manner [166].

In Germany, the treatment rate for people with depression of any age group is 50% [20]. It is similar for children and adolescents [23]. The main reasons for people with mental health issues not utilizing professional help include uncertainty whether the health problem is sufficiently serious, worries about potential stigmatization, and lack of knowledge about contact points and available services [144].

In 2008, the Robert Koch Institute also concluded that there is an east-west differential regarding the availability of child and adolescent psychotherapists, with a 4 times lower rate of professionals being available in the regions formerly belonging to East Germany. Likewise, a difference between rural and urban areas was observed, showing a lower density of services in rural areas. The additional long waits for psychotherapy for children and adolescents further suggest underprovision, even in areas enjoying relatively high density of services. According to a 2008 study, children and adolescents wait an average of 2 months for the initial diagnostic visit and 4.5 months for a treatment slot [151]. In recent years, however, the availability of services has increased in Germany. Positions for SHI-registered child and adolescent psychiatrists and psychotherapists have doubled [149]. In addition, patients who do not receive a therapy slot within an appropriate waiting period (up to 6 weeks in children and adolescents) are now entitled to consult professionals without SHI registration and bill their health insurance fund for these services [151]. In practice, health insurance funds often reject applications for cost coverage [167]. However, cost coverage is deemed essential because it strengthens adolescents' independence from their parents (according to interviews with child and adolescent psychiatrist/psychotherapist). Despite treatment slots having been increased in recent years, the BELLA study (with surveys conducted 2009–2012) concludes that insufficient treatment slots are available for children and adolescents in Germany [144].

6.4.2 Influence on processes

In children and adolescents with depression, the recommended treatment is active monitoring as an alternative to psychotherapy in case of mild depression or the antidepressant fluoxetine (as monotherapy or in combination with psychotherapy) in case of severe depression or nonresponse. Health insurance funds pay for all treatment types [6]. Psychotherapy can be performed by the same professionals who are responsible for active

monitoring and antidepressant therapy, but also by nonmedical professionals with psychotherapeutic training. No shifts in services are therefore expected in this area. However, psychotherapy is more resource intensive than drug therapy or active monitoring. Since, in Germany, many professional groups can be responsible for the diagnostics and therapy of children and adolescents, these professional groups must communicate and collaborate well to ensure diagnostics and adequate care.

7 Synthesis of results

The general question of whether psychotherapy leads to better results than other therapies in children and adolescents with depression can be answered to some degree. Evidence was found for comparisons between psychotherapy and inactive comparator interventions or antidepressant treatment, but not for non-drug comparator interventions such as exercise or relaxation exercises or active monitoring (mental health education).

Both for CBT and for IPT, indications of benefit were found in comparison with inactive controls. Depressive symptoms in children and adults are reduced more effectively by CBT than by inactive controls [38]. This was shown for CBT in general as well as for the subtypes of "mindfulness-based CBT" and "computer-based CBT", but not for the subtype of "problem-solving therapy" [36,42,47,48]. In a separate analysis of children and adolescents, CBT was found to be more effective than the control condition for each group [38]. Subgroup analyses show that CBT reduces depressive symptoms in children without comorbidities, but not in children with comorbidities. According to a subgroup analysis, CBT is more effective when parents are not involved than when they are [46]. Regarding subgroup analyses which show no statistically significant results, however, it must be noted that, in some cases, very few studies were included per subgroup, and, consequently, the absence of a statistically significant effect might also be due to lack of statistical power. IPT likewise resulted in more effective reduction in depressive symptoms and higher functioning than no active treatment [42,44,47,48]. A subgroup analysis showed that IPT both as one-on-one and group therapy was more effective than no active therapy [44]. Due to wide confidence intervals, no conclusions can be drawn from the evidence on CBT, IPT, or DYN with regard to suicide risk.

The direct comparison with other treatment options showed no evidence of any of the 3 types of psychotherapy being associated with greater or lesser benefit than treatment with an SSRI (typically fluoxetine). CBT, IPT, and DYN were similarly effective as antidepressant therapy in reducing depressive symptoms [37,47]. Likewise, there was no hint that children and adolescents receiving CBT are at lower risk of suicide than those on antidepressants [37].

Likewise, there was no hint of antidepressant therapy with add-on CBT being more effective than antidepressant monotherapy in achieving remission or improvement of depressive symptoms [37]. In the long term, add-on CBT led to better functioning, but this effect was not found in the short term or medium term. With regard to suicide risk and response, antidepressant therapy with add-on CBT did not produce any better results than antidepressant monotherapy [37,40,47]. The identified systematic reviews did not investigate IPT and DYN as add-ons.

None of the included systematic reviews reported on the effects of psychotherapy on mortality, health-related quality of life, or adverse events.

The calculation of intervention costs for the German healthcare context shows that higher direct costs result from psychotherapy than from treatment alternatives. In Germany, CBT and DYN (depth psychology-based and analytical psychotherapy) can be billed to the health insurance funds [13]. For 12 weeks of short-term one-on-one therapy with 12 sessions at 50 minutes or 2 x 25 minutes each, including all component services, the total cost for all CBTs and DYNs range from € 1793.08 to € 2104.68. The billing of IPT costs is not clearly regulated, since IPT is not defined as a guideline-recommended therapy. In clinical practice, however, SHI physicians can often bill its costs to the SHI [98]. The calculated costs for 12 weeks of one-on-one therapy with 12 sessions at 50 minutes or 2 x 25 minutes each, including all component services, equal € 1793.08 to € 2104.68. Fluoxetine is currently the only drug approved in Germany for the pharmacotherapy of depressive children and adolescents 8 years or older. In addition to the cost for the drug itself, costs arise for 1 initial interview, 4 follow-up visits, and 2 complete blood counts. Moreover, responses should be checked after 4 weeks and 8 weeks to document effectiveness and symptoms. In total, 8 weeks of therapy cost between € 311.23 and € 318.47 depending on the required dose (minimum of 10 mg, maximum of 20 mg) and drug product. The costs can be billed to the SHI. As an active monitoring intervention, mental health education was examined in more detail. For 9 units, including 4 units of psychotherapeutic consultation for the accompanying person, the costs total € 659.88. In addition, the costs for relaxation therapy as another nonmedicinal intervention were calculated. Six to 8 weeks of relaxation therapy with 8 to 10 sessions of relaxation therapy at 60 minutes each cost a total of € 349.36 to € 411.32. The cost of mental health education and relaxation exercises are likewise covered by the SHI funds. However, the above figures do not include the diverse (long-term) consequential costs of depression (e.g. lower income in adulthood).

Five studies, all examining CBT, were found on cost effectiveness. They demonstrated CBT not to be cost effective in comparison with no active treatment or antidepressant monotherapy [84]. The same applies to a combination of CBT and antidepressants versus antidepressant monotherapy – but only in the short term; it was in fact cost effective in the long term [84,88]. This concurs with the results of the benefit assessment, which likewise did not derive any greater benefit for CBT versus antidepressant treatment and showed a benefit of add-on CBT regarding the outcome of functioning only in the long term, but not the short term or medium term. Although the studies were not impeded by substantial methodological limitations, the differences between the systems are too great to allow the results to be applied directly to the German healthcare context

The diagnosis of depression presents social, ethical, and organizational challenges. While depression is an established disorder in children and adolescents which can lead to increased vulnerability and can persist into adulthood, it is often recognized late or not at all because other symptoms and comorbidities overlap with the disorder, or depressive symptoms are

misinterpreted as typical adolescent behaviour [108,141,142]. Primary care providers such as general practitioners and paediatricians should therefore refer children and adolescents with suspected depression to qualified specialists.

Further reasons for professional help not being utilized by people with mental health issues include uncertainty whether the health problem is sufficiently serious, worries about potential stigmatization, lack of knowledge about contact points and treatment options as well as lack of available services [144]. In Germany, service availability for children and adolescents with depression is better in urban than in rural areas, and the service networks are denser in the west than in the east [151]. Adding qualified professionals as well as raising public awareness of available services might contribute to increasing the treatment rate.

Many people accept psychotherapy as a treatment option [143,145]. Adolescents view psychotherapy as a causative treatment option for their disorder, while antidepressants are perceived as symptomatic treatment [139]. Both parents and adolescents deem psychotherapy as being associated with few risks, while considering antidepressant treatment to be associated with risks such as dependency, loss of autonomy, and self-harming behaviours [139,147]. They fear that as a side effect of psychotherapy, trauma might be reawakened, leading to deterioration of the child's health [168]. According to the experts, parents also worry about the child having excessive autonomy. Some children and adolescents worry about stigmatization [56].

Psychotherapy aims to strengthen the child's or adolescent's autonomy and self-esteem [131,132]. Therefore, it is ethically and legally necessary to obtain the child's consent from the outset, provided that the child possesses the necessary mental maturity. Voluntary participation and a good, trustful patient-therapist relationship are prerequisites for treatment acceptance and long-term compliance. Although a subgroup analysis shows that psychotherapy without involvement of parents/guardians was more effective, a certain degree of involvement is necessary, especially in younger children. It must be noted, however, that the child's or adolescent's interests take priority and might not coincide with the needs of parents/guardians [122]. From an ethical and legal perspective, the duty of confidentiality by which healthcare professionals are bound can lead to conflicts between confidentiality and duties to notify parents or guardians.

8 Discussion

The benefit assessment revealed indications of CBT and IPT reducing depressive symptoms in children and adolescents more effectively than inactive controls. Nevertheless, German SHI funds cover the costs of CBT and DYN in children and adolescents with depression, but not the costs of IPT since it does not meet the G-BA's Guidelines for Psychotherapy [13]. Treatment guidelines, however, recommend IPT for the treatment of children and adolescents [78]. Future revisions of the Guidelines for Psychotherapy should reassess IPT for children and adolescents. Regarding DYN, it was not possible to draw any conclusions on benefit or harm in children and adolescents with depression. The relevant results stem from only 1 study of a network metaanalysis and cover only the outcomes of suicide risk and change in depressive symptoms, resulting in very limited informative value of the evidence. In future, international and German randomized controlled trials on this type of psychotherapy in children and adolescents would be desirable.

The identified evidence does not allow drawing any conclusions on differences in effectiveness of psychotherapy based on severity of depression because the studies often analysed mild, moderate, and severe forms of depression jointly and rarely investigated the influence of comorbidities separately. Likewise, no valid conclusions can be drawn regarding comparative effectiveness versus different inactive control interventions because the metaanalyses combined different comparator groups like "no intervention", "psychological placebo", and "usual care" as inactive control interventions. In addition, the systematic reviews did not define the terms "usual care" and "psychological placebo" in any detail, further complicating interpretation. Studies differentiating these interventions more clearly are needed.

The results of health economic systematic reviews cannot be adapted to Germany. Nevertheless, they are relevant for this HTA report since they provide input on cost structures and model parameters which give health planners in Germany insight into clinical routine and can be used for health economic analyses of the German healthcare context. It was possible to calculate intervention costs specifically for Germany. However, these calculations are generally incomplete because they lack the cost–benefit aspect and disregard the potential long-term economic burden of disease caused by depression in childhood or adolescence.

For children under 8 years of age, no evidence was available. Regarding this patient group, any conclusions on the effectiveness and safety of psychotherapy must therefore be inferred from studies with older children but doing so is complicated by differences in neurobiology and risk factors [4]. The implementation of psychotherapy can differ in young children because family involvement plays a much greater role and treatment approaches are pursued in a more playful way and in interaction with an attachment figure. Studies in younger children are needed in order to derive treatment recommendations specifically for this age group. However, such studies present major ethical and legal challenges because young children with

depression are deemed to require particular protection. The lack of evidence for this age group also poses an ethical problem because study results on older children and adolescents cannot be fully extrapolated to younger children.

The involvement of parents/guardians can lead to tensions in the implementation of psychotherapy because the children's and adolescents' needs may not coincide with the ideas of parents/guardians. However, psychotherapy must always serve the best interests of the child or adolescent. Autonomy, for instance, is an important goal of psychotherapy. Parents and guardians, however, may perceive the child's or adolescent's strengthened autonomy as rebellion and hence in a negative manner. Another parent-related field of tension results from therapists being bound by a duty of confidentiality toward their patients. Simultaneously, parents/guardians often have difficulty with not being told what has been discussed in therapy. Despite these possible tensions, it is often necessary to involve parents in psychotherapy because depressive symptoms must be viewed in a psychosocial context and the family environment typically plays an important role. The extent of parental involvement can decrease as the child or adolescent becomes older.

One systematic review investigated which outcomes were surveyed in RCTs with depressive children and adolescents; it found that changes in depressive symptoms and functioning were most frequently surveyed [169]. The same was found in the present benefit assessment. The included systematic reviews did not provide any data on important outcomes such as side effects, health-related quality of life, and (suicide) mortality. For future studies, it would be important to establish a standard set of outcomes and methods for measuring the success and safety of the treatment of depression in children and adolescents.

8.1 HTA report compared with other publications

An umbrella review (systematic review of systematic reviews) was published in Norwegian in 2020; it covers, among other things, the effectiveness and safety of psychotherapy in the treatment of depression in children and adolescents [170,171]. The results of this paper largely concur with those of the benefit assessment in this HTA report. The umbrella review demonstrates that CBT and IPT can effectively reduce depressive symptoms in children and adolescents. The comparison of CBT versus antidepressant treatment showed few to no differences with regard to remission and depressive symptoms, but a lower risk of suicide under CBT than on antidepressant therapy. The authors concluded that a combination of CBT and antidepressants leads to better treatment success than antidepressant monotherapy [170,171].

Another umbrella review published in 2020 investigated the effectiveness and safety of antidepressants in children and adolescents in comparison with placebo [172]. Although this topic was not covered in the benefit assessment, the comparison of antidepressants versus

no treatment is relevant for putting the comparison of psychotherapy versus antidepressants in the proper context. The umbrella review demonstrated that fluoxetine compared with placebo can effectively reduce depressive symptoms in children and adolescents. It was impossible to determine whether fluoxetine is associated with an increased risk of adverse events and suicide. Only the antidepressant velafaxine, which is not approved for children and adolescents in Germany, was associated with a higher risk of suicide [172].

After the literature search for the benefit assessment had been completed, the Agency for Healthcare Research and Quality published a systematic review on the treatment options for depression in children and adolescents [173]. This review was consequently not included in the benefit assessment of this HTA report. Its results, however, concur with the results of this HTA report. The systematic review showed that CBT and IPT improve depressive symptoms in children and adolescents. As in the present HTA report, no data were found on adverse events of psychotherapy. Said systematic review also investigated SSRIs compared with placebo, showing an increased risk of adverse events for SSRIs [173]. One systematic review on DYN was published after completion of the temporary HTA report in April 2021 [174] and another in September 2021 [175]. However, these systematic reviews included the same RCTs already covered by the systematic reviews included in this HTA report. In the commenting procedure, additional studies [176-179] were mentioned, but they did not meet the inclusion criteria of this HTA report. In the benefit assessment, no systematic review was found comparing psychotherapy with other non-drug therapies such as exercise. Two recent systematic reviews which investigated the effectiveness of exercise [180,181] versus sham treatment or no treatment demonstrated a moderate but statistically significant favourable effect of exercise on depressive symptoms in children and adolescents. This effect increased with the intensity of physical activity. The treatment effect found for the comparison of exercise versus active control interventions, e.g. playing board games, was smaller than for the comparison of exercise versus no active intervention. Future research should also compare exercise with psychotherapy and antidepressant treatment [180].

8.2 HTA report compared with guidelines

The most current guideline is “Depression in children and young people: identification and management” by the National Institute for Health and Care Excellence (NICE) [182]. The guideline covers the aspects of diagnostics, access to treatment, and treatment itself and recommends providing patients and their carers with good information, taking into account the principles of informed decision-making and consent in the treatment of children, adolescents, and their parents. These aspects are deemed to form the basis of a trustful relationship with healthcare providers. The results of the NICE guideline [182] are difficult to compare with those of the benefit assessment because the guideline consistently explicitly distinguishes mild forms of depression (including dysthymia) versus moderate to severe forms.

The evidence report on which this guideline is based identifies evidence for the age group of 5- to 11-year-old children with **mild depression** exclusively for the comparison of group CBT versus waiting list or no treatment: CBT treatment in a group setting reduced depressive symptoms in the short term, but no long-term effect was shown. In 12- to 18-year-old adolescents with mild depression, computer-based CBT, CBT, group IPT as well as one-on-one CBT effectively reduced depressive symptoms, and adolescents' functioning improved both immediately after as well as up to 6 months after therapy when compared with waiting list or no treatment. Concerning children (5 to 11 years of age) with **moderate to severe forms of depression**, the evidence showed that immediately after treatment, group CBT reduced depressive symptoms more effectively than inactive control (waiting list, no treatment). In 12- to 18-year-old patients with moderate to severe depression, one-on-one CBT reduced symptoms and improved functioning, quality of life, and suicidal thoughts more effectively than waiting list, no treatment, or usual care. IPT likewise reduced depressive symptoms and increased functioning by the end of treatment compared with waiting list, no treatment, or usual care. With regard to the outcomes of reduction in depressive symptoms, remission, and quality of life, each measured at the end of therapy, psychodynamic therapy was not more effective than brief psychosocial intervention.

Based on this evidence, the guideline recommends the following: patients with mild depression, regardless of age, should initially receive active monitoring. If symptoms persist after 2 weeks, computer-based CBT or CBT, IPT, or nondirective supportive psychotherapy in a group setting is recommended, or, if this does not meet the person's needs, alternatively CBT in a one-on-one setting. The special needs of children should be taken into account. In children (5 to 11 years of age) affected by moderate to severe depression, family-based IPT or family therapy, psychodynamic psychotherapy, one-on-one CBT, or fluoxetine therapy (either in combination or monotherapy) are the treatments of choice. In adolescents (12 to 18 years of age), one-on-one CBT or fluoxetine (either in combination or monotherapy) is recommended. For adolescents who do not accept this therapy, IPT, family therapy, psychodynamic therapy, or brief psychosocial intervention (including in combination with fluoxetine) can be used as well.

The S3 guideline [6] from Germany was published in 2013 and is currently being reviewed; therefore, this review focuses on the more current NICE guideline.

8.3 Critical reflection on the approach used

The benefit assessment of this HTA report employed the umbrella review method – a preferred procedure for comprehensively analysing a broad topic and providing decision makers with an overview of the best available evidence [183]. This method allowed answering a comprehensive research question with many possible treatment comparisons by means of the available resources. A weakness of the method, however, is lower granularity in the

presentation of results and the fact that only general conclusions can be derived [184]. In the present benefit assessment, conclusions on the effectiveness of CBT, IPT, and DYN can be drawn, but not on the effectiveness of special subforms of these therapeutic schools, on the duration and number of treatment sessions, on the extent of parental involvement, or on differences in effectiveness based on the severity of depression. Such conclusions would require the underlying systematic reviews to contain detailed information on these topics. Since such subgroup results were not reported, however, no conclusions can be drawn on this topic in this HTA report.

In some cases, results from metaanalyses were incorporated despite some studies not meeting the inclusion criteria at 80% or above. This inclusive approach was chosen for NMAs because important information from the indirect comparison would otherwise have been lost. Results were also extracted from metaanalyses even if they included a small number of studies involving patients in whom depression was identified by way of cutoffs predefined in questionnaires.

For the originally planned patient interviews, the ethics committee did not grant a favourable opinion. The main grounds for the unfavourable opinion was that children with depression represent a particularly vulnerable group. This underscores the fact that depression in children is an ethically and legally complex area. As an alternative approach, interviews were held with a child and adolescent psychiatrist and a child and adolescent psychotherapist who also led a self-help group. In this manner, at least indirect insights in the patient situation were obtained.

9 Conclusion

Regarding the effectiveness and safety of psychotherapy in children and adolescents with depression, 13 systematic reviews with data from 150 primary studies were included in the present report. Six systematic reviews investigated cognitive behavioural therapy, 2 focused on interpersonal psychotherapy, 3 investigated both types of psychotherapy, and 2 focused on cognitive behavioural therapy, interpersonal psychotherapy as well as psychodynamic psychotherapy (short-term psychoanalytical psychotherapy and focused psychodynamic psychotherapy). Systematic reviews on systemic therapy were disregarded in this HTA report because it is covered by another IQWiG project which will be commissioned shortly. Nine systematic reviews looked at the evidence available for children and adolescents jointly. Two systematic reviews focused only on children (7–13 years) and 2 only on adolescents (13–18 years). The psychotherapies included in the systematic reviews varied in duration between 4 and 54 weeks, and the number of sessions ranged from 4 to 36 units. The investigated psychotherapies took place in outpatient settings, in schools, communities, or primary care. The psychotherapy types were analysed for effectiveness compared to inactive controls or antidepressants, or as add-ons to antidepressants. Inactive control was defined as an approach without standardized treatment (e.g. waiting list or “usual care” in which the control group is, for ethical reasons, free to utilize services from routine care) or the use of sham treatment (psychological placebo). No ongoing systematic reviews were identified. No data were found on the outcomes of all-cause or suicide mortality, health-related quality of life, or adverse events. Likewise, no evidence was found for a comparison with other non-drug therapies (e.g. exercise, relaxation exercises) or active monitoring (e.g. mental health education). In this HTA report, benefit was assessed on the basis of systematic reviews, whose reporting quality heavily impacts the result. For instance, the publications typically did not carry out subgroup analyses by patient age or depression severity. No conclusions can consequently be drawn on the benefit or harm of psychotherapy for certain subgroups (e.g. children or adolescents with mild depression).

Below, the results on the reported outcomes are summarized for each comparison. To the extent reported in the systematic reviews, the time when the outcome was surveyed is provided by categorizing the follow-up as 12 to 16 weeks (short term), about 6 months (medium term), and 12 months or more (long term).

Cognitive behavioural therapy versus inactive controls: There is an indication of cognitive behavioural therapy reducing depressive symptoms more effectively than inactive controls. The comparison shows no hint of cognitive behavioural therapy increasing or reducing suicide risk. The systematic reviews did not show whether these effects are short-term, medium-term, or long-term effects. For this comparison, no data are available regarding the outcomes of response, remission, or functioning.

Cognitive behavioural therapy versus antidepressants: When compared with antidepressant treatment, there is no hint of cognitive behavioural therapy reducing suicide risk. Likewise, the comparison shows no hint of cognitive behavioural therapy or antidepressant therapy more commonly leading to short-term or medium-term remission, reduction of depressive symptoms, or better functioning. For this comparison, no data are available on the outcome of response.

Cognitive behavioural therapy + antidepressants versus antidepressants: No hint of greater benefit was found regarding short-term or long-term treatment response for the combination of cognitive behavioural therapy and antidepressants in comparison with antidepressant monotherapy. Likewise, there is no hint of greater benefit with regard to short-term, medium-term, or long-term remission, changes in depressive symptoms, or short-term or long-term suicide risk. With regard to functioning, a hint of greater benefit of add-on behavioural therapy was found in the long term, but not in the short or medium term.

Interpersonal psychotherapy versus inactive controls: In comparison with inactive controls, there is a hint of short-term, medium-term, and long-term benefit with regard to the reduction of depressive symptoms as well as a short-term benefit with regard to functioning. However, there is no hint of interpersonal psychotherapy increasing or decreasing suicide risk in the short term. The data on treatment response were disregarded in the derivation of added benefit since all studies were also included in the “changes in depressive symptoms” study pool, and response was surveyed using the same scales. Regarding the outcome of remission, no data are available for this comparison.

Interpersonal psychotherapy versus antidepressants: Compared with antidepressant treatment, there is no hint of greater or lesser benefit with regard to changes in depressive symptoms. No data were available on the time the outcome was surveyed. Likewise, this comparison lacks data on the outcomes of suicide risk, response, remission, and functioning.

Interpersonal psychotherapy + antidepressants versus antidepressants: No data are available on the combination of interpersonal psychotherapy plus antidepressants versus antidepressant monotherapy.

Psychodynamic psychotherapy versus inactive controls: In comparison with inactive controls, there is no hint of greater or lesser benefit with regard to reduction in depressive symptoms. There is also no hint of psychodynamic psychotherapy increasing or reducing suicide risk when compared with inactive controls. For this comparison, data were available neither on the time of outcome measurement nor on the outcomes of response, remission, and functioning.

Psychodynamic psychotherapy versus antidepressants: In comparison with antidepressant treatment, there is no hint of greater or lesser benefit with regard to reduction in depressive

symptoms. No data were available on the time the outcome was surveyed. For this comparison, there is a lack of data regarding the outcomes of suicide risk, response, remission, and functioning.

Psychodynamic psychotherapy + antidepressants versus antidepressants: No data are available for a comparison of psychodynamic psychotherapy in combination with antidepressants versus antidepressant monotherapy.

Psychotherapy in general versus inactive controls: One systematic review analysed different types of psychotherapy together, comparing them with inactive controls. For the outcome of changes in depressive symptoms, it showed an indication of short-term benefit, but no medium-term or long-term benefit, of psychotherapy in general. For this comparison, no data are available regarding the outcomes of suicide risk, response, remission, or functioning.

The calculation of intervention costs for the German healthcare context shows that psychotherapy incurs higher direct costs than do treatment alternatives. Short-term one-on-one psychotherapy costs between € 1793 and € 2105 for a time period of 12 weeks. While the cost of cognitive behavioural therapy and psychodynamic psychotherapy (short-term psychoanalytical psychotherapy and focused psychodynamic psychotherapy) is covered by health insurance funds, interpersonal therapy is not governed by clear legal provisions. According to service providers, however, qualified professionals have been able to bill interpersonal psychotherapy practised thus far as a behavioural therapeutic method (in some cases also as psychodynamic therapy). In addition, some large health insurance funds have included interpersonal psychotherapy in their selective contracts. Treatment with the antidepressant fluoxetine – the only antidepressant approved in Germany for children 8 years and above – costs between € 311 and € 319 for 8 weeks of therapy. Mental health education – a form of active monitoring – costs € 305 to € 660. Six to 8 weeks of relaxation therapy costs € 349 to € 411. However, these figures do not include the diverse (long-term) consequential costs of untreated depression (e.g. lower income in adulthood).

Regarding cost effectiveness, 5 studies from the United States and the United Kingdom were found, all of which investigated cognitive behavioural therapy. Due to excessive differences between the systems, the results cannot be directly adapted to the German healthcare context.

Diagnosing depression in children and adolescents represents a social, ethical, and organizational challenge because other symptoms and comorbidities often overlap with the symptoms of the disorder, and depressive symptoms are frequently misinterpreted as typical adolescent behaviour. Further reasons for people with mental health issues not utilizing professional help include uncertainty whether the health problem is serious enough, worries about potential stigmatization, lack of knowledge about contact points and treatment options

as well as a lack of services. In Germany, more services for children and adolescents with depression are available in urban than in rural areas, and the service networks are denser in the west than in the east.

Many children, adolescents, and parents accept psychotherapy as a treatment option and perceive it as being associated with fewer side effects than antidepressants. The objective of psychotherapy is to strengthen the child's or adolescent's autonomy and self-esteem. Therefore, obtaining the minor's consent already at the start of therapy is an ethical and legal necessity. Voluntary participation and a good, trusting patient-therapist relationship are important for long-term therapy. From an ethical and legal perspective, healthcare professionals' duty of confidentiality can lead to conflicts between the obligation of secrecy and duties to inform parents or guardians.

Overall conclusion across domains

The general question of whether psychotherapy leads to better results than other therapies in children and adolescents with depression can be answered to some degree. Both for cognitive behavioural therapy and interpersonal psychotherapy, indications of benefit were found in comparison with no active treatment. Due to limited available evidence, no conclusion can currently be drawn on the question of whether psychodynamic psychotherapy is associated with any benefit or harm. This is due to the fact that the results concerning this question are from individual studies from network metaanalyses and are available only for the outcomes of suicide risk and change in depressive symptoms. In future, further research on this type of psychotherapy in children and adolescents would be needed to draw valid conclusions on effectiveness and safety. Concerning the comparison between cognitive behavioural therapy or interpersonal psychotherapy versus antidepressants, no hint of greater or lesser benefit was derived. However, patients perceive psychotherapy as being associated with fewer side effects than antidepressants. Only cognitive behavioural therapy was investigated as an add-on to antidepressant treatment; while it led to better functioning in the long term, it was not associated with any other added benefit. None of the included systematic reviews reported on the effects of psychotherapy on mortality, health-related quality of life, and adverse events, making it virtually impossible to weigh the benefit versus harm of psychotherapy in children and adolescents with depression. Since the systematic reviews did not distinguish between mild, moderate, and severe forms of depression, the chosen method, umbrella review, does not allow drawing separate conclusions on the treatment, broken down by severity of depression.

The calculation of short-term intervention costs for the German healthcare context shows that higher direct costs result from psychotherapy than from treatment alternatives. From a patient perspective, this is a less relevant issue, however, since the costs – at least for guideline therapies – are covered by the SHI funds. While health economic analyses which

include the treatments' long-term costs as well as short-term and long-term benefit and harm were found for English-speaking countries, their results cannot be adapted to the framework conditions in Germany due to the difference in healthcare systems.

In addition, it should be noted that most systematic reviews analyse children and adolescents together. A separate analysis would have been desirable because children and adolescents differ in their neurobiology and risk factors. Evidence regarding the effectiveness of cognitive, interpersonal, and psychodynamic psychotherapy is completely lacking, particularly for children up to 8 years of age and is insufficient up to age 12 years. For this age group, additional studies with a sufficiently sized sample would be desirable to examine the effectiveness of the different types of psychotherapy in comparison with a waiting list control group. For adolescents as well as children, it would be desirable for studies to increasingly focus on the outcomes of health-related quality of life, functioning, and adverse events as well. Likewise, it would be helpful to carry out randomized controlled trials in Germany since this study design is best suited for identifying cause-effect relationships, and data of this type are currently lacking for the Germany healthcare context. Long-term follow-up would be important as well. The establishment of a national registry could provide relevant data for this purpose in the long term.

Particularly in view of the limited evidence available on severity of depression and insufficient reporting on adverse events, it is all the more important to select therapies taking into account the expertise of treating psychotherapists or physicians as well as the needs and preferences of affected children and adolescents regarding the available treatment options. Since untreated depressive disorders can have substantial long-term consequences for the affected people, their environment, and society, even mild depressive symptoms persisting for a longer period should be diagnostically clarified by professionals who are adequately qualified to correctly diagnose and treat depression. Because the general public's awareness of treatment options is often limited, contacts within the healthcare system (e.g. general practitioners) as well as in children's and adolescents' social environment (e.g. teachers) should assist patients and their families in contacting qualified professionals.

Options for increasing the availability of services, e.g. in often underserved rural areas, include expanding locally available psychotherapeutic services and increasing the use of online psychotherapy services by psychotherapists. In addition, it is important to improve the image of mental disorders and the utilization of treatment options, e.g. through image campaigns in (social) media.

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Please see full HTA report for the full reference list.

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The full HTA report (German version) is published under

https://www.iqwig.de/sich-einbringen/themencheck-medizin-thema-vorschlagen/hta-berichte/ht19-04.html

Appendix A – Topics of the EUnetHTA Core Model

The European Network for Health Technology Assessment (EUnetHTA) is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [185] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table 5 indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 5: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** Section 3.1; Chapter 4; Section A3
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.2; Chapter 5; Chapter A4
Ethical analysis (ETH)	**Ethical aspects** Section 3.3; Section 6.1; Section A5.1
Patients and social aspects (SOC)	**Social aspects** Section 3.4; Section 6.2; Section A5.2
Legal aspects (LEG)	**Legal aspects** Section 3.4; Section 6.3; Section A5.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.4; Section 6.4; Section A5.4

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1 – Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to March Week 4 2020,
- Ovid MEDLINE(R) Daily Update April 06, 2020

The following filters were adopted:

- Systematic review: Wong [186] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp Depressive Disorder/
2	Depression/
3	depress*.ti,ab.
4	or/1-3
5	exp Psychotherapy/
6	Problem Solving/
7	((psychological or group) adj1 therap*).ti,ab.
8	(cognitive adj3 (treatment or therapy or bibliotherapy or intervention* or prevention)).ti,ab.
9	psychotherap*.ti,ab.
10	CBT.ti,ab.
11	(problem adj1 solving).ti,ab.
12	or/5-11
13	exp pediatrics/
14	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
15	(school child* or school*).ti,ab.
16	or/13-15
17	meta analysis.mp,pt.
18	search*.tw.
19	review.pt.

#	Searches
20	or/17-19 [Wong - Strategy minimizing difference between sensitivity and specificity]
21	20 not (exp animals/ not humans.sh.)
22	and/4,12,16,20
23	22 and (english or german).lg.
24	..l/ 22 yr=2010-Current

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to April 06, 2020,
- Ovid MEDLINE(R) Epub Ahead of Print April 06, 2020

#	Searches
1	depress*.ti,ab.
2	((psychological or group) adj3 therap*).ti,ab.
3	(cognitive adj5 (treatment or therapy or bibliotherapy or intervention* or prevention)).ti,ab.
4	psychotherap*.ti,ab.
5	CBT.ti,ab.
6	(problem adj1 solving).ti,ab.
7	or/2-6
8	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
9	(school child* or school*).ti,ab.
10	or/8-9
11	(meta analysis or review or search*).ti,ab.
12	and/1,7,10,11
13	12 and (english or german).lg.
14	..l/ 12 yr=2010-Current

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 April 07

The following filters were adopted:

- Systematic review: Wong [186] – High specificity strategy

#	Searches
1	exp Depression/
2	depress*.ti,ab.
3	or/1-2
4	exp Psychotherapy/
5	Problem Solving/
6	((psychological or group) adj1 therap*).ti,ab.
7	(cognitive adj3 (treatment or therapy or bibliotherapy or intervention* or prevention)).ti,ab.
8	psychotherap*.ti,ab.
9	CBT.ti,ab.
10	(problem adj1 solving).ti,ab.
11	or/4-9
12	exp pediatrics/
13	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
14	(school child* or school*).ti,ab.
15	or/12-14
16	(meta analysis or systematic review or MEDLINE).tw.
17	16 not (exp animal/ not exp human/)
18	and/3,11,15,17
19	18 not medline.cr.
20	19 not (Conference Abstract or Conference Review or Editorial).pt.
21	20 and (english or german).lg.
22	limit 21 to yr="2010 -Current"

3. Health Technology Assessment Database (INAHTA)

Search interface: INAHTA

#	Searches
1	Depressive Disorder[mhe]
2	Depression[mh]
3	depress*[Title] OR depress*[abs]
4	#3 OR #2 OR #1
5	Psychotherapy[mhe]
6	Problem Solving[mh]
7	(psychological or group) and therap*[Title] OR (psychological or group) and therap*[abs]
8	cognitive and (treatment or therapy or bibliotherapy or intervention* or prevention)[Title] OR cognitive and (treatment or therapy or bibliotherapy or intervention* or prevention)[abs]
9	psychotherap*[Title] OR psychotherap*[abs]

#	Searches
10	CBT[Title] OR CBT[abs]
11	problem and solving[Title] OR problem and solving[abs]
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
13	Pediatrics[mhe]
14	infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*
15	school child* or school*[Title] OR school child* or school*[abs]
16	#15 OR #14 OR #13
17	#16 AND #12 AND #4

B.1.2 – Searches in study registries

Exploratory search in Prospero on 20 January 2020

Search strategy (search only in title)

(depress* AND (child* OR adolescent)):TI

Treffer: 84

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to April 08, 2020

The following filters were adopted:

- Health economic studies: Woodworth [187] –Cost-Benefit Studies

#	Searches
	exp Depressive Disorder/
2	Depression/
3	depress*.ti,ab.
4	or/1-3
5	exp Psychotherapy/
6	Problem Solving/
7	((psychological or group) adj1 therap*).ti,ab.
8	(cognitive adj3 (treatment or therapy or bibliotherapy or intervention* or prevention)).ti,ab.
9	psychotherap*.ti,ab.
10	CBT.ti,ab.

#	Searches
11	(problem adj1 solving).ti,ab.
12	or/5-11
13	exp pediatrics/
14	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
15	(school child* or school*).ti,ab.
16	or/13-15
17	(economic$ or cost$).ti.
18	cost benefit analysis/
19	treatment outcome/ and ec.fs.
20	or/17-19
21	20 not ((animals/ not humans/) or letter.pt.)
22	and/4,12,16,20
23	22 not (comment or editorial).pt.
24	23 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 April 08

The following filters were adopted:

- Health economic studies: Glanville [188] – Embase G

#	Searches
1	exp Depression/
2	depress*.ti,ab.
3	or/1-2
4	exp Psychotherapy/
5	Problem Solving/
6	((psychological or group) adj1 therap*).ti,ab.
7	(cognitive adj3 (treatment or therapy or bibliotherapy or intervention* or prevention)).ti,ab.
8	psychotherap*.ti,ab.
9	CBT.ti,ab.
10	(problem adj1 solving).ti,ab.
11	or/4-9
12	exp pediatrics/

#	Searches
13	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
14	(school child* or school*).ti,ab.
15	or/12-14
16	(Cost adj effectiveness).ab.
17	(Cost adj effectiveness).ti.
18	(Life adj years).ab.
19	(Life adj year).ab.
20	Qaly.ab.
21	(Cost or costs).ab. and Controlled Study/
22	(Cost and costs).ab.
23	or/16-22
24	and/3,11,15,23
25	24 not medline.cr.
26	25 not (exp animal/ not exp human/)
27	26 not (Conference Abstract or Conference Review or Editorial).pt.
28	27 and (english or german).lg.

3. Health Technology Assessment Database (INAHTA)

Search interface: INAHTA

#	Searches
1	Depressive Disorder[mhe]
2	Depression[mh]
3	depress*[Title] OR depress*[abs]
4	#3 OR #2 OR #1
5	Psychotherapy[mhe]
6	Problem Solving[mh]
7	(psychological or group) and therap*[Title] OR (psychological or group) and therap*[abs]
8	cognitive and (treatment or therapy or bibliotherapy or intervention* or prevention)[Title] OR cognitive and (treatment or therapy or bibliotherapy or intervention* or prevention)[abs]
9	psychotherap*[Title] OR psychotherap*[abs]
10	CBT[Title] OR CBT[abs]
11	problem and solving[Title] OR problem and solving[abs]
12	#11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
13	Pediatrics[mhe]
14	infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or

#	Searches
	children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*
15	school child* or school*[Title] OR school child* or school*[abs]
16	#15 OR #14 OR #13
17	#16 AND #12 AND #4