ThemenCheck Medizin

Extract of HTA report

Suicidal crises in unipolar depression:

How do non-drug interventions impact their management? [1]

Health technology assessment commissioned by IQWiG

IQWiG Reports – Commission No. HT17-03

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[1] Translation of Chapters 1 to 9 of the HTA report HT17-03 *Suizidale Krisen bei unipolarer Depression: Welchen Einfluss haben nicht medikamentöse Maßnahmen auf deren Bewältigung?* (Version 1.0; Status: 26 September 2019 [German original], 8 October 2020 [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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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?

For "ThemenCheck Medizin" (Topic Check Medicine), published by the Institute for Quality and Efficiency in Health Care (IQWiG), interested individuals are invited to propose topics for the assessment of medical procedures and technologies. 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 topics are selected each year from among all submitted proposals. According to the legal mandate, these topics should be of particular importance for patients [1]. IQWiG then commissions external teams of scientists who investigate the topics in accordance with IQWiG methods and acts as the publisher of the HTA reports.

To draft the HTA report, IQWiG selected 5 topics from the ones suggested in 2017, the first year, 2017. The selection included "Suicidal crises in unipolar depression: How do non-drug interventions impact their management?" The topic was investigated by a team of scientists from Technische Universität (TU) Berlin; the team included HTA methodologists, a health economist, and a psychological psychotherapist.

Why is the HTA report important?

In Germany, about every 10th adult has symptoms of depression. Women are more commonly affected by depression than men, at 11.6% versus 8.6% [2]. This widespread disease can also have major consequences: Depression is a major risk factor for suicidal behaviour. Often, additional factors such as alcohol abuse and a sense of isolation have a cumulative effect and increase a person's susceptibility to suicidal acts [3]. Patients with depression are at about 20 times higher risk of suicide than the average population [4]. The annual number of suicide attempts is many times higher than the number of completed suicides [3].

In case of imminent or attempted suicide, responding rapidly is the top priority. Patients are typically first treated at a psychiatric hospital. It is important for outpatient treatment to directly follow inpatient acute care since the risk of suicide is particularly high in the first few days and weeks after discharge [5]. According to the "Unipolar Depression" National Disease Management Guideline, follow-up treatment should be planned directly after discharge from inpatient treatment. As part of therapy, which may include drugs such as antidepressants or mood stabilizers, suicide-focused psychotherapy should be offered [5].

This topic was selected in light of the above aspects and particularly in consideration of the fact that affected patients represent a vulnerable population. Various perspectives of an HTA report were to be investigated in terms of the influence of various outpatient non-drug interventions on the management of suicidal crises in adults with unipolar depression.

Which questions are answered – and which are not?

The team of scientists from TU Berlin found that suicidality-focused cognitive behavioural therapy (CBT) was the only non-drug intervention used in studies of informative value to investigate affected people with suicidal crises and unipolar depression. Certain forms of CBT as an add-on to treatment as usual (TAU) have been found to help manage suicidal crises. For instance, there were indications of depressive symptoms, hopelessness, suicidal ideation and (follow-up) suicide attempts being reduced at some measurement time points after the start of therapy. There was no hint of CBT having any effect on anxiety or posttraumatic stress. The studies did not investigate any further patient-relevant aspects, such as physical role functioning for managing everyday activities, health-related quality of life, mortality due to suicide or serious adverse events.

The results on medical benefit are of moderate qualitative certainty of results and are based on 4 studies with randomized controlled comparisons investigating suicidality-focused CBT as an add-on to TAU versus TAU alone in adult outpatients. The studies used different definitions of TAU, but it always consisted of elements also recommended by the National Disease Management Guideline [5]. The content and organization of CBT varied between studies as well. In addition, data on patient-relevant aspects were surveyed at different time points after treatment start. At the beginning of the project, the team of scientists of TU Berlin decided, on the basis of the literature and the clinical expert's opinion, to report data for the measurement time points of 1, 3, 6, 18, and ≥ 18 months. Benefits in favour of CBT were found only for some of these time points. While at the 1-month time point, almost all investigated patient-relevant aspects failed to reveal any benefits yet, some aspects exhibited indications of added benefit of suicide-focused CBT as an add-on to TAU, particularly after 6 months. Given that one of the included studies [6] was performed on US soldiers and another [7] on Asian patients, it would also be prudent to critically discuss the extent to which the results can be applied to the German healthcare context.

No health economic studies comparing the benefit and cost of the therapy were found. It is difficult to specify the cost of the overall treatment since the duration and frequency of therapeutic sessions may vary, and TAU often combines various drug and non-drug interventions. Hence, the report presented only the costs of individual treatment measures.

From an ethical, social, legal, and organizational perspective, access barriers to therapy are a central topic of the HTA report. Access barriers have numerous causes: In our society, people

with unipolar depression are often stigmatized, and in some cases, they stigmatize themselves as well. Affected persons, particularly men and people with prior suicide attempts, are often reluctant to take advantage of offers of assistance or to talk about their disorder. Access to therapy can be further obstructed by long waits for appointments or difficulty reaching psychiatrists or psychotherapists, especially in rural areas. In many cases, this results in discontinuity between inpatient and outpatient care, which is problematic in view of the elevated risk of suicide directly after discharge from inpatient care. Despite the coverage of CBT costs by the statutory health insurance (SHI), SHI members may experience greater access problems due to their choices being limited to SHI-accredited treatment providers.

From an organizational perspective, among the items highlighted by the HTA report was the need for multidisciplinary collaboration between various groups of individuals and occupations in order to eliminate access barriers. For instance, it can be helpful for psychiatrists, psychotherapists, and general practitioners to closely collaborate and for patients to receive support from their social environment. Despite the currently weak proof of benefit due to the limited number of available studies, the expansion of outpatient, community-based care structures for the early detection and treatment of suicidal crises in people with unipolar depression seems to be an important topic for the future.

What's the next step?

It remains unclear to what extent the results of this HTA report on outpatient suicide-focused CBT in the treatment of adults with unipolar depression who are in suicidal crises will be taken into account and integrated into the German healthcare context. However, it might conceivably be considered in the next update of the "Unipolar Depression" National Disease Management Guideline [5].

In view of the large number of patients and their vulnerabilities, there is an undisputed need for high quality studies investigating the medical benefit of (other) non-drug interventions with regard to patient-relevant aspects such as health-related quality of life. Particularly interventions with internet-based elements might gain in importance in view of the physician shortage and long appointment wait times. Therefore, these interventions should also be included in well-designed studies to initially draw conclusions on benefit and then offer patients effective, low-threshold assistance – particularly in the period directly following discharge from inpatient care. As transitional interventions, the HTA report lists interventions such as safe retreats or telephone counselling. These interventions might also help reduce patient anxiety and further reduce (self-)stigmatization.

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HTA key statements

Research questions of the HTA report

The aims of this investigation are to

– assess the benefit of
(1) crisis intervention programmes/services or
(2) psychosocial interventions

(technology based or not) in outpatient care in comparison with a different non-drug therapy, drug therapy, inpatient treatment, or no therapy / waiting list in adult suicidal patients with unipolar depression with regard to patient-relevant outcomes,

– determine the costs incurred by
(1) crisis intervention programmes/services or
(2) psychosocial interventions

(technology based or not) in outpatient care in comparison with a different non-drug therapy, drug therapy, inpatient treatment, or no therapy / waiting list in adult suicidal patients with unipolar depression (intervention costs),

– assess the cost effectiveness of
(1) crisis intervention programmes/services or
(2) psychosocial interventions in outpatient care (technology based or not) in comparison with another non-drug therapy, drug therapy, inpatient treatment, or no therapy / waiting list in adult suicidal patients with unipolar depression was well as

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

Conclusion of the HTA report (see Chapter 9)

To answer the question submitted to ThemenCheck, “Suicidal crises in unipolar depression: How do non-drug measures impact their management?”, the following interventions were investigated: (1) crisis intervention programmes/services in outpatient care and (2) psychosocial interventions in outpatient care, namely (i) psychotherapeutic strategies for preventing suicide and (ii) suicide preventive follow-up services and contact offers.

Despite this initially broad definition of interventions to be investigated in the outpatient care of adult suicidal patients with unipolar depression, only studies on cognitive behavioural therapy (CBT) were found, all of which focused on suicidality. These studies examined CBTs from the second and third “waves” of behavioural therapy (BT). The second wave of BT

originated in the developments of the 1960s and 1970s, where classic BT was for the first time expanded to include cognitive aspects such as thoughts and convictions. In the 1980s, these considerations led to the approach of CBT. In the third wave of BT, the classic cognitive-behavioural concept, which largely focuses on restructuring processes, is expanded by the additional aspects of mindfulness and acceptance of difficult-to-control internal experiences. Additional conceptual differences concern the fundamental attitude and the patient-therapist relationship. CBT is a service already covered by the statutory health insurance.

Four randomized controlled trials (RCTs) of moderate qualitative certainty of results were included. They primarily investigated the patient-relevant outcomes of anxiety, depressive symptoms, hopelessness, posttraumatic stress, suicidal ideation, and (follow-up) suicide attempts, each at the survey time points of 1, 3, 6, 18, and ≥ 18 months.

With regard to the patient-relevant outcomes of suicidal ideation (6 months), suicide attempts (≥ 18 months), depressive symptoms (3, 6, and 18 months), and hopelessness (6 and 18 months), the results revealed an indication of (added) benefit of second-wave CBT in comparison with treatment as usual (TAU).

With regard to the patient-relevant outcome of depressive symptoms, the results revealed a hint of (added) benefit at the survey time point of 1 month for third-wave CBT in comparison with TAU. These results are based on the data from one study. The currently still outstanding results from another study might supplement the results of this health technology assessment (HTA).

For the outcomes of anxiety and posttraumatic stress (each at 3, 6, and 18 months), suicidal ideation (1, 3, and 18 months), depressive symptoms (1 month), and hopelessness (1 month and 3 months), no hint of (added) benefit of second-wave CBT versus TAU was found.

With regard to third-wave CBT, for the outcome of depressive symptoms at the survey time point of 3 months, no hint of (added) benefit of third-wave CBT versus TAU was found. For the outcome of suicidal ideation at the time point of 1 month, no hint of (added) benefit of third-wave CBT versus TAU was found.

For the following outcomes, data on second or third-wave CBT were either unavailable or unusable: all-cause mortality / overall survival, suicide mortality, physical functioning including activities of daily living / everyday functioning, inpatient admission, serious adverse events, discontinuation due to adverse events, health-related quality of life, and health-related social functioning, including occupational and social participation. Concerning second-wave CBT, data were also reported on social problem-solving ability, but they were disregarded due to reporting bias. However, patients in the initially conducted discussions highlighted the patient-relevant outcomes listed above as being particularly relevant.

Therefore, there is clearly a need for further research, particularly high-quality RCTs, in this area.

No studies were found with regard to cost effectiveness, and no conclusion can be drawn on this topic. To generate more evidence in this area as well, future investigations might concurrently collect data on both effectiveness as well as resource use and the costs of the intervention and comparator treatment. The costs listed in the present report are stated as ranges for patients with mild and severe disease courses. They range from EUR188.67 per treatment case for solely drug-based treatment to EUR2684.14 for one-on-one short-term outpatient therapy, and up to EUR15,314.23 for long-term outpatient therapy. However, comparability between the costs of the individual interventions per patient or per patient and treatment case is limited since their separate analyses do not fully reflect the realities of care. Depressive disorders differ widely between individuals in terms of their severity and course; therefore, actual costs might be lower or higher than those presented herein.

Interventions other than CBT, including some low-threshold interventions such as telephone counselling or internet-based services, were also mentioned both in the focus groups and in the literature. Due to a lack of studies, however, it was not possible to compare these interventions to TAU. As already concluded by authors of other reviews, future studies should include such interventions as well and determine their effectiveness at early survey time points in order to ensure rapid treatment in crisis situations.

The analysis of the ethical, social, legal, and organizational aspects has shown that they are highly relevant to the topic and, in particular, have a major impact on access to measures. Due to the complexity and multidimensional nature of the topic, the individual domains cannot and should not be analysed in isolation. Rather, their mutual interactions should be contemplated and discussed, as illustrated in the logical model.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
BPtK	Bundespsychotherapeutenkammer (German Federal Chamber of Psychotherapists)
BT	behavioural therapy
CADTH	Canadian Agency for Drugs and Technologies in Health
CBT	cognitive behavioural therapy
DALYs	disability-adjusted life years
DGPPN	Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e. V. (German Association for Psychiatry, Psychotherapy, and Psychosomatics)
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	health technology assessment
ICD-10-GM	International Classification of Diseases and Related Health Problems, 10th Revision, German Modification
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NDMG	National Disease Management Guideline
PEPP	Pauschalierende Entgeltsystem Psychiatrie und Psychosomatik (Flat Rate Charges in Psychiatry and Psychosomatics)
PHI	private health insurance
PICO	Patient Population Intervention Comparison Outcome
PsychKG	Psychisch-Kranken-Gesetz (Mental Health Act)
RCT	randomized controlled trial
SAE	serious adverse event
SCI-EXPANDED	Science Citation Index Expanded
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
TAU	treatment as usual
WHO	World Health Organization

HTA overview

1 Background

1.1 Health policy background and commission

According to §139b (5) of Social Code Book V, Statutory Health Insurance, statutory health insurance members and other interested individuals 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 a year, IQWiG, in collaboration with patient representatives, 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 together with 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 health care services and structures. This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

1.2.1 Epidemiology

Unipolar depression

Depression is a mental disorder characterized by low mood, reduced drive, fatigue, and loss of interest for an extended time period [1]. It can be accompanied by further symptoms such as reduced self-esteem and self-confidence or loss of appetite. The International Statistical Classification of Diseases and Related Health Problems (ICD-10-GM Version 2018) [2] lists depression under "mood [affective] disorders". Affective disorders is a collective term for various forms of depressive and manic/manic-depressive disorders (also known as bipolar disorders). The planned report is to look at unipolar depressive disorders, i.e., depressive episodes (F32.0–F32.2), recurrent depressive disorders (F33.0–F33.2), persistent mood [affective] disorders (exclusively dysthymia, F34.1), and other mood [F38.1] disorders (in this case, exclusively recurrent brief depressive episodes, F38.1). Unipolar depressive disorders are characterized by the absence of phases of heightened, euphoric, or irritable moods, which are typical for bipolar disorders. Based on the number and severity of symptoms, ICD-10-GM

categorizes depressive symptoms as mild (F32.0 / 33.0), moderate (F32.1 / 33.1), or severe (F32.2 / 33.2). Alternatively, depressive disorders can be classified by their course and duration as well as by the frequency of recurrent phases of disease.

Depression is among the most common and most consequential disorders worldwide: According to estimates by the World Health Organization (WHO), depression affects more than 300 million people, representing 4.4% of the total world population [3]. In 2016, this made depression the 17th most common cause of disability-adjusted life years (DALYs) lost worldwide. Since 1990, the disease burden has increased by 7% as measured by DALYs [4].

According to the "2014/2015 German Health Update" study integrating the European Health Interview Survey, the prevalence of depressive symptoms in adults in Germany is 10.1%, with women having a higher prevalence than men, at 11.6% versus 8.6% [5]. The 12-month prevalence of self-reported, medically diagnosed depression in the population is 8.1% [6]. Once again, more women than men reported a diagnosis of depression within the preceding 12 months, at 9.7% versus 6.3% [6].

Depression exhibits high comorbidity with other psychological and somatic disorders as well as with alcohol and (prescription) drug addiction [7].

Suicidality

Suicidality is defined as the experiences and behaviours of people who, in their thoughts, by their actions or inactions, seek death or accept it as the potential result of an action [8-10]. Suicidality can take different forms, ranging from the wish to die and suicidal ideation to specific suicide plans and suicide attempts, which develop with a growing sense of urgency [10].

According to the German Federal Statistical Office, slightly more than 10,000 people die due to suicide every year in Germany [11]. About twice as many men as women die due to suicide. Overall, the suicide rate distinctly rises beyond age 70, a pattern also seen in international data [12]. Depression is one of the most common disorders associated with suicidal behaviour [12]. This association is also reflected by suicide rates, which are about 20 times higher in people with depression than in the general population [13]. About 59–87% of suicidal people suffer from major depression at the time of suicide [14,15]. In people with depression, an elevated suicide risk is significantly associated not only with the severity of depression, but also with male sex, prior suicide attempts, and comorbidities [16].

1.3 Treatment/therapy

Alongside pharmacotherapy and inpatient admission, the S3 Guideline and National Disease Management Guideline (NDMG) for the treatment of unipolar depression list numerous non-

drug measures as elements of treatment as usual (TAU) in individuals at risk of suicide [7]. The non-drug measures mentioned for the outpatient sector are briefly discussed below.

As the short-term goal of crisis intervention or psychotherapy in acute suicidality, the NDMG [7] specifies intensive contact and active immediate support and relief until the crisis subsides (clinical consensus, treatment standard). This includes, for instance, a no-suicide contract between the therapist and patient. Further suicide-preventive elements of psychotherapy can include drawing up an emergency or safety plan [17,18]. In persons with a depressive episode who are at risk of suicide, psychotherapy initially focusing on suicidality should be offered (recommendation grade B[2]) [7]. Psychotherapy specifically for suicide prevention comprises problem-solving and insight-oriented strategies related to suicidality and can optionally be technology-based (conducted via the Internet or smartphone apps). Examples include dialectical BT or short-term, suicide-focused CBT [18,19]. In addition, ultra-short-term psychotherapy, such as the Attempted Suicide Short Intervention Program (ASSIP), is available to complement the regular treatment programme [18].

According to the NDMG [7], follow-up treatment of patients who were hospitalized due to suicidality should be planned in the short run (at most 1 week after discharge) because the risk of further suicidal acts is maximal after discharge. Patients who did not keep a follow-up appointment after discharge must be contacted directly to evaluate the risk of suicide or self-harm (recommendation grade A for both[3]). This contact may be established via telephone, email, or smartphone apps [20].

In addition to the discussed NDMG recommendations, low-threshold services are available in case of acute suicidality. This includes, for instance, crisis hotlines or telephone counselling programmes as well as the socio-psychiatric service. In addition, mobile crisis teams which provide assistance via home visits or which can be visited at specific centres are available in some countries (not typically in Germany).

In recent years, specific smartphone apps for suicide prevention have been developed as well [21,22].

1.4 Utilization

On the basis of the available data, it is difficult to determine whether and to what extent patients in suicidal crisis utilize the listed outpatient intervention options in Germany. However, the 2016 statistics of the nationwide telephone counselling service show that

[2] "Should do" recommendation: Well conducted, but not randomized clinical studies, directly related to the recommendation (evidence levels II or III) or extrapolation from evidence level I if there is no relation to the specific question.

[3] "Do" recommendation: At least one randomized, controlled study of overall good quality and consistency, directly related to the recommendation and not extrapolated (evidence levels Ia and Ib).

suicidality plays a role in 7% of the 726,467 callers and that the majority of them have suicidal thoughts (68%) or suicidal intent (12%) [23].

A multicentre study on suicidal behaviour in Europe revealed that after a suicide attempt, most people come into contact with the healthcare system in both the outpatient and inpatient settings either immediately after or within 4 weeks of the attempt [24]. In most cases, secondary follow-up care is provided on an outpatient basis. The study demonstrated treatment discontinuity and, on average, contact to a total of about 5 different (outpatient and inpatient) service providers.

Although the NDMG highlights the period after hospital discharge as particularly critical for suicidal patients, evidence suggests that the German healthcare system has deficits and hence requires optimization particularly concerning the outpatient care of patients with depression and with regard to suicidal crises [18,25-27]. This should involve the expansion of outpatient care structures, e.g. by implementing suicide-specific services in general care, networking the stakeholders, or organizing the transition from inpatient to outpatient care.

2 Research questions

The aims of this investigation are to

- assess the benefit of
  (1) crisis intervention programmes/services or
  (2) psychosocial interventions

  (technology based or not) in outpatient care in comparison with a different non-drug therapy, drug therapy, inpatient treatment, or no therapy / waiting list in adult suicidal patients with unipolar depression with regard to patient-relevant outcomes,
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- review ethical, social, legal, and organizational aspects associated with the medical interventions.

3 Methods

3.1 Methods – benefit assessment

The target population of the benefit assessment was adults (≥ 18 years of age) with a medical or psychotherapeutic clinical diagnosis of a depressive episode (ICD F32.0–32.2), recurrent depressive disorder (ICD F33.0–F33.2; not in remission), dysthymia (F34.1), or recurrent brief depressive disorder (F38.1) as well as self-reported, medically diagnosed depression. Patients with depressive symptoms recorded solely by a validated psychometric questionnaire (without establishment of a diagnosis) were disregarded since they lacked a confirmed diagnosis. Included were patients with one (or more) prior suicide attempt(s) and/or patients with a current or past suicidal crisis. Patients in suicidal crisis exhibit a wish to die, suicidal thoughts, specific suicide plans, or suicide attempts. Individuals engaging solely in self-harm without intention to bring about death were disregarded.

Experimental interventions were, firstly, crisis intervention programmes/services in out-patient care. Secondly, suicide-preventive psychotherapeutic strategies as well as offers of suicide-preventive follow-up services and contacts were investigated as psychosocial interventions in outpatient care.

The comparator intervention was either another non-drug therapy, drug-based therapy, inpatient care, or no therapy / waiting list.

The investigation examined the following patient-relevant outcomes[4]:

- Mortality (overall mortality, suicide mortality)
- Morbidity (anxiety, depressive symptoms, hopelessness, physical functioning including activities of daily living / everyday functioning, posttraumatic stress, hospitalization, suicidal thoughts [follow-up] suicide attempts)
- Health-related quality of life
- Adverse events (AEs) / discontinuation due to AEs
- Health-related social functioning, occupational and social participation
- Social problem-solving ability

Randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

[4] The outcomes were determined in collaboration with the clinical expert and as part of guided patient interviews.

A systematic search for primary literature was conducted in the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and PsycINFO databases. In parallel, a search for relevant systematic reviews was conducted in MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and the Health Technology Assessment Database. The following sources of information and search techniques were additionally used: study registries, systematic reviews, as well as documents and requests to authors made available from commenting procedures.

Relevant studies were selected by 2 reviewers independently from one another. Any discrepancies between the reviewers were resolved by discussion between them. Data were extracted into standardized tables by 2 reviewers independently from one another. To assess the qualitative certainty of results, the risk of bias at study and outcome levels was assessed and rated as high or low by 2 reviewers independently from one another. The results of the individual studies were organized according to outcomes and described.

To the extent that the studies were comparable in terms of their research questions and relevant characteristics, with no meaningful heterogeneity being observed, the results from individual studies were quantitatively combined in meta-analyses. The estimated effects and confidence intervals from the studies were summarized using forest plots. Potential heterogeneity was estimated using the measure of I^2 and the statistical test for the presence of heterogeneity [28]. The I^2 value was interpreted using the classification from the Cochrane Handbook for Systematic Reviews of Interventions [29]: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. The relevance of the observed value of I^2 depends on (i) the strength and direction of the effects and (ii) the strength of evidence for heterogeneity (e.g. p-value from the chi square test or a confidence interval for I^2). Since heterogeneity cannot be reliably estimated if only few studies are available, models with fixed effect were used where 4 or fewer studies were available.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter is the case if no data are available or the available data do not permit classification into one of the 3 other categories. In that case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

Although the included studies each investigated interventions from the realm of CBT with focus on suicidality, the benefit assessment distinguished the “waves” of BT. This is due to the fact that the waves differ in various fundamental aspects and are therefore not comparable (also see Section 4.2).

The benefit assessment was conducted only for selected survey time points. The survey time points of 1 month, 3 months, and 6 months were selected because the literature describes suicidal patients (regardless of their diagnosis) as being most vulnerable in the first 3 to 6 months [30,31], with the first few weeks after a suicide attempt or discharge from psychiatric inpatient care being associated with a particularly high risk of a (follow-up) suicide attempt [32,33]. A discussion with the clinical expert confirmed these survey time points as relevant for the population investigated in the report. In collaboration with the clinical expert, the survey time point of 18 months was defined as supplementary data in an effort to also cover the interventions' long-term effects. No other survey time points were taken into account. To allow a benefit assessment with regard to the long-term effect on the outcome of (follow-up) suicide attempts on the basis of a meta-analysis, the results of the survey time points of 18 and 24 months from two studies were combined to form the survey time point of ≥ 18 months.

Where results on an outcome were collected using several survey instruments, the selection was made along methodological and technical considerations, taking into account validity, informative value, and comparability in order to allow a meta-analysis of results.

Where multiple operationalizations of an outcome were used, the selection was based on methodological and technical considerations. Aspects of validity, informative value, and comparability of operationalizations were taken into account to facilitate a meta-analysis of results.

Prior to the generation of the report protocol, 3 guided interviews were conducted with patients (recruited by IQWiG); the interviews served to determine the above-listed patient-relevant outcomes as well as potential subgroups and initial contextual factors (see Sections 3.3 and 3.5).

3.2 Methods – health economic assessment

3.2.1 Intervention costs

To calculate the intervention costs, the average resources required directly when performing the experimental and comparator intervention were determined. For this purpose, in addition to the experimental and comparator interventions, the services directly associated with the intervention were taken into account. The relevant regulated or negotiated prices of these services, e.g. the Uniform Value Scale (UVS), the Flat Rate Charges in Psychiatry and Psychosomatics (PEPP) catalogue, or similar suitable lists, were used wherever possible. Resource consumption was illustrated using examples (e.g. the costs of a commonly used drug). The costs were presented per treatment case. Reimbursable and non-reimbursable costs were listed separately.

3.2.2 Cost effectiveness

For assessing health economic aspects, a systematic search in the form of a focused information retrieval was carried out. The systematic search for relevant studies/documents was conducted in the MEDLINE and Embase databases as well as in the Health Technology Assessment database. Furthermore, documents made available in commenting procedures and requests to authors were included as sources of information.

3.3 Methods – ethical aspects

Potential ethically relevant arguments and aspects were evaluated based on the INTEGRATE-HTA framework developed especially for the assessment of complex interventions and the Lysdahl 2016 framework for ethical analysis described therein [34]. It is composed of the following steps: assessment of the complexity of the intervention(s) (step 1), selection of the ethical approach (step 2), confirmation or modification of the selected approach (step 3), and its application (step 4) as well as validation of results (step 5). We followed the 5 steps, taking into account the health technology context (e.g. conversations with patients to initially narrow down central questions) and the HTA/ethical context (e.g. commissioning by IQWiG and the associated methodological and procedural specifications, use of the results of the other domains). The explicit methodological approach was defined depending on the ethical approach selected and is therefore discussed in Section 6.1.

For the evaluation of ethical aspects, a scoping search was conducted in PubMed, ETHICSWEB, Social Sciences Citation Index (SSCI), Science Citation Index Expanded (SCI-EXPANDED), and stakeholder-based information sources (e.g. websites of German-language stakeholders). Other sources of information were the publications included in the benefit assessment as well as publications in the IQWiG WebTSTB database which were marked as potentially relevant to ethical aspects during the screening for the benefit assessment.

Information from the information sources of the scoping search was screened by one reviewer for statements on ethical arguments and aspects of the technology to be investigated. Quality assurance of the result was performed by a second person.

For the evaluation of ethical (and social) aspects, 3 moderated discussion rounds (methodological term for focus groups) were conducted with relevant stakeholders (patients or their legal representatives, family members as well as patient advocacy organizations). The moderated discussion rounds were structured based on the methodological approach selected in step 2 and described in Section 6.1.

In advance of the moderated discussion rounds and scoping literature searches, initial contextual factors with regard to the research question were determined through discussions with patients and background research, and the complexity of the intervention(s) was

determined (step 1, see above). The obtained contextual factors were presented in a figure (see also Section 3.5), while complexity considerations were shown in tabular form.

All arguments and aspects necessary for information processing from the scoping search and the moderated discussion rounds were extracted into tables. In a first step, the generated tables were discussed among the reporters, and in a second step, they were validated in terms of content and methodology by a team including further stakeholders (see Section A5.1.1 of the full report).

3.4 Methods – social, legal, and organizational aspects

In the HTA, social and sociocultural aspects address the mutual interactions between investigation/treatment methods and the social environment (e.g. patient preferences, social norms, and values). The information on social aspects was processed on the basis of the questionnaire suggested by Stich [35], which represents a guideline for the practical implementation of the conceptual framework developed by Mozygemba 2016 [36]. This questionnaire was developed specifically for generating the HTA reports and represents an advancement of the Gerhardus checklist (2008) [37]. It consists of three topic areas with a total of 13 detailed questions: 1. health technology and groups (e.g. social, cultural, ethnic, religious groups, people with certain disorders/impairments and their family members), 2. society and healthcare system-related, and 3. patients and family, workplace.

Legal aspects in the HTA relate, firstly, to the legal framework in which the examination/treatment method and its assessment is embedded, and secondly, to the legal aspects associated with the implementation and utilization of the health technology (e.g. patient autonomy). Technology-related legal aspects are distinguished from patient-related ones. Information processing was based on the guideline developed by Brönneke 2016 [38] for the identification of legal aspects.

Organizational aspects comprise the interactions resulting from an examination/treatment method with the organization of care. The information processing of organizational aspects follows the grid template proposed by Perleth 2014 [39] for the assessment of the organizational consequences of examination/treatment methods.

For the evaluation of social, legal, and organizational aspects, scoping searches were conducted in PubMed, Web of Science (SSCI, SCI-EXPANDED), Beck-online, guideline databases, data from regional registries, laws, directives, or guidelines, and advocacy-based information sources (e.g. advocacy organizations' websites). In addition to the scoping search, the results of the moderated discussion rounds (see Section 3.3) were used to identify statements on social, legal, and/or organizational arguments and aspects. Further information sources are the publications included in the benefit assessment and the publications marked

as potentially relevant to social, legal, and organizational domains during the screening for the benefit assessment in the IQWiG WebTSTB database.

One reviewer screened information from all information sources for statements on legal and/or organizational arguments and aspects of the technology to be investigated. A second person performed quality assurance of the result. All legal, social, and organizational aspects needed for information processing were extracted into tables. In a first step, the generated tables were discussed among the reporters, and in a second step, they were validated in terms of content and methodology by a team including further stakeholders (see Section A5.1.1 of the full report).

3.5 Methods – cross-domain discussion

Finally, the relevant lines of argument regarding ethical, social, legal, and organizational questions were qualitatively synthesized. The results of the benefit assessment and the economic assessment were included in this process (see Section 7). For this synthesis, potential overlap in the analysis of ethical, social, legal, and organizational questions was taken into account, and any duplication potentially resulting from this overlap was eliminated. The results were presented using an adapted version of the logical model developed in INTEGRATE-HTA [40], which shows not only the aspects and their interactions as well as contextual factors, but also the results of the evidence available on the aspects on the other. A first version of the model was generated in collaboration with all reporters and with the aid of the patient meetings for discussing patient-relevant outcomes (also see Sections 3.3 and 3.5); in the course of the work on the report and its domains, the model was then advanced and completed. In a further step, the synthesis of results was discussed with all reporters (see Section 8).

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

The information retrieval found 4 RCTs (6 documents) to be relevant for the research question of this benefit assessment. One ongoing study was found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 09 May 2018.

Table 1: Study pool of the benefit assessment

Study	**Available documents**		
	Full publication (in professional journals)	**Results report from the study registries**	**Clinical study report from manufacturer documents (not publicly accessible)**
Barnhofer 2009/ Hargus 2010	Yes [41]/[42]	No	No
Brown 2005/ Ghahramanlou-Holloway 2012	Yes [43]/[44]	No	No
Rudd 2015	Yes [45]	Yes [46][a]	No
Sinniah 2017	Yes [47]	No	No
a: Baseline characteristics only: NCT02038075.			

4.2 Characteristics of the studies included in the assessment

The 4 identified studies all investigate a form of CBT focusing on suicide prevention (CBT-SP) as an add-on to TAU versus TAU alone. The specific design of CBT and TAU varies between studies. Since no studies of other interventions (including technology-based interventions) were found, they are disregarded in the remaining report.

Three of the included studies (Brown 2005/Ghahramanlou-Holloway 2012, Rudd 2015, Sinniah 2017) [43-45,47] investigate CBT, which is part of the second wave of behavioural therapy (BT). It originated from the developments of the 1960s and 1970s, when classic BT was first expanded by cognitive aspects such as thoughts and convictions. In the 1980s, these considerations led to the approach of CBT. The other study (Barnhofer 2009/Hargus 2010) [41,42] involves third-wave BT. In this approach, the classic cognitive-behavioural concept, which largely focuses on restructuring processes, has been expanded to include the aspect of mindfulness and acceptance of difficult-to-control inner experience. Additional conceptual differences concern the fundamental attitude and the patient-therapist relationship.

The Brown 2005/Ghahramanlou-Holloway 2012 study investigates (one-on-one) CBT from the second wave of BT as an add-on to TAU in comparison with TAU alone. In its more than 10

sessions (weekly or every 2 weeks; total duration of 10 hours), it follows the content and format of Brown 2002 [48] (the study's author); this format was developed specifically for the prevention of suicide attempts. The intervention is compared with TAU, which comprises care provided by community-based clinicians and services from the study's case manager (e.g. community mental health treatment), regular contact by the case manager and/or the utilization of other psychotherapy, medication, and addiction treatment. The study was conducted in the United States of America (USA) in the years 2000 and 2002 and included 120 patients, of which 35 (29.2%) dropped out of the study.

The Rudd 2015 study investigated brief (one-on-one) CBT from the second wave of BT as an add-on to TAU in comparison with TAU alone. The intervention involved 12 sessions (weekly or every 2 weeks, 1 x 90 minutes, 11 x 60 minutes; total duration of 12.5 hours). Therapy included the creation of a crisis plan and the learning of cognitive strategies. This was compared with TAU, which comprised one-on-one and group psychotherapy, medication, addiction treatment, and/or support groups. Spiritual and religious services were allowed as well. The study was conducted in the years 2011 and 2012 in Fort Carson, a military installation in Colorado (USA), and included 152 patients, of which 25 (9.9%) dropped out of the study.

The Sianniah 2017 study investigated (one-on-one) CBT from the second wave of BT as an add-on to TAU in comparison with TAU. The intervention involved 16 sessions (twice weekly, 2 hours per session; total duration of 32 hours), thereby following the content of the CBT group programme for depression developed by Oei 2010 [49], which was adapted by the authors for use with individual patients. Therapy entailed learning cognitive behavioural strategies. This was compared with TAU, which comprised follow-up visits with a psychiatrist, but no psychotherapy. The study was conducted in Malaysia with 69 patients, of which 27 (39.1%) dropped out of the study.

The Barnhofer 2009/Hargus 2010 study compared mindfulness-based cognitive therapy (MBCT) from third-wave BT as an add-on to TAU versus TAU. In 8 weekly group sessions (2 hours each; total duration of 16 hours), the content and format of Segal 2002 [50] were followed, which the authors expanded to include a crisis plan as well as cognitive components in order to address suicidality. In addition, 45 minutes of mindfulness exercises were to be conducted at home daily. This intervention was compared with the waiting list (MBCT, but delayed start) and TAU, which consisted of continuation of the medication and appointments with the psychologist or general practitioner, but patients were not to start meditating. The study was conducted in the United Kingdom (UK) in 2007 and included 28 patients, of which 3 (> 10%) dropped out of the study.

4.3 Overview of assessment-relevant outcomes

Data on patient-relevant outcomes were extracted from 4 studies. Table 2 presents an overview of the data on patient-relevant outcomes available from the included studies. Data on the outcome of social problem-solving ability were reported in 1 study, but reporting bias rendered them unusable. None of the studies reported any data on the outcomes of all-cause mortality / overall survival, suicide mortality, physical functioning including activities of daily living / everyday functioning, inpatient admission, serious adverse events (SAEs), discontinuation due to AEs, health-related quality of life, health-related social functioning, including occupational and social participation.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes														
	Mortality		Morbidity									HRQoL			
	All-cause mortality / overall survival	Suicide mortality	Anxiety	Depressive symptoms	Hopelessness	Physical functioning including activities of daily living / everyday functioning	Posttraumatic stress	Inpatient admission	Suicidal ideation	(Follow-up) Suicide attempts	SAEs (+ discontinuation due to AEs)	Health-related quality of life	Health-related social functioning, occupational and social participation	Social problem-solving ability
Studies comparing second-wave CBT versus TAU														
Brown 2005/ Ghahramanlou-Holloway 2012	-	-	-	●	●	-	-	-	○[a]	●	-	-	-	○[b]
Rudd 2015	-	-	●	●	●	-	●	-	●	●	-	-	-	-
Sinniah 2017	-	-	-	●	●	-	-	-	●	-	-	-	-	-
Studies comparing third-wave CBT versus TAU														
Barnhofer 2009/Hargus 2010	-	-	-	●	-	-	-	-	●	-	-	-	-	-

● Data were reported and usable.

○ Data were reported but unusable.

- No data were reported (no further information) / The outcome was not surveyed.

a: Due to the operationalization differing from the other studies, the data were excluded from the benefit assessment.

b: Results were available for only 2 out of 5 subscales; reporting bias is likely.

AE: adverse event; HRQoL: health-related quality of life; SAE: serious adverse event

4.4 Assessment of the risk of bias at study and outcome levels

The risk of bias at study level was rated as high for all studies. This was particularly due to lack of clarity regarding both allocation concealment and result-independent reporting.

Since the risk of bias at study level was already rated as high, the risk of bias was also rated as high for the results of all investigated outcomes.

4.5 Results on patient-relevant outcomes

4.5.1 Comparison of second-wave CBT versus TAU

4.5.1.1 Results on the outcome of anxiety

The results of 1 study were included in the benefit assessment regarding the outcome of anxiety. In the Rudd 2015 study, no statistically significant difference between treatment groups was found at any survey time point (3, 6, and 18 months). With regard to the outcome of anxiety, there is therefore no hint of (added) benefit of second-wave CBT in comparison with TAU.

4.5.1.2 Results on the outcome of depressive symptoms

The benefit assessment for the outcome of depressive symptoms is based on the results of 3 studies. For this outcome, the meta-analysis at the time point of 1 month does not show a hint of (added) benefit of second-wave CBT in comparison with TAU. For time points 3, 6, and 18 months, the meta-analysis shows, at a moderate certainty of results, an indication of (added) benefit of second-wave CBT in comparison with TAU with regard to the outcome of depressive symptoms.

4.5.1.3 Results on the outcome of hopelessness

The benefit assessment for the outcome of hopelessness is based on the results of 3 studies (Brown 2005/Ghahramanlou-Holloway 2012, Rudd 2015 and Sinniah 2017). With regard to the outcome of hopelessness, the results for the time points of 1 month and 3 months show no hint of (added) benefit of second-wave CBT in comparison with TAU. For each of the survey time points of 3, 6, and 18 months, the meta-analysis shows, at a moderate certainty of results, an indication of (added) benefit of second-wave CBT versus TAU with regard to hopelessness.

4.5.1.4 Results on the outcome of posttraumatic stress

The benefit assessment on the outcome of posttraumatic stress is based on the results from 1 study. In the Rudd 2015 study, no statistically significant difference between treatment groups was found at any survey time point (3, 6, and 18 months). With regard to the outcome

of posttraumatic stress, there is therefore no hint of (added) benefit of second-wave CBT in comparison with TAU.

4.5.1.5 Results on the outcome of suicidal ideation

The benefit assessment for the outcome of suicidal ideation is based on the results of 2 studies. In the Sinniah 2017 study, no statistically significant difference between treatment groups was found for the survey time point of 1 month. With regard to the outcome of suicidal ideation at the survey time point of 1 month, there is therefore no hint of (added) benefit of second-wave CBT in comparison with TAU.

Due to heterogeneity and the absence of effects in the same direction, the meta-analysis of the Rudd 2015 and Sinniah 2017 studies for the survey time point of 3 months does not result in any hint of (greater) benefit of second-wave CBT in comparison with TAU.

In contrast, the meta-analysis of the Rudd 2015 and Sinniah 2017 studies for the survey time point of 6 months shows, at moderate certainty of results, an indication of (added) benefit of second-wave CBT in comparison with TAU with regard to the outcome of suicidal ideation.

For the survey time point of 18 months, the Rudd 2015 study shows no statistically significant difference between treatment groups. With regard to the outcome of suicidal ideation, for the survey time point of 18 months, there is therefore no hint of (added) benefit of second-wave CBT in comparison with TAU.

4.5.1.6 Results on the outcome of (follow-up) suicide attempts

The benefit assessment for the outcome of (follow-up) suicide attempts is based on the results from 2 studies. The meta-analysis found, at moderate qualitative certainty of results, an indication of (added) benefit of second-wave CBT in comparison with TAU, suggesting a long-term effect (at the survey time points of 18 and 24 months) for the outcome of suicide attempt.

4.5.1.7 Results on further patient-relevant outcomes

No data were reported on the outcomes of all-cause mortality / overall survival, suicide mortality, physical functioning including activities of daily living / everyday functioning, inpatient admission, SAEs, discontinuation due to AEs, health-related quality of life, health-related social functioning including occupational and social participation. Data on social problem-solving ability were reported but disregarded due to reporting bias.

4.5.1.8 Evidence map on the comparison of second-wave CBT versus TAU

Table 3 below shows the evidence map regarding patient-relevant outcomes.

Table 3: Evidence map regarding patient-relevant outcomes (second wave)

Survey time point	Outcomes													
	Mortality		Morbidity									HRQoL		
	All-cause mortality / overall survival	Suicide mortality	Anxiety	Depressive symptoms	Hopelessness	Physical functioning including activities of daily living / everyday functioning	Posttraumatic stress	Inpatient admission	Suicidal ideation	(Follow-up) Suicide attempts	SAEs (+ discontinuation due to AEs)	Health-related quality of life	Health-related social functioning, occupational and social participation	Social problem-solving ability
1 month	-	-	-	⇔	⇔	-	-	-	↔	-	-	-	-	-
3 months	-	-	↔	⇑	⇔	-	↔	-	⇑⇓	-	-	-	-	-
6 months	-	-	↔	⇑	⇑	-	↔	-	⇑	-	-	-	-	-[a]
18 months	-	-	↔	⇑	⇑	-	↔	-	↔	-	-	-	-	-
≥ 18 months	-	-	-	-	-	-	-	-	-	⇑	-	-	-	-

⇑: indication of (greater) benefit or indication of lesser harm
⇔: no hint, indication, or proof; homogeneous result
⇑⇓: no hint, indication or proof, heterogeneous result
↔: individual study, no statistically significant difference
-: no data reported
a: Data were reported but unusable (reporting bias).
AE: adverse event; HRQoL: health-related quality of life; SAE: serious adverse event

4.5.2 Comparison of third-wave CBT versus TAU

4.5.2.1 Results on the outcome of depressive symptoms

The benefit assessment for the outcome of depressive symptoms is based on the results from 1 study. For this outcome, the Barnhofer 2009/Hargus 2010 study shows, at the survey time point of 1 month, a hint of (added) benefit of third-wave CBT in comparison with TAU, at a moderate certainty of results. No hint was found for the survey time point of 3 months. No data are available for the survey time points of 6 and 18 months.

4.5.2.2 Results on the outcome of suicidal ideation

The benefit assessment for the outcome of suicidal ideation is based on the results from 1 study. In the Barnhofer 2009/Hargus 2010 study, no statistically significant difference between treatment groups was found at the survey time point of 1 month. With regard to the outcome of suicidal ideation, at this survey time point, there is therefore no hint of (added) benefit of third-wave CBT in comparison with TAU. No data are available on this outcome at other survey time points.

4.5.2.3 Results on further patient-relevant outcomes

No data were reported on the outcomes of all-cause mortality / overall survival, suicide mortality, anxiety, hopelessness, posttraumatic stress, physical functioning including activities of daily living / everyday functioning, inpatient admission, (follow-up) suicide attempts; SAEs, discontinuation due to AEs, health-related quality of life, health-related social functioning including occupational and social participation.

4.5.2.4 Evidence map

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

Table 4: Evidence map regarding patient-relevant outcomes (third wave)

Survey time point	Outcomes														
	Mortality		Morbidity								HRQoL				
	All-cause mortality / overall survival	Suicide mortality	Anxiety	Depressive symptoms	Hopelessness	Physical functioning including activities of daily living / everyday functioning	Posttraumatic stress	Inpatient admission	Suicidal ideation	(Follow-up) Suicide attempts	SAEs (+ discontinuation due to AEs)	Health-related quality of life	Health-related social functioning, occupational and social participation	Social problem-solving ability
1 month	-	-	-	⇗	-	-	-	-	↔	-	-	-	-	-
3 months	-	-	-	↔[a]	-	-	-	-	-	-	-	-	-	-
6 months	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18 months	-	-	-	-	-	-	-	-	-	-	-	-	-	-
≥ 18 months	-	-	-	-	-	-	-	-	-	-	-	-	-	-

⇗: hint of (added) benefit or hint of lesser harm
↔: individual study, no statistically significant difference
-: no data reported
a: Only the significance level was reported, resulting in a lack of transparency of results and in downgrading of the certainty of results from moderate to minor.
AE: adverse event; HRQoL: health-related quality of life; SAE: serious adverse event

5 Results: Health economic assessment

5.1 Intervention costs

The intervention costs take into account (one-on-one and group) psychotherapy and the case manager for the experimental intervention. For the comparator intervention, the costs of drug therapy and inpatient treatment are identified. For all interventions, the minimum and maximum costs per patient and treatment case are listed in the form of a range.

The costs for psychotherapy are broken down into short-term and long-term therapies. Elements of therapy include the initial psychotherapeutic consultation, the trial session, short-term therapy (2 sets of up to 12 sessions) as well as long-term therapy (up to 60 sessions) including therapy extension (up to 80 sessions). The 2017 structural reform of psycho-therapeutic care [51] introduced acute treatment. This was disregarded in the cost calculation since, in terms of billing, it is akin to short-term therapy (1 set). The difference in costs is marginal: For acute care, an extra EUR1.20 can be billed for twelve 50-minute sessions.

For short-term and long-term therapy, the minimum was defined as one initial therapeutic psychotherapeutic consultation plus two trial sessions, and the maximum as six initial therapeutic psychotherapeutic consultations plus four trial sessions. In long-term therapy, the 24 short-term therapy sessions are followed by 60 therapy sessions as the minimum, which can in turn be followed by a treatment extension of 80 sessions as the maximum. The same approach was used for group therapy. However, reimbursement for short-term and long-term therapy differs depending on group size. On the basis of the studies of the benefit assessment and for the sake of clarity, group sizes of up to 5 participants were considered (the Uniform Value Scale fee schedule contains another subcategory of up to 9 participants).

One study of the benefit assessment [41] also integrated meditation elements into psychotherapy. In the German healthcare context, this would take the form of an adjunct to therapy. Various health insurance funds cover a portion of the costs of courses such as meditation classes. The remaining costs must be paid by the patient.

Case managers are taken into account since they were an element of a study in the benefit assessment. In the German healthcare context, both the social psychiatric service and sociotherapy are equivalents to case management in psychotherapeutic care. Since no cost calculations are available for the social psychiatric service, sociotherapy was included in the further calculation of intervention costs. Sociotherapy can be prescribed by a physician or psychotherapist and is intended to support the patient in structuring everyday life and taking advantage of outpatient medical/psychotherapeutic care. Thirty 60-minute sessions can be prescribed, with a possible extension to a maximum of 120 hours over 3 years. The reimbursement of sociotherapists, who are typically social workers or psychiatric nurses, is negotiated between the health insurance funds and the service providers. In the calculation,

the flat fee reimbursement for the federal state of Lower Saxony was used as an example. In addition, patients are responsible for a copayment of 10% of the cost of sociotherapy per calendar day, with a defined minimum of EUR5 and maximum of EUR10 per day (§61 Social Code Book [SGB] V).

For the drug-based treatment as the comparator intervention, a commonly prescribed antidepressant (citalopram) was used. The cost calculation included both drug and prescription costs. A range of 6–12 months was defined for the duration of drug treatment. This value roughly follows the NDMG recommendations for unipolar depression and the guideline on depression of the Drug Commission of the German Medical Association [52], as well as a 2015 international cohort study conducted by Coupland et al. [53].

The cost calculation of inpatient care was based on the PEPP Flat Rate Charges in Psychiatry and Psychosomatics. The minutely broken-down Detailed Diagnostic Data of Hospital Patients [54] were used to determine the average length of stay. Since no hospital-specific base rates are available, the value of EUR280 was derived from an agreement between GKV, PKV, and the German Hospital Federation [55]; this value is to be used by hospitals if no hospital-specific base rate for remuneration is available yet. Furthermore, the patient is responsible for copayments in the amount of EUR10 per calendar day (Sections 39 and 61 SGB V). Length of hospital stay was calculated separately for each considered ICD code. The minutely broken-down 2016 Detailed Diagnostic Data of Hospital Patients were used for this purpose, and the occupancy days were divided by the number of cases so as to obtain the average occupancy days per case. The length of stay varies by ICD code, ranging from 13 days (F32.0) to 39 days (F33.2). In another step, the relevant PEPP structural categories (PA04A, PA04B, and PA04C) were identified. To calculate the remuneration amount, the base rate was first multiplied by the valuation ratio of the respective PEPP structural category to then multiply the resulting product with the calculated length of stay. A detailed listing of the average length of stay and the remuneration amounts is provided in Section A4.1.1 of the full report.

Finally, the cost per patient or per patient and treatment case is discussed, revealing costs of short-term therapy between EUR2327.57 and EUR2684.14 and costs of long-term therapy between EUR7732.23 and EUR15 314.23. The cost of group therapy is lower due to lower point scores per patient. The cost of drug therapy lies between EUR188.67 and EUR362.32, while the cost of inpatient care ranges from EUR3644.06 to EUR11,901.06.

5.2 Cost effectiveness

No data are available on the cost effectiveness of the intervention.

5.2.1 Results of the information retrieval

No relevant studies or documents were found through the focused information retrieval or other search steps.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 13 April 2018.

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

6.1 Results on ethical and social aspects

6.1.1 Evaluation of ethical and social aspects

The evaluation of ethically relevant arguments and aspects is based on the INTEGRATE-HTA framework and the approach described therein for ethical analysis according to Lysdahl 2016 [34]; its steps and results are briefly described below. Alongside the 5 steps, the contextual aspects illustrated in the framework were considered.

In step 1, the complexity of the interventions (from the initially established definition) was determined with regard to the main points set forth by Wahlster [40]:

- 1. Multiple and changing perspectives (e.g. various degrees of severity of depression, various stages of suicidality; various stakeholders)
- 2. Indeterminate phenomena (e.g. suicide attempts despite full remission)
- 3. Uncertain causality (e.g. effects on the environment)
- 4. Unpredictable outcomes (e.g. suicide yes/no)
- 5. Historicity, time and path dependence (e.g. urban versus rural; dependent on specific measure)

Moreover, other points mentioned by Wahlster [40] with regard to non-drug interventions were looked at, including multiple interacting components, different groups or organizational levels, and differences in intervention design. Accordingly, many interacting components impact access to care (e.g. severity of depression, different service providers, social environment). In addition, some of the interventions to be assessed can be complex, and their approaches both target the specific disorder and start at the individual and background level. Patient interviews conducted while the report template was being devised already provided initial information on this topic. Addressing the complexity for the other domains (legal, organizational) is also relevant.

The second step involved the selection of the ethical approach. The Socratic approach (revised version) was chosen since it is broad based, combines various ethical approaches and perspectives, and was developed especially for HTA processes. Further, it has already been used to assess a wide range of technologies. Since no comprehensive overview of potential ethical aspects is currently available for HTAs, an exploratory identification of ethical aspects using the Socratic approach is particularly suitable [56]. In addition, this approach is appropriate for assessing complex interventions [57] such as those considered (see step 1). The Socratic approach presents output in a descriptive manner without taking a position or providing recommendations and thereby complies with the specifications and objectives of

ThemenCheck Medizin. The specific procedure for the analysis of ethical aspects was based on Hofmann's questionnaire [58], which can be embedded in the INTEGRATE-HTA framework as well as in HTA reporting. The questionnaire consists of 7 main questions (e.g. *"What are the ethical, social, cultural, legal, and religious challenges related to the health technology?")* and 33 detailed questions (e.g. *"What are the morally relevant consequences of the implementation, use or withdrawal of the technology?"*). As suggested by Lysdahl, any overlap with the other domains was taken into account, and consequently, ethical aspects were analysed and presented together with social aspects.

The selected approach was modified (step 3) with regard to the sequence of the scoping search and the identification and selection of questions (see Section 6.1.3). The wording of the questions for the moderated discussion rounds was adapted as well (see Section 6.1.2).

Once the questions were used and the results determined (step 4; see Sections 6.1.2 through 6.1.4), the latter were validated (step 5; see Section 6.1.5).

The information processing regarding social aspects was based on the questionnaire suggested by Stich [35], which represents a guideline for the practical implementation of the conceptual framework developed by Mozygemba 2016 [36]. The questions are categorized into 3 topic areas (1. patient group; 2. ethical and moral aspects of interventions (+ structural challenges); 3. family and work) with a total of 7 detailed questions.

6.1.2 Moderated discussion rounds

To identify ethical and social aspects, 3 moderated discussion rounds (hereinafter [methodologically] referred to as focus groups) were conducted using a selection of questions from the Hofmann and Stich questionnaires. The focus groups were recorded and externally transcribed.

In total, 3 patient representatives, 4 family members, and 8 patients participated in the focus group meetings, each of which took about 2 hours. The majority of participants were female (n = 11, 73%). Regarding the utilization of non-drug interventions[5], participants particularly mentioned emergency appointments with the specialist (n = 7, 58.3%), psychotherapist contact offers, e.g. per email or telephone, as well as stays at a psychiatric day-care hospital (each n = 5, 42.7%).

6.1.3 Scoping searches

Before the focus groups were held, initial scoping searches were conducted to narrow down the Hofmann and Stich questionnaires and select questions relevant for the focus groups. An

[5] Only applies to family members and patients as determined by a brief questionnaire administered in the focus groups.

initial selection of items was then coded with regard to the detailed questions from the two questionnaires. The most frequently coded questions were selected and compared once again (in view of the 2 questionnaires) with regard to overlapping content.

In a next step, the search was refined and conducted again in the above-mentioned databases as well as in PubMed. The bibliographic search identified and extracted a total of 6 quotations [59-64].

Through stakeholder websites (e.g. the National Association of Statutory Health Insurance Physicians [KBV] and the German Depression League [DDL]), guideline databases (Association of the Scientific Medical Societies in Germany [AWMF]), guidelines (Federal Joint Committee [G-BA]), regulations and laws (including through the German Federal Chamber of Psychotherapists [BPtK]), 9 quotations were identified and extracted [7,65-72]. The design of the search was greatly simplified as permitted by the websites and search options. In most cases, the search was performed using the term “depression” or “suicide”. The information sources were selected in accordance with the population, intervention, and combination of ethical and social aspects considered in the report.

While screening for the benefit assessment, potentially interesting literature on ethical, social, legal, and organizational aspects was noted and viewed in the IQWiG WebTSTB database. However, no additionally relevant quotation was identified in this process. In addition, 2 items of the benefit assessment [44,45] were used to identify relevant aspects. In the background search for the report template and the HTA report, 2 further quotations were also identified and extracted [18,25].

Overall, the use of the various information sources resulted in the identification and extraction of 19 quotations on ethical and social aspects.

6.1.4 Identified aspects

The ethical and social aspects identified in the focus groups (Section 6.1.2) and scoping searches (Section 6.1.3) are presented in aggregated form below since many overlaps between ethical and social aspects became apparent during the analysis of results (Section 6.1.1). The aspects were allocated to the overarching questions according to Hofmann and Stich. The allocation to the respective detail-level questions of both questionnaires as well as all complete focus group quotations and sources are presented in Table 47 (Section A5.2.5.1) of the full report.

6.1.4.1 What are the morally relevant issues related to the disease and the patient group? (Question 1 according to Hofmann)

In total, the focus groups and literature [18,44,60,61,63,65-68,70-72] identified 5 aspects related to question 1. They are (1.1) vulnerable groups of persons (non-utilization, high-risk

group), (1.2) member of statutory health insurance (SHI) versus private health insurance (PHI) (access), (1.3) severity of depression (access barrier), (1.4) stigma of depression (non-utilization), and (1.5) different care situation (access barrier). The identified aspects can be allocated to Stich question areas 1 (health technology and groups), 2 (society and healthcare system), and 3 (patients and family, workplace).

In a first aspect (1.1), 5 different groups of persons were identified as particularly vulnerable, either with regard to non-utilization (socioeconomic status / financial dependence, people with language barriers) or poor baseline conditions (people with prior suicide attempts, certain occupational groups), or with regard to both (men). Below, this is illustrated using one example each. Socioeconomic status or financial dependency can affect utilization behaviours since therapy-related travel or child care costs are not covered [18]. Persons with prior suicide attempts were identified as an example of a high-risk group since the probability of a follow-up attempt is highest in the 3–6 months after the suicide attempt [44]. Men in this situation rarely or never contact their general practitioner, and consequently, depression often remains undiagnosed or untreated [61,63,71]. The first aspect was identified through both focus groups and the literature [18,44,61,63,71].

Aspect 1.2 was identified via the focus groups and relates to the insured status (PHI versus SHI) and the resulting differences in options, e.g. in terms of switching the therapist. In addition to the identified specific patient groups and the associated moral aspects, disease-related aspects were identified. The severity of depression (1.3) is mentioned as emotional vulnerability (“disease of slow self-isolation”) and the associated impact on the effectiveness of the interventions. This aspect was identified through the focus groups and literature [70].

Another disorder-related aspect is the stigma of depression (1.4), particularly with regard to barriers to access and utilization of non-drug interventions [18,60,61,65-67,70,72]. This aspect, which overlaps with organizational aspects (see Section 6.3.2), has been repeatedly discussed in the literature and by focus groups. The stigma of mental disorders in general involves negative stereotypes and resulting negative evaluative responses. The consequences of this stigma are, firstly, self-stigmatization, where people with a mental disorder internalize these negative stereotypes, and, secondly, public attitudes and structural discrimination which, whether intended or not, places those suffering from mental disorders at a disadvantage [60]. Such consequences have an adverse effect on both the utilization of psychosocial interventions and help-seeking behaviour, such as opening up to the general practitioner [60,61]. According to the German Association for Psychiatry, Psychotherapy, and Psychosomatics (DGPPN) [66], involuntary hospitalization is similarly associated with such stereotypes, with people considered *“troublesome” or “annoying”* being admitted to psychiatric hospitals against their will under the pretext of alleged *“endangerment of others”*. With regard to the discussed compulsory treatment, experts criticized the draft version of the

"Mental Health Law" in the federal state of Bavaria, stating that *"instead of helping mentally ill patients with this draft legislation, it stigmatizes them and puts them on a par with criminals".* The German Bundestag's call for destigmatization, e.g. in the form of targeted and comprehensive information campaigns is supported, for instance, by various interest groups [18,65,72].

Another identified aspect (1.5) of question 1 relates to the availability of therapists (also in terms of waiting times) in urban and rural areas and the associated access differences or delays. The BPtK [68] highlights this aspect by pointing out that needs planning is predicated on the belief that mental disorders are much less common in rural areas than in large cities and consequently, far fewer psychotherapists are planned in rural areas than in large cities. The BPtK demonstrated that this assumption conflicts with large, representative studies by the Robert Koch Institute, which show that the prevalence of mental disorders hardly differs between urban and rural regions.

6.1.4.2 What are the ethical, social, cultural, legal, and religious challenges related to the health technology? (Hofmann question 2)

For question 2, a total of 6 aspects were identified in the focus groups and the literature [7,59,62,66,70]: (2.1) autonomy; (2.2) right to illness; (2.3) privacy: patients; (2.4) privacy: family members; (2.5) religious support; (2.6) equitable distribution of health services. The aspects of autonomy and privacy are each composed of subcategories. Most aspects (some of them contradictory) were identified for the detailed question of whether the use of non-drug interventions challenges patient autonomy, integrity, privacy, or dignity. Most of the identified aspects can be assigned to Stich topic area 1 (health technology and groups).

Autonomy (2.1) was identified, firstly, as a prerequisite for good medical care [66]. According to DGPPN [66], autonomy is a human right, and autonomous patient decision-making is a basic requirement for good medical care. Autonomy (as well as privacy) may be restricted under some circumstances, e.g. when people are treated against their will (heteronomy, compulsory guardianship) [70]. However, it has been noted that in emergencies, both autonomy and dignity can be of secondary importance [7]. The NDMG on unipolar depression [7] recommends considering inpatient admission against the patient's will in case of suicide risk and unwillingness to be treated, referring to the Hospitalization Acts (Unterbringungsgesetze) or Mental Health Acts (PsychKGs) of the individual federal states or the provision in the Substitute Decisions Act (Betreuungsgesetz). However, using the examples of (day) clinics and the structures provided, focus groups discussions described non-drug interventions as potentially strengthening autonomy as well.

On the other hand, patients capable of self-determination may reject treatment indicated according to the state of the art of medical practice since they also have a (2.2) right to illness [66,73].

As far as (2.3) privacy is concerned, contradictory statements were identified, which appraised interventions, e.g. by the social psychiatric service or home visits, as either positive (associated with support, opportunity) or negative (associated with anxiety, coercion, or shame). According to the focus groups, the intervention design should take into account privacy as well as autonomy. From the patient perspective (focus groups), a certain degree of "intrusiveness" is all right for measures taken by family members; likewise, the NDMG [7] recommends for family members or friends to take the patient to the competent psychiatric hospital as the least intrusive measure. From the (2.4) family members' perspective (focus groups), however, limits should be set to their assistance in order to protect their own privacy, dignity, and autonomy.

Alongside the mentioned aspects, particularly with respect to autonomy and privacy, (2.5) religious support was also seen as a way for family members to help patients, for instance by scheduling appointments with pastoral care. This aspect was not addressed in the focus groups and was identified solely through the literature [59].

With regard to the distribution of health services, both the literature [62] and the focus groups highlighted the fact that (2.6) equitable distribution of health services depends on the identification of depressive and/or suicidal persons.

6.1.4.3 What are the moral challenges with structural changes related to the health technology? (Hofmann question 3)

Regarding question 3, the literature [7,25] and focus groups each revealed 2 aspects. They were fit into the Stich question areas 1 and 2.

Firstly, (3.1) access barriers for people with depression were highlighted, particularly during times of crisis or in critical situations [25]; they include a lack of appointments, no accessibility (telephone counselling), and the organization of crisis interventions being too time intensive for physicians in private practice. Secondly, it was pointed out that a (3.2) trustful relationship with (a) professional(s) is of the utmost importance but is also associated with a risk of dependency [7].

Other aspects which were mentioned in the focus group but are more closely related to the specific structural optimization potential were categorized under organizational aspects (see Section 6.3.2).

6.1.4.4 What are the moral issues related to the characteristics of the health technology? (Hofmann question 4)

This question was not used a priori in the focus groups; nevertheless, 1 aspect was inductively identified on this topic via the focus groups and the literature [18,74]. It relates to the fear of being stigmatized due to the use of psychotherapy. The aspect was allocated to Stich question area 1. This result was corroborated by the WHO World Mental Health Survey [74], according to which, in industrial countries, 56% of persons who had attempted suicide explained the low demand for treatment with attitudinal barriers, e.g. fear of stigmatization (17%).

6.1.4.5 What are the moral issues related to stakeholders? (Hofmann question 5)

The following 5 aspects were identified through the focus groups and literature [64,69-71]: (5.1) social environment, (5.2) protection of family members, (5.3) psychotherapy as a safe space, (5.4) creation of space for interventions, and (5.5) social pressure. The aspects related to question 5 exhibit extensive overlap with the Stich questionnaire.

The (5.1) social environment was identified as an important aspect with a variety of effects. Firstly, it acts as a reference point and external sensor. Secondly, family and friends can potentially contact the therapist. In addition, the social environment is described as decisive for help-seeking behaviour and as influencing the utilization of interventions (e.g. emergency appointments with a specialist). In the absence of a social environment, in contrast, patients tend to experience isolation [64,69,71].

However, the social environment is also at (5.2) risk of co-dependency. Family members particularly noted that they are not responsible for the healing process and must therefore protect themselves and obtain relief as well [70].

For (5.3) patients, psychotherapy represents a safe space for achieving some distance from family and friends. In order to utilize therapy, (5.4) spaces must be created. After all, therapy requires an effort, which can affect everyday and working life. At that point, reference was made to the presence of some (5.5) social pressure with an expectation of patients functioning despite the disorder as a result of a lack of understanding of the unforeseeable duration of the healing process.

No aspects relating to Hofmann questions 6 and 7 were identified. These questions were deliberately omitted from the focus groups since they have more to do with compiling the HTA report (e.g. “Why was it commissioned?”). No aspects relating to either of the questions were inductively recorded either. Aspects were identified on each of the 3 areas of the Stich questionnaire. Except for the aspect of potential consideration of religious support (Hofmann question 3), no allocation to the Stich questionnaire was possible .

6.1.5 Validation by stakeholders

In accordance with the INTEGRATE-HTA approach, the corresponding stakeholders provided written validations of the final results tables on the ethical, social, legal, and organizational aspects with regard to their transparency and support by evidence. For this purpose, stakeholders with either methodological or technical knowledge regarding the topic of the HTA report were initially identified (see Section A5.1.1 of the full report). Three stakeholders (clinical, sociomedical, and ethics experts) commented on the table of ethical and social aspects. Notes regarding the presentation, e.g. terminology or the consolidation of aspects, were entered in Table 47 of the full report. Other comments related to the subsequent aspects (for a complete list of comments per stakeholder, see Table 48 in Section A5.2.6 of the full report).

Overall, the validation by stakeholders showed that the aspects have been cogently analysed and well categorized. Questions or comments concerned the way the results were combined with the results of the other domains, the identification of Hofmann questions which were not addressed, and the highlighting of limitations, such as the absence of a systematic search and hence of literature references for certain aspects. From an ethical perspective, the combined presentation of social and religious aspects in the table was noted as being inappropriate. The descriptive/exploratory approach for establishing aspects was deemed adequate for presenting ethical and social aspects in the HTA report (problem description). A need for a theoretical and normative framework was discussed if recommendations were to be issued.

Detailed comments related to individual aspects. This includes the aspect of vulnerable groups, which should be better differentiated with regard to the entities (non-utilization or high risk); this was done in Table 47 of the full report. Concerning the vulnerable group of “people with language barriers”, it was pointed out that patients are not entitled to therapy in a foreign language, and the cost of an interpreter must be borne by the patients themselves. Access differences between PHI and SHI members with regard to various services were commented by pointing out that there are difficulties for PHI members as well as SHI members (as expressed in the quotation). One comment concerned the quotation on the aspect of right to illness (2.2), questioning to what extent crisis teams are in fact authorized to use coercive measures. This issue was examined and the presentation is correct. According to a comment regarding the aspect of the social environment (5.1) and the possibility of family/friends contacting the therapist, this is an issue which requires careful weighing of pros and cons since family involvement can also be experienced as a betrayal or privacy violation. It was also annotated that further comment noted that, in one quotation, the aspect of stigmatization (1.5) was brought up only under the topic of heteronomy. The annotation also asked that the correctness of the stated quotation be reviewed; a review confirmed correct presentation.

Overall, the stakeholders highlighted major relevant aspects, e.g. high-risk groups and a special review of the indication, individual and systemic access barriers, support offers (but also structural access problems), destigmatization as a prerequisite for utilization (some measures being listed), the balancing act between autonomy and heteronomy, and the call for an awareness campaign (might in part be linked to destigmatization) as well as individualized strategies (e.g. involvement of friends or family members). Vulnerable groups, stigma, dignity, access, autonomy/privacy, and equity were deemed particularly relevant from an ethical perspective. The aspects of dependency on (professional) reference persons and social pressure were deemed to be poorly classified.

6.2 Results on legal aspects

6.2.1 Scoping searches

Except for the search term used, the search steps for legal aspects are the same as those for the ethical and social aspects. Moreover, the Beck Online database was additionally searched. In total, 9 quotations were identified and extracted [51,75-82]; this includes quotations which overlap with ethical, social, and legal aspects. The quotations from relevant publications are found Section A9.3.2 of the full report.

6.2.2 Identified aspects

The information processing and results presentation for the scoping search are based on the (9-point) guideline developed by Brönneke for the identification of legal aspects, as used within the INTEGRATE-HTA framework. The presentation of legal aspects refers particularly to manual-based (cognitive) BT provided by the major service providers (psychotherapists), with other non-drug interventions (e.g. sociopsychiatric service) also being taken into account.

1. Patient autonomy I: Declaration of informed consent

According to Section 7(1) of the German Model Professional Code of Conduct (MBO) for Psychotherapists [75], a patient declaration of informed consent and an informed-consent discussion conducted by the psychotherapist or another person with the requisite training to conduct the respective measure are obligatory before any psychotherapeutic therapy.

2. Patient autonomy II: Alternative forms of informed consent

In accordance with Section 13(1) MBO for Psychotherapists, patients with limited capacity to give consent may give informed consent only if they possess the natural ability of comprehending the treatment [75]. If the patient does not possess this ability of comprehension, the psychotherapist must provide the appropriate information and obtain informed consent from the legal representative. In case of conflict between the legal

representative and the patient, the psychotherapist is obligated to act with particular regard for patient welfare.

Mental health acts (PsychKGs) in individual German federal states govern mentally ill persons' coercive treatment and involuntary admission in a psychiatric establishment based on criminal or guardianship law. According to the Berlin PsychKG, the purpose of placement in a psychiatric establishment is the *"cure, improvement, or alleviation or prevention of deterioration of the mental illness or disorder of the admitted person"* [77] and in case of current substantial risk of harm to self or others, provided that *"this risk cannot be otherwise averted"* [77]. In all German federal states, coercive treatment requires prior approval by the competent court [76-78].

Differences in the laws concern, for instance, the assistance provided. For example, Bavarian law contains no provision for sociopsychiatric service. However, the districts themselves *"or their authorized representatives are to establish, operate, and further develop in a needs-based manner psychosocial counselling and assistance services for people in psychiatric crises (crisis services)"* [76]. Placement in psychiatric establishments is to be avoided and self-help and participation promoted [76]. In Berlin, in contrast, the law provides for sociopsychiatric service and low-threshold services [77]. By means of timely, comprehensive counselling, personal support or mediation or through other suitable measures, particularly early outpatient treatment, inpatient treatment or placement into a psychiatric establishment are to be avoided or shortened in order to promote social participation and reintegration [77].

3. Patient autonomy III: Privacy and data protection

The European Union's (EU) General Data Protection Regulation (GDPR), which unifies the rules on the processing of personal data by private companies and public authorities within the EU, governs the right of access, right to rectification, right to erasure, restrictions on processing, and the right to data portability as well as data safety measures. The processing of health-related data is permissible in the context of prevention, diagnostics, therapy, and follow-up care as well as for the fulfilment of the duties of contract psychotherapists or on the basis of social regulations [79]: This pertains to the duty to disclosure vis-a-vis payers such as the health insurance, accident insurance, or pension insurance (Section 100 SGB V), the National Association of Statutory Health Insurance Physicians and the health insurer (Section 295 SBG V), or the Medical Service of Health Insurers (MDK) (Section 276 SGB V). Health data may also be processed in order to pursue legal claims, e.g. to assert remuneration claims vis-à-vis the patient.

With regard to privacy and data protection, the MBO for Psychotherapists [75] defines as important and governs professional secrecy (Section 8), documentation requirements (Section 9 [1]), and a 10-year retention obligation for medical records (Section 9 [3]). With

regard to collected data and personal records, it must be ensured that they are *"securely stored and fully safeguarded from access by unauthorized third parties"*. The same applies to electronically stored data and records [75].

4. Medical specialities

BT (Section 17) as well as its forms of application (Section 20) are listed in the Guidelines for Psychotherapy [51]. Professional practice, licensure, and the state examination are covered by Sections 1 to 12 of the Psychotherapists' Law (PsychThG) [81], the law governing the occupations of psychological psychotherapist and child and adolescent psychotherapist.

The Psychotherapy Agreement for Psychological Psychotherapists [80] lists the following billing prerequisites: *"The professional qualification in accordance with Section 3 is considered proven for the performance and billing of behavioural therapy in accordance with the service content of Uniform Value Scale fee schedule items 35130, 35131, 35140, 35141, 35150, 35421, 35422 and 35425: through the proof of qualification in accordance with Section 95c SGB V on the basis of in-depth training with the acquisition of knowledge and experience in behavioural therapy."* This similarly applies for medical psychotherapists [80]. To conduct group therapies (by medical and psychological psychotherapists), the presented certificates and documents must show that extensive knowledge and practical experience in group BT have been acquired [80].

5. Intellectual property

Use of manuals (see Table 12 of the full report) within CBT (from the publications of the benefit assessment) does not require any specific continuing education other than meeting the general requirements listed under item 4 (licensure). Conducting group CBT, however, does requires advanced education on group therapy leadership (e.g. mindfulness-based cognitive therapy with specific suicidality focus according to Barnhofer [41], group sessions) (see 4. Medical specialties).

6. Reimbursement of costs in the public health system

In accordance with the Guidelines for Psychotherapy, CBT is already eligible for reimbursement as an SHI service (Section 4); the specific scope is defined in Annex E [51]. Section 5.1 contains detailed cost information in relation to the research question.

In addition, there has been a court judgement relating to the recognition of depression / suicide attempt as an occupational illness, which, had it been successful, might have resulted in reimbursement by statutory accident insurance.

The items of *Marketing authorization I: medical devices and Marketing authorization II: medicinal products and clinical studies* were disregarded.

6.2.3 Validation by stakeholders

As discussed in Section 6.1.5, the final results table on legal aspects was commented by 1 stakeholder (clinical expert). Comments on the presentation, such as terminology or the consolidation of aspects, were entered in the table. Other comments addressed subsequent aspects (for a complete list of comments per stakeholder, see Table 50 in Section A5.3.3 of the full report).

The validation has shown that all legal aspects important for this topic have been listed. Regarding aspect 1, the limited duration and prerequisites for coercive measures were pointed out with regard to PsychKG. Regarding aspect 7 (intellectual property), it was confirmed that, in principle, any psychotherapist may apply the manuals, provided that other prerequisites are met (licensure as psychotherapist, continued education for leading groups).

6.3 Results on organizational aspects

6.3.1 Scoping searches

Except for the search term used, the search steps for organizational aspects are the same as those for ethical and social aspects. In total, 11 quotations [18,25,45,51,59,62,68,83-86] were identified and extracted, some overlapping with quotations used for ethical, social, or legal aspects. The quotations from the relevant publications are found in Section A9.3.3 of the full report. During focus group analysis, aspects relevant for the analysis of the organizational aspects came up. These were included.

6.3.2 Identified aspects

The identified organizational aspects are presented in accordance with the grid template developed by Perleth 2014 [39]. The grid template contains 9 central questions on the 3 topic areas: (1) influence on the prerequisites of service provision, (2) influence on processes, and (3) further aspects. The grid template was modified since the search for the benefit assessment had not identified any technology not yet represented in the system. Results from the focus groups were additionally taken into account.

6.3.2.1 Influence on the prerequisites of service provision

Central question 1: Changes in the location of medical care (modified: Conditions for the improved care of the observed target group)

With regard to the treatment of people with unipolar depression during periods of crisis, conditions were identified to achieve improved care in terms of non-drug interventions in the

outpatient sector. The expansion of outpatient community-based structures for the early detection, prevention, and treatment of mental disorders (particularly depression) is to be strengthened and the availabilities of therapists in rural areas improved [68,83]. Specifically, particularly low-threshold interventions [18,25] such as no-suicide contracts, ultra-brief psychotherapy interventions (safety planning), and safe retreats were mentioned. One focus group participant highlighted the latter as a good way to remove patients from their everyday lives and provide social contact in a low-threshold manner and without requiring major care resources.

Even beyond safe retreats, focus group participants often mentioned that many services can be designed in collaboration with non-experts or experienced laypeople and do not require the (exclusive) involvement of medically or psychologically trained staff. In addition, patient-tailored services as well as shared or participative decision making were mentioned as worthy of further promotion [84].

Central question 2: Changes in the qualification requirements for service providers / additional or reduced staff (modified: Qualification requirements for service providers in the treatment of the observed target group)

Both the literature [25,59,84,85] and the focus groups highlighted a need for professional, continuing, and advanced training/education for general practitioners and specialists regarding the diagnostics and treatment of depression, suicidality and crises / suicide prevention as well as on the topic of suicidality and crises, specifically in patients with depression. The DGPPN additionally calls for the topics of suicidality and suicide prevention to become a standard component of for professional, continuing, and advanced training/education in all healthcare and social service professions.

The use and application of the manuals identified in the studies of the benefit assessment (see Table 12 of the full report) are not associated with any qualification requirements for psychotherapists, except for general qualifications and the qualification to lead group therapies (see Section 6.2.2).

Central question 3: Changes in the requirements pertaining to the staff and material as well as to organizing the service provision (structural quality) (modified: Calls for better access conditions [structural quality])

The literature [25,85] and focus groups call for better/easier and faster access to care for patients with unipolar depression during crises, e.g. via low-threshold services and contact options (also see central question 1).

Although some changes to access conditions are already being made [51,86] as a result of the 2017 structural reform of psychotherapy – including initial psychotherapeutic consultation as

an obligatory service (establishment of appointment service offices) and acute treatment – there are calls for improved access.

With regard to central question 3, there is some overlap with ethical and social aspects (see Section 6.1.4).

Central question 4: Alternative technologies for the same research question

Alternative technologies are the comparator interventions defined in the report: drug therapy, inpatient stay, and other non-drug interventions.

Central question 5: Utilization of health services / resources

With regard to the utilization of CBT or psychotherapy in general, the literature discusses a low demand for treatment (particularly after a suicide attempt) [18]. Brief CBT might additionally reduce the cost of inpatient care [45].

This area has similar overlaps with ethical and social aspects (e.g. stigma of depression and/or psychotherapy, see Section 6.1.4) as well as with intervention costs (see Section 5.1).

Central question 6: Forms of communication and cooperation

With regard to the form of communication and cooperation, there is a call for multidisciplinary cooperation between general practitioners and specialists [62,84]. To facilitate the transition from inpatient to outpatient care, (ultra-)brief therapies might be used as a good transitional intervention [18]. Improved interactions between experts and self-reflected patients have also been called for [18].

There is some overlap with central question 1 and the call for shared and participatory decision making.

Central question 7: Interest groups

Interest groups related to the research question are from the outpatient sector and particularly include psychotherapists, but also general practitioners and the sociopsychiatric service. Conflicts of interest exist particularly between the outpatient and inpatient sectors.

Central question 8: Acceptance

With regard to the acceptance of CBT or psychotherapy in general, the literature points out a low demand for treatment (particularly after a suicide attempt). Among the reasons listed in this regard are attitudinal barriers, such as worries about stigmatization or fear of (in-voluntary) hospitalization [18,74].

In this area, there is some overlap with ethical aspects (e.g. stigma of psychotherapy).

Central question 9: Planning of capacities, investments

The use of the manuals from the studies included in the benefit assessment does not incur any additional costs. To improve utilization behaviour and treatment compliance, however, the use of low-threshold, ultra-brief psychotherapy interventions is recommended. According to Teismann [18], the "option of acute care, which was created by the new Guidelines for Psychotherapy [...], represents a good (billing) framework for such interventions".

In this area, there is some overlap with central questions 1, 3, and 5.

6.3.3 Validation by stakeholders

As described in Section 6.1.5, 1 stakeholder (clinical expert) and 2 stakeholders (clinical and regulatory experts) commented on the final results table on organizational aspects. Comments on the presentation, such as terminology or consolidation of aspects, were entered in Table 51 of the full report; further comments related to the subsequent aspects (for a complete list of the comments of each stakeholder, see Table 51 in Section A5.4.2 of the full report).

Overall, the presentation was deemed plausible. Specific comments were made on the central questions. Regarding the first question, the no-suicide contract was reiterated as one of the most important measures in the therapeutic context. With regard to the calls for continued education on the topic of suicidality (question 2), it was noted that in practice, this is not yet specifically being pursued. With regard to question 3, it was pointed out that changes have been made to the system, with the initial psychotherapeutic consultation playing a guiding role, and noted that little awareness had been raised and little information provided on this topic. Central question 4, in contrast, was deemed to be adequately presented. With regard to central question 5, it was noted that a new technology could cause shifts in the service structure with effects on resource use and might be associated with conflicts between affected service providers. Regarding the topic of the HTA report, the stakeholders called for a discussion of the question whether increased utilization of brief psychotherapy might lead to psychotherapists no longer being available for other, longer-duration interventions, which are also needed. Therefore, the question of access to services should be considered as well (reference to central question 9). Additional references were made to 2 publications [87,88]. A comment on the call for professionals' improved handling of self-reflected patients in response to question 6 demanded more transparency regarding applied methods as well as psychoeducation.

The results of the analysis of ethical, social, legal, and organizational aspects and their mutual interactions as well as the aspects of the benefit assessment and costs are synthesized with regard to the research question using a model in Section 7 and discussed in Section 8.

7 Synthesis of results

In this section, the domain-specific individual results regarding the initially formulated research questions are synthesized to produce an overall result. For this purpose, the individual results of the domains are presented first, followed by their interactions to answer the questions of the HTA report in an all-encompassing manner.

With regard to the initially broadly worded definition of crisis intervention programmes/ services or psychosocial interventions in the outpatient care of adult suicidal patients with unipolar depression, the benefit assessment revealed a total of 4 studies (6 articles) on CBT (differentiated by “waves”); all of their designs focused on suicidality. No conclusions can therefore be drawn regarding other non-drug interventions.

For several patient-relevant outcomes, the results suggest (added) benefit of second-wave CBT in comparison with TAU, but only at some survey time points (see bottom right box in Figure **1**). Indications were found both for a reduction in suicide attempts at the survey time point of ≥ 18 months and for an improvement in depressive symptoms at the survey time points of 3, 6, and 18 months. For the outcome of depressive symptoms at the survey time point of 1 month, no hint of (added) benefit was found for second-wave CBT in comparison with TAU. With regard to the outcome of hopelessness, indications of (added) benefit were found at the survey time points of 6 and 18 months, but not at the survey time points of 1 month and 3 months. For the outcomes of anxiety and posttraumatic stress, there was no hint of (added) benefit of second-wave CBT in comparison with TAU. For the outcome of suicidal ideation, an indication of (added) benefit was found at the survey time point of 6 months, but not at 1, 3, and 18 months. In the comparison of third-wave CBT with TAU regarding the outcome of depressive symptoms, there was a hint of (added) benefit at the survey time point of 1 month, but not at the survey time point of 3 months. For the outcome of suicidal ideation, no hint of (added) benefit was found either. For both second-wave and third-wave CBT, no data were reported on the outcomes of all-cause mortality / overall survival, suicide mortality, physical functioning including activities of daily living / everyday functioning, inpatient admission, SAEs, discontinuation due to AEs, health-related quality of life, and health-related social functioning including occupational and social participation. While data on social problem-solving ability had been reported for second-wave CBT, they were not used due to reporting bias.

In addition, no studies were found for assessing cost effectiveness. Therefore, conclusions can be drawn only on intervention cost, while a cost comparison is impossible due to treatment approaches being frequently and variably combined. The costs are presented as a range for patients with a mild or severe course of disease. They range from EUR188.67 per treatment case for purely drug-based treatment to EUR2684.14 for one-on-one short-term outpatient therapy and up to EUR15,314.23 for long-term outpatient therapy.

As far as the analysis of ethical and social aspects is concerned, disorder-related and population-related morally relevant aspects have emerged which particularly impact the utilization of and/or access to interventions. They include especially vulnerable populations, differences in the severity of depression, and the existing stigma of depression. Concerning the ethical, social, cultural, legal, and religious challenges related to the intervention, relevant areas were found to be autonomy (particularly the balancing act between autonomy and heteronomy), the right to illness, privacy (particularly the protection of patients as well as family members), equitable allocation, and religious support. Additional legal aspects which were highlighted included, in particular, patient consent with regard to coercive treatment and placement in a psychiatric establishment as ordered under criminal or guardianship law (mental health laws) (with some overlap with ethical aspects). The social environment, protection of family members, and social pressure were identified as factors relevant to the access to as well as effective implementation of interventions. With regard to moral challenges related to structural changes associated with the intervention, access barriers were mentioned for people with depression, particularly during times of crisis, and it was noted that a trusting relationship with experts is critically important but also associated with a risk of dependency. Further identified structural and organizational aspects (implementation factors) concerned the conditions required to improve the care of the target group in question, e.g. by expanding outpatient, community-based structures for the early detection, prevention, and treatment of mental disorders. In addition, qualification requirements were determined for service providers treating the target group in question (e.g. a need for professional, continuing, and advanced training/education on the diagnostics and treatment of depression and on the topic of suicidality, crises, and suicide prevention for general practitioners and specialists), and optimization potential was identified in terms of access conditions (e.g. easier and faster access to care for patients with unipolar depression during crises, including through low-threshold services). The fear of being stigmatized due to the utilization of psychotherapy was identified as a moral and structural (acceptance) issue related to the characteristics of the intervention.

The above individual results of the domains are synthesized below. In accordance with the INTEGRATE-HTA approach, this is done with the aid of the expanded logical model (step 4), which allows the structured integration of results into the initially established model (steps 1 and 2).

The structure of the initial model (see Figure **1**) consists of the contextual factors, the Patient Population Intervention Comparison Outcome (PICO) components of the research question as well as the implementation. The field of utilization/access was added, which the analysis revealed as a moderating variable, particularly in relation to the intervention. The icons illustrate the evidence base in terms of the benefit assessment, health economics, the scoping searches on ethical, social, legal, and organizational aspects, the focus groups, the patient

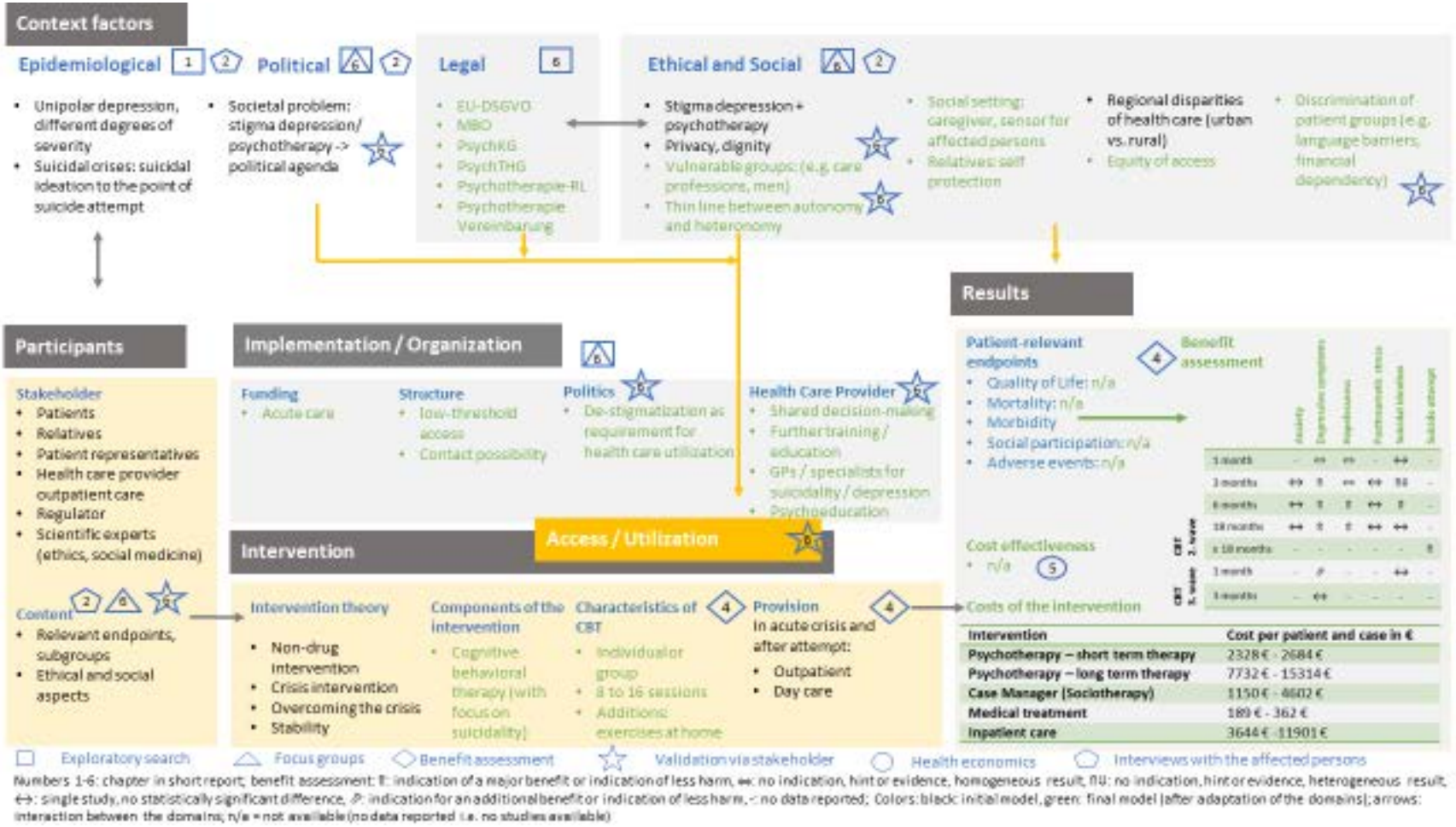
interviews, and/or validation by stakeholders. Numbers 1 through 6 represent the references to the sections in the HTA (HTA overview). The evidence map (Table 3 and Table 4) was used to present the results for the outcomes. Font colours illustrate the contents of the initial model (black) versus the final model (green). Interactions between the domains are shown by arrows. The benefit assessment and health economy domains are presented in the "Results" box on the right. Ethical, social, and legal aspects are found in the field above (under "Context"), while organizational aspects are shown in the "Implementation" field in the centre of the model. The contextual factors also include epidemiological and political aspects.

The research question of the HTA report, particularly with regard to patient-relevant outcomes and potential subgroups, was initially discussed with patients in the course of the generation of the report protocol (see box on the left in Figure **1**). The outcomes of survival, quality of life, suicidality, ability to work, body awareness, and activities of daily living were highlighted as important. Severity of depression as well as comorbidities were considered important with regard to the subgroups. In addition, stakeholders were identified (see left box in Figure **1**) and involved in the various phases of the report in accordance with the INTEGRATE-HTA approach. Family members, patients, and patient representatives were included in the focus groups (triangle icon). Service providers, regulators as well as scientific experts (star icon) were consulted to validate the ethical, social, legal, or organizational results. The contextual factors (top portion of the figure) were initially determined on the basis of patient conversations and the background research. This resulted in the initial identification of epidemiological, political, but also ethical aspects (e.g. regional differences in access, stigma of depression) related to the research question. The information obtained was entered into an initial model (black font), which was supplemented and finalized (green font) in the course of HTA processing using the results of the benefit assessment (prism icon) and health economy (oval icon) as well as the analysis of ethical, social, legal, and organizational aspects (triangle and/or rectangle icon).

Below, particularly interactions between the domains/aspects as well as moderating variables are discussed (also see arrows in Figure **1**). The analysis of ethical and social aspects associated with the listed intervention confirms the aspects of stigma of depression, which was initially identified in patient interviews, as well as differences in regional access to psychotherapy. Furthermore, certain vulnerable groups (e.g. high disease-related baseline risk: person with prior suicide attempt; non-utilization due to language barriers, low socioeconomic status) were identified, particularly with regard to access to the above-mentioned intervention. In this context, the social environment was deemed a relevant reference point and sensor for patients; it particularly impacts utilization behaviour and access. The aspects of patient autonomy and heteronomy were additionally noted as ethically relevant aspects, with different arguments applying. The legal framework conditions for conducting CBT were identified; in this area, overlap is particularly noted with the ethical aspect of heteronomy

(PsychKG). The analysis of organizational aspects predominantly resulted in suggestions for improving conditions in the outpatient sector with regard to structures and specific measures (e.g. expansion of low-threshold services, contact options), processes (e.g. multidisciplinary nature, inpatient-outpatient transition), and the qualification of service providers (e.g. continued education on suicidality in depression, participative decision-making), but also in terms of financing (e.g. billing of CBT in acute care). The stigma of depression has already been touched upon as a key aspect and was also identified in the form a political demand for destigmatization as a prerequisite for the utilization of the intervention (and psychotherapy in general).

The importance of the listed aspects and interactions is revisited in the discussion (Section 8).



Numbers 1-6: chapter in short report; benefit assessment: !!: indication of a major benefit or indication of less harm, ↔: no indication, hint or evidence, homogeneous result, ⇅: no indication, hint or evidence, heterogeneous result, ↔: single study, no statistically significant difference, ↗: indication for an additional benefit or indication of less harm, -: no data reported; Colors: black: initial model, green: final model (after adaptation of the domains); arrows: interaction between the domains; n/a = not available (no data reported i.e. no studies available)

Figure 1: Logical model, adapted using the INTEGRATE-HTA model [40]

8 Discussion

8.1 Cross-domain discussion on the basis of the INTEGRATE-HTA method

The logical model established in Section 7 is intended to serve as basis for discussion in this section.

Regarding the initial question of which non-drug interventions are effective in an acute crisis, this HTA found only CBT interventions. This is in line with current scientific knowledge, according to which CBT is also the most commonly investigated form of psychotherapy [89]. The different programme modules can be completed in as little as a few (8 to 16) sessions. Estimating actual costs (in comparison with other therapies, e.g. long-term therapy) is difficult since, in most cases, multiple interventions take place in parallel – as is also reflected by the included studies. In addition, further interventions are likely utilized after the acute crisis has subsided. On the other hand, the programmes' short duration touches upon the aspect of treatment being provided as quickly as possible, as mentioned in the literature and focus groups of therapy, in order to achieve rapid alleviation of the acute phase as well as patient stabilization in accordance with the NDMG. According to focus group participants, the high social pressure regarding rapid recovery should also be taken into account, however.

The 2017 structural reform of the Guidelines for Psychotherapy [51] introduced acute care, which allows for easy integration and billing of CBT. Any resulting increased utilization of acute care (which is comparable with short-term therapy) should be investigated to determine whether there are any shifts with regard to the time available for other procedures. In its report [68], the German Chamber of Psychotherapists already concluded that, since the introduction of initial psychotherapeutic consultation and acute care, less treatment has been provided (33.5% of psychotherapists: on average 2.6 hours less per week), but, on the other hand, more treatment sessions have been offered (12.6% of psychotherapists: about 2.6 additional treatment sessions). Long-term evaluations must be awaited to enable a better assessment of resource use.

Although the interventions included in the benefit assessment fulfil the demand for rapid assistance in acute crisis and therefore achieve (added) benefit in comparison with TAU for some patient-relevant outcomes, no hints of benefit were found with regard to second-wave CBT at the survey time point of 1 month. An indication of added benefit was present only starting at 3 months. For third-wave CBT, there was a hint of (added) benefit at the survey time point of 1 month, but unlike in other studies, where the outcome was surveyed during treatment, here it was done as late as 1 month after treatment. According to the literature [30,31,33] and our clinical expert, however, the first 3 to 6 months after a suicide attempt are the most vulnerable period with the highest risk of follow-up suicide attempts the first few weeks being associated with a particularly high risk of (follow-up) suicide attempts [32,33].

According to the identified aspects in the conducted focus groups, any add-on low-threshold and potentially layperson-supported services, particularly in an acute suicidal crisis, might contribute to supporting favourable treatment results with regard to patient-relevant outcomes. The optimization potential for outpatient care structures, which was mentioned initially and in the NDMG, was confirmed by the focus groups. In this context, it was mentioned that interventions during the crisis situation need not necessarily be expert-based. Rather, the importance of services which consider patients as experts on their disorder was highlighted. This perspective can reportedly promote autonomy and counteract heteronomy. With regard to the balancing act between autonomy and heteronomy, the focus group participants pointed out, however, that this is perceived differently by every patient and increased heteronomy may have a stabilizing effect on some people while being perceived as violating their autonomy by others. They continue that therefore, the assistance provided in suicidal crises must be tailored to the individual patient.

Specific options for addressing the above aspects have been mentioned in the literature and focus groups. This includes safe retreats and the involvement of the social network or volunteers. Safe retreats or so-called crisis hostels are currently not regularly available to people in crisis and offer support and a retreat outside of inpatient treatment options or psychiatric day hospitals [90]. Currently, this is most commonly implemented in the form of integrated care (IC) contracts, e.g. in “IC safe retreats” (GABSY project in Bremen) [91] and “IC VERSA Rhein Main” (elements of crisis intervention and safe retreat) [92]. However, the involvement of laypersons is not necessarily easy and must take into account the emerging strains and large responsibilities, which might be addressed by offering relevant training for volunteers and/or family members. As an exemplary service, our focus groups mentioned the concept of volunteer hospice aid workers, which have been established in palliative care and receive appropriate training [93]. When integrating and activating the social network, it is generally important to take into account the extent to which the network itself is affected, which can take the form of co-dependencies, for instance. Consequently, services which may contribute to the relief and protection of family members were identified as important as well. In this context, a current review [94] on suicide prevention notes that more research is needed on the effectiveness of such low-threshold interventions (also see Section 8.2).

Improvements regarding the starting conditions in terms of more rapid establishment of contact to service providers and equitable access to interventions have already been set in motion by the legislature. For instance, the establishment of appointment service offices and initial psychotherapeutic consultations in 2017 was intended to schedule appointments more rapidly.

The latter aspects were identified as also being ethically relevant in the HTA and listed, in particular, as access barriers: Restrictions in the freedom of choice or differences therein were

identified in the focus groups as well, e.g. in view of differences between SHI and PHI as well as regional differences in provider density. Destigmatization of both depression and psychotherapy is a prerequisite for the utilization of care in acute crises. However, as in the above-mentioned draft legislation, this represents a balancing act between improving the starting conditions and taking into account the particular vulnerability resulting from the disease. In this context, therefore, further information and public awareness of the disorder and the interventions are necessary to ensure that existing prejudice is reduced and access to help improved. This includes, for instance, various initiatives of the German Depression Foundation (*Deutsche Depressionshilfe*), which has increased awareness of depression via a TV spot and a poster advertising campaign [95].

8.2 HTA report compared with other publications

In their meta-analysis on cognitive therapy for suicide prevention, Tarrier et al. 2008 [96] already suggested that specific effective suicide prevention elements within CBT should be identified for high-risk groups, but also pointed out that *"whether suicide prevention methods can be incorporated into already-existing CBT protocols – for example, the treatment of depression or psychosis – or whether they need to be delivered in parallel or sequentially is currently unknown."* Ten years after this publication, various suicide prevention elements have been incorporated into CBTs originally developed for depression, and these CBTs were identified in the benefit assessment for this HTA report. Below, the results are discussed together with other reviews on the topic, particularly with regard to any discrepancies and contradictions. It must be noted that comparisons are difficult to make at this point because little to no cross-domain discussion can be found in HTA reports. In addition, neither HTA reports nor systematic reviews which fully match our initially defined population were found. The reports discussed below differ greatly in terms of their definition of suicide. For instance, the U.S. Agency for Healthcare Research and Quality (AHRQ) [97] and Cochrane [98] also include self-harm (without intention to die), which was excluded in this HTA. Moreover, the literature below, unlike this HTA, included any form of CBT.

In 2017, a meta-analysis by Goetzsche & Goetzsche [99] investigated whether CBT can reduce suicide attempts in people with prior suicide attempts. The different forms of BT were not distinguished. Ten studies were included, of which 2 are also in our study pool (Brown 2005 and Rudd 2015). Their analyses revealed that CBT reduces the number of follow-up suicide attempts by half when compared with TAU. This result is reflected by our HTA report as well. However, it should be mentioned that the authors did not define depression as an inclusion criterion but suspected its presence: *"However, it is likely that most patients attempting*

suicide will fulfil the criteria for a depression diagnosis, which the trial with the most events confirmed: the Beck depression inventory showed that most patients were depressed." [6]

In a Cochrane Review by Hawton (2016) [98], 29 RCTs comparing psychosocial treatment (including CBT) with (expanded) TAU or other forms of psychotherapy were identified across various psychiatric diagnoses in patients with a prior episode (within the past 6 months) of (fatal or non-fatal) self-harm behaviour. Brown 2005 / Ghahramanlou-Holloway 2012 were identified here as well. CBT and problem-solving therapy were considered jointly (18 RCTs, including Brown 2005) and associated with less self-harm behaviour of participants over a period of 18 months, an aspect also reflected in this HTA. In addition, significant improvements in the outcomes of depression, hopelessness, suicidal ideation, and problem-solving ability were reported. The results are consistent with those of the present HTA report, including in terms of significant effects being found only at later survey time points (6 months and later).

In an article published in Lancet in 2016, Zalsman [94] systematically analysed the evidence regarding the effectiveness of suicide-preventive interventions over a period of 10 years (update of Mann 2005) [100]. In total, 23 systematic reviews (including 67 cohort studies, 12 meta-analyses, 40 RCTs, and 22 ecological or population studies) were included. Due to heterogeneous study methods and populations, no meta-analysis was conducted. A total of 55 interventions were identified, showing that suicide can be prevented particularly by restricted access to lethal weapons as well as by school-based awareness programmes, effective pharmacological and psychological treatment of depression, and continued medical education for physicians with regard to the diagnosis and the treatment of depression. The latter is another organizational aspect which was previously mentioned in both the focus groups and the literature. With regard to the identified studies on psychotherapy, CBT was investigated for schizophrenia (1 RCT) and suicidal behaviour (1 MA), while cognitive psychotherapy was used in borderline disorder (2 RCTs) and schizophrenia (1 SR). Psychosocial interventions in clinical settings (1 SR) were conducted in adolescents only. Due to the differences in inclusion and exclusion criteria defined by Zalsman and the present HTA report, the inclusion of similar studies was impossible. With regard to the interventions defined by us a priori, the authors conclude that the benefit of interventions, e.g. internet-based interventions and emergency hotlines, must be demonstrated using, in particular, high-quality RCTs since these interventions clearly have potential.

In 2013, O'Connor and her colleagues at the AHRQ [97] investigated not only suicide risk screening, but also the associated treatment. They found no effects on the outcome of suicide

[6] Original quotation: *"However, it is likely that most patients attempting suicide will fulfil the criteria for a depression diagnosis, which the trial with the most events confirmed: the Beck depression inventory showed that most patients were depressed."*

mortality, noting, however, that little evidence was available. Our report found no results on this topic either. Psychotherapy (including CBT without differentiation of its forms) reduced the risk of suicide attempts in comparison with TAU by 32%. Moreover, improvements were found with regard to depressive symptoms, as also found in our HTA. However, it should be noted that unipolar depression was not defined as an inclusion criterion in this HTA either.

In a 2013 Cochrane Review, Churchill 2013 [101] found (little) evidence for third-wave BT being more effective in the treatment of acute depression than TAU. However, the review failed to specifically include suicidal patients.

8.3 HTA report compared with guidelines

Any consistencies and contradictions with national and international guidelines are highlighted and discussed below.

The S3 Guideline and National Disease Management Guideline for the treatment of unipolar depression recommend initially suicidality-focused psychotherapy for persons at risk of suicide (recommendation grade B). These specific psychotherapies for suicide prevention comprise problem-solving and insight-oriented strategies focused on suicidality. The recommendation is based on the meta-analyses by Mann 2005 (predecessor of Zalsman 2016), Hawton 2000 (predecessor of Hawton 2016) and O'Connor 2013 [94,97,98,100,102] (see Section 8.2). It is justified in part by indications of psychotherapeutic interventions leading to a significant reduction in suicide attempts when compared to TAU. As already discussed in the previous section, the studies included in the respective reviews and meta-analyses differed greatly with regard to the population (psychiatric diagnosis of unipolar depression), and except for Brown 2005, none of them would have been included in our study pool. Therefore, it is not possible to draw any conclusions regarding unipolar depression on the basis of these 3 publications. The NDMG (2015) additionally concludes that few available studies have explicitly evaluated the suicide-preventive effectiveness of specific psychotherapeutic approaches. This lack of evidence has also been confirmed by our HTA report [7]. Moreover, according to the NDMG [7], a follow-up examination of patients who were hospitalized for suicidality should be scheduled soon (no later than one week after discharge) since the risk of further suicidal actions is greatest during this time (recommendation grade A) [7]. This is an aspect also identified as relevant in the analysis of ethical aspects. Patients who do not keep a follow-up appointment are to be contacted directly to evaluate the risk of suicide or self-harm (recommendation grade A) [7]. The search performed for the benefit assessment did not find any contact interventions, but the short questionnaire administered prior to the focus groups showed that the action most commonly taken in emergencies was to contact the specialist by email or telephone.

In terms of international guidelines, 8 guidelines for depression were identified for the period of 2013 to 2018 through the Guidelines International Network [7,103-109], with 3 of them focusing on unipolar depression [7,103,108]. Three guidelines refer to suicidality or crises and emergencies [7,104,105]. For language reasons, the Ukrainian guidelines [106,107] were disregarded; the NDMG [7] has already been mentioned above and is only used for comparative purposes here.

In the guideline for the treatment of depression in adults (last update 2018), [105], NICE states that for patients with severe or complex depression who are at substantial risk of suicide or self-harm, an inpatient stay should be considered. This concurs with the NDMG recommendations [7]. For patients with depression who would benefit from early discharge from inpatient care, crisis management and home treatment teams should be considered. It was not possible to identify the latter as an intervention in the benefit assessment; therefore, no comparison is possible here.

The Danish guideline [108] for non-drug treatment of unipolar depression issued in 2016 by the Danish health authority does not provide any information on suicidality or times of crisis. Instead, it refers to mindfulness training being offered for "follow-up prevention" in patients whose depression has become more severe. Mindfulness is also an element of the included Barnhofer 2009/Hargus 2010 study.

The 2014 Belgian guideline [104] on the treatment of elderly people with major depression states that patients who are at acute risk of suicide should not start new psychotherapy, and it recommends hospitalization until the acute phase subsides. This contradicts the approach of the studies identified in our pool, which are specifically intended for acute phases.

The 2014 first Korean guideline [103] on the treatment of mild to moderate depression with non-drug interventions as well as the 2012 version of the Dutch guideline on the treatment of depression [109] (currently being revised) do not refer to suicidality or crisis but mention suicidality as a risk factor.

8.4 Critical reflection on the approach used

8.4.1 Benefit assessment

Although all studies included in the study pool cover CBT interventions, the benefit assessment distinguished between different waves of BT. This conflicts with the approach taken in other studies (e.g. Goetzsche & Goetzsche 2017; Hawton 2016 [98,99]), whose benefit assessment did not differentiate between them. Since the interventions of the various waves differ fundamentally, e.g. in terms of the basic attitude or patient-therapist relationship [100], and the literature contains multiple references to analysing homogeneous treatment concepts (or individual components) being preferable (Zalsman et al. 2016, Mann et al. 2005

[94,100]), the methodology of a differentiated assessment was selected for this HTA report. A synthesized analysis of the effects of all CBT interventions might have led to different results.

Concerns regarding the transferability of results were rated as low for all 4 studies since the intervention (CBT), in particular, as well as the comparator intervention reflect the healthcare situation in Germany. For suicidal crises, the German S3 guideline (NDMG) for the treatment of unipolar depression identifies multiple options, which can be used individually or in combination (see Section 1) [7]. The TAUs in the studies reflect all of these options. Despite slight differences in the manuals on conducting suicide-focused CBT, as used in the studies, the manuals do include elements of CBT which are applied in Germany as well. With regard to the population of the Rudd 2015 study [45], it must be noted that the effects of the intervention in active soldiers might be biased due to traumatization, on which no information was recorded. No data were available on corresponding subgroup analyses. Concerning the Sinniah 2017 study [47], whose population consisted of Asian patients, the discussion with the clinical expert did not reveal any concerns regarding the transferability of results since there are no differences in the clinical picture of unipolar depression.

8.4.2 Health economics

Depending on the severity of disease, the interventions available to manage a suicidal crisis differ greatly in terms of their form, duration, and potential combination with other measures. This makes it difficult to determine the costs of TAU and comparator interventions. In an effort to provide a best possible estimate of intervention costs nonetheless, they were presented in the form of a range based on the typical care routes used by patients with mild to severe disease courses. This was done in collaboration with the consulting clinical expert and on the basis of publicly accessible data, e.g. from the German Federal Statistical Office. Given that no hospital-specific base rates are available, the value of EUR280 was gleaned from an agreement between GKV, PKV, and the German Hospital Federation [55]; this value is to be used by hospitals when no hospital-specific base rate is available. The cost of drug treatment was calculated using the example of a commonly used drug for a treatment duration recommended by guidelines and used in studies. The comparatively presented costs per patient or per patient and treatment case for intervention and comparator treatment do not necessarily reflect the realities of care because, in many cases, multiple interventions are combined. A case manager is often involved as an add-on to psychotherapeutic care, and the same applies to drug treatment. Moreover, treatment duration differs widely between the various interventions. Comparing the costs of long-term therapy versus hospitalization, a stay of a maximum of 39 days is tantamount to 164 sessions of long-term therapy. All in all, the chosen approach might have resulted in costs being overestimated or underestimated.

8.4.3 INTEGRATE-HTA methods

The INTEGRATE-HTA framework provides comprehensive and helpful instructions for taking into account essential aspects of the assessment of a complex intervention or research question as found in this HTA report. It allows integrating a broad perspective on the topic in the various phases of report generation. It was not possible to fully complete all steps, particularly due to time constraints and the complexity of the framework. However, the option of using individual elements was in itself very helpful for compiling the HTA report. The items for gauging the complexity were found to be particularly useful (a point also highlighted by the Canadian Agency for Drugs and Technologies in Health, CADTH) [111]. These items provided a first clue of the degree of complexity as well as initial interacting components. Providing notes and comments as well as specific suggestions of grid templates and questionnaires, the methodological instructions for the ethical, social, and legal domains supported the analysis of the respective aspects, particularly with regard to the individual steps suggested therein. Furthermore, the logical model was a good way to graphically illustrate the most important aspects (PICO, contextual factors, and implementation) and the identified evidence as well as the interactions between aspects. It thereby facilitates a synthesis across domains and discussion of the results and hence answering the research questions across domains. But above all, it fed the narrative that certain moderating factors affect both the access to an intervention and the underlying process to different degrees.

Stakeholder involvement in the HTA report compilation is a central component both of the INTEGRATE-HTA framework as well as in this report, and it further highlights the relevance of the HTA. Simultaneously, however, this is very resource-intensive in terms of time, as was already reported by the Canadian agency after applying the INTEGRATE framework [111]; the required time resources must be weighed against the obtained benefit [112]. Since the topics for the HTA reports are suggested by patients within ThemenCheck Medizin, patients should be involved once again at the end of the process (step 5 of the INTEGRATE method). In step 5, a recommendation or decision is to be taken in collaboration with stakeholders/decision makers on the basis of the evidence summarized in the model. While the commenting procedure devised for the HTA report within ThemenCheck Medizin does give both the self-governing stakeholders and the patients the opportunity to comment, a more in-depth exchange could be offered, e.g., through patient dialogue.

The framework also aims to uncover shared goals of the domains and hence overlap. As already pointed out by Bond and Weeks from the CADTH [111], no recommendations are available regarding the handling of redundancies. In this HTA report, this was pointed out in the appropriate places, and social aspects, for instance, were processed and presented together with ethical aspects in the same table.

8.4.4 Selection of the ethical approach

After being selected with the aid of the INTEGRATE-HTA framework, the ethical aspects were analysed based on the Socratic approach. According to Hofmann [58], this approach permits a descriptive summary of the results without taking a position on the determined values or making recommendations. Using this approach is also sufficient as an integrative component of an HTA report. The use of Hofmann's questionnaire therefore led to an exploratory approach and deliberately avoided a normative model. Concrete decision-making help in the form of a recommendation would, in this case, also require a model-based discussion [133] with an ethics expert or, as suggested as the last step in the INTEGRATE-HTA framework, with the relevant decision makers. The logical model could be used as the basis in the latter case as well.

The decision to specifically implement the Socratic approach by using Hofmann's questionnaire was taken due to its easy integration into HTA report compilation. However, minor deviations in the approach occurred, which may have brought different or additional aspects to light. Hofmann recommends specific, separate searches for ethical aspects. This recommendation was not implemented. Instead, a more sensitive search was conducted since the searches had been carried out before the focus groups were held when no aspects were known yet.

On the other hand, it was found that using the selection of questions from Hofmann's questionnaire in the focus groups, particularly in their original wording, was neither perfectly suitable nor expedient. To remain close to the original wording, the questions were reworded only slightly. Nevertheless, feedback from 2 out of the 3 focus groups described the questions as very difficult to understand. For the application of the questionnaire, so-called suggestions were therefore developed, representing a rewording of the questions to simplify their content. However, these suggestions were used only if there was a delayed or no response to the question. In general, making reference to a specific technology would have made the questions easier to understand as well. The fact that the interventions considered here were based on a broad definition likely led to delayed answers as well. However, this problem had been anticipated and was to be alleviated by discussing the interventions in the beginning. Moreover, during the identification of ethical aspects in the focus groups, the terms "autonomy" and "privacy" were often mentioned together, which sometimes made it more difficult to document them separately. The focus group participants did not use the terms "autonomy" and "integrity". For future HTA reports, we therefore suggest developing an easily understandable questionnaire, e.g. for use in focus groups.

Some identified ethical aspects were brought up only in the focus groups, without any pertinent references being found in the scoping search; the reverse case was less common. It must be noted, however, that aspects detected solely by the focus groups were not followed

up by additional searches. The scoping nature of the search therefore may have led to some sources being missed. It would therefore be prudent to combine the scoping searches with focus groups or patient involvement. Despite this approach being more resource-intensive in terms of preparation, execution, and analysis, it is recommended for subsequent HTA reports. Moreover, focus groups should discuss not only ethical and social aspects, but also legal and organizational aspects. After all, if the organizational aspects had been captured solely by way of literature searches, it would have hardly yielded any results in this HTA. Hence, it would be helpful in this regard to integrate central questions from the grid template for surveying legal and organizational aspects [38,39] in the focus groups.

9 Conclusion

To answer the question submitted to ThemenCheck, “Suicidal crises in unipolar depression: How do non-drug measures impact their management?”, the following interventions were investigated: (1) crisis intervention programmes/services in outpatient care and (2) psychosocial interventions in outpatient care, namely (i) psychotherapeutic strategies for preventing suicide and (ii) suicide preventive follow-up services and contact offers.

Despite this initially broad definition of interventions to be investigated in the outpatient care of adult suicidal patients with unipolar depression, only studies on CBT were found, all of which focused on suicidality. These studies examined CBTs from the second and third “waves” of BT. The second wave of BT originated in the developments of the 1960s and 1970s, where classic BT was for the first time expanded to include cognitive aspects such as thoughts and convictions. In the 1980s, these considerations led to the approach of CBT. In the third wave of BT, the classic cognitive-behavioural concept, which largely focuses on restructuring processes, is expanded by the additional aspects of mindfulness and acceptance of difficult-to-control internal experiences. Additional conceptual differences concern the fundamental attitude and the patient-therapist relationship. CBT is a service already covered by the SHI.

Four RCTs of moderate qualitative certainty of results were included. They primarily investigated the patient-relevant outcomes of anxiety, depressive symptoms, hopelessness, posttraumatic stress, suicidal ideation, and (follow-up) suicide attempts, each at the survey time points of 1, 3, 6, 18, and ≥ 18 months.

With regard to the patient-relevant outcomes of suicidal ideation (6 months), suicide attempts (≥ 18 months), depressive symptoms (3, 6, and 18 months), and hopelessness (6 and 18 months), the results revealed an indication of (added) benefit of second-wave CBT in comparison with TAU.

With regard to the patient-relevant outcome of depressive symptoms, the results revealed a hint of (added) benefit at the survey time point of 1 month for third-wave CBT in comparison with TAU. These results are based on the data from one study. The currently still outstanding results from another study might supplement the results of this HTA.

For the outcomes of anxiety and posttraumatic stress (each at 3, 6, and 18 months), suicidal ideation (1, 3, and 18 months), depressive symptoms (1 month), and hopelessness (1 month and 3 months), no hint of (added) benefit of second-wave CBT versus TAU was found.

With regard to third-wave CBT, for the outcome of depressive symptoms at the survey time point of 3 months, no hint of (added) benefit of third-wave CBT versus TAU was found. For the outcome of suicidal ideation at the time point of 1 month, no hint of (added) benefit of third-wave CBT versus TAU was found.

For the following outcomes, data on second or third-wave CBT were either unavailable or unusable: all-cause mortality / overall survival, suicide mortality, physical functioning including activities of daily living / everyday functioning, inpatient admission, serious adverse events (SAEs), discontinuation due to AEs, health-related quality of life, and health-related social functioning, including occupational and social participation. Concerning second-wave CBT, data were also reported on social problem-solving ability, but they were disregarded due to reporting bias. However, patients in the initially conducted discussions highlighted the patient-relevant outcomes listed above as being particularly relevant. Therefore, there is clearly a need for further research, particularly high-quality RCTs, in this area.

No studies were found with regard to cost effectiveness, and no conclusion can be drawn on this topic. To generate more evidence in this area as well, future investigations might concurrently collect data on both effectiveness as well as resource use and the costs of the intervention and comparator treatment. The costs listed in the present report are stated as ranges for patients with mild and severe disease courses. They range from EUR188.67 per treatment case for solely drug-based treatment to EUR2684.14 for one-on-one short-term outpatient therapy, and up to EUR15,314.23 for long-term outpatient therapy. However, comparability between the costs of the individual interventions per patient or per patient and treatment case is limited since their separate analyses do not fully reflect the realities of care. Depressive disorders differ widely between individuals in terms of their severity and course; therefore, actual costs might be lower or higher than those presented herein.

Interventions other than CBT, including some low-threshold interventions such as telephone counselling or internet-based services, were also mentioned both in the focus groups and in the literature. Due to a lack of studies, however, it was not possible to compare these interventions to TAU. As already concluded by authors of other reviews, future studies should include such interventions as well and determine their effectiveness at early survey time points in order to ensure rapid treatment in crisis situations.

The analysis of the ethical, social, legal, and organizational aspects has shown that they are highly relevant to the topic and, in particular, have a major impact on access to measures. Due to the complexity and multidimensional nature of the topic, the individual domains cannot and should not be analysed in isolation. Rather, their mutual interactions should be contemplated and discussed, as illustrated in the logical model.

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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.themencheck-medizin.iqwig.de/de/hta-berichte/08-ht17-03-suizidale-krisen-bei-unipolarer-depression-welchen-einfluss-haben-nicht-medikamentoese-massnahmen-auf-deren-bewaeltigung.124.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 [114] 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
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.2, Chapter 5
Ethical analysis (ETH)	**Ethical aspects** Section 3.3, Section 6.1
Patients and social aspects (SOC)	**Social aspects** Section 3.4, Section 6.1
Legal aspects (LEG)	**Legal aspects** Section 3.4, Section 6.2
Organizational aspects (ORG)	**Organizational aspects** Section 3.4, Section 6.3

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1– Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to April Week 1 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 12, 2018
- Ovid MEDLINE(R) Daily Update April 12, 2018
- Ovid MEDLINE(R) Epub Ahead of Print April 12, 2018

The following filters were adopted:

- Systematic review: Wong [115] – High specificity strategy
- RCT: Lefebvre [116] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	*Self-Injurious Behavior/pc
2	exp *Suicide/pc
3	or/1-2
4	Suicide, Attempted/
5	Suicidal Ideation/
6	((attempt* or ideation* or thought* or intention*) adj1 suicid*).ti,ab.
7	or/4-6
8	exp *Psychotherapy/
9	((brief* or postcard*) adj intervention*).ti,ab.
10	((group* or behavior* or behaviour* or cognitiv*) adj therapy*).ti,ab.
11	problem solving*.ti,ab.
12	telephone*.ti.
13	Suicide/pc
14	(prevent* adj4 suicid*).ti,ab.
15	(reduc* adj3 suicid*).ti,ab.
16	or/8-15
17	and/7,16
18	randomized controlled trial.pt.
19	controlled clinical trial.pt.
20	(randomized or placebo or randomly or trial or groups).ab.

#	Searches
21	drug therapy.fs.
22	or/18-21
23	exp animals/ not humans.sh.
24	22 not 23
25	cochrane database of systematic reviews.jn.
26	(search or MEDLINE or systematic review).tw.
27	meta analysis.pt.
28	or/25-27
29	or/24,28
30	(3 or 17) and 29
31	30 not (comment or editorial).pt.

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search (attempt* [TIAB] OR ideation* [TIAB] OR thought* [TIAB] OR intention* [TIAB]) AND suicid* [TIAB]
#2	Search (brief* [TIAB] OR postcard* [TIAB]) AND intervention* [TIAB]
#3	Search (group* [TIAB] OR behavior* [TIAB] OR behaviour* [TIAB] OR cognitiv* [TIAB]) AND therapy* [TIAB]
#4	Search problem solving*[TIAB]
#5	Search telephone*[TI]
#6	Search prevent* [TIAB] AND suicid* [TIAB]
#7	Search reduc* [TIAB] AND suicid* [TIAB]
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	Search #1 AND #8
#10	Search (clinical trial*[TIAB] OR random*[TIAB] OR placebo[TIAB] OR trial[TI])
#11	Search (search[TIAB] OR meta analysis[TIAB] OR MEDLINE[TIAB] OR systematic review[TIAB])
#12	Search #10 OR #11
#13	Search #9 AND #12
#14	Search #13 NOT Medline[SB]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 April 12

The following filters were adopted:

- Systematic review: Wong [115] – High specificity strategy
- RCT: Wong [115] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	*automutilation/pc, th
2	exp *suicidal behavior/pc, th
3	or/1-2
4	*suicide attempt/
5	*suicidal ideation/
6	((attempt* or ideation* or thought* or Intention*) adj1 suicid*).ti,ab.
7	or/4-6
8	exp psychotherapy/
9	problem solving/
10	psychosocial care/
11	crisis intervention/
12	social support/
13	((brief* or postcard*) adj Intervention*).ti,ab.
14	((group* or behavior* or behaviour* or cognitiv*) adj therapy*).ti,ab.
15	problem solving*.ti,ab.
16	telephone*.ti.
17	exp suicidal behavior/pc, th
18	(prevent* adj4 suicid*).ti,ab.
19	(reduc* adj3 suicid*).ti,ab.
20	or/8-19
21	and/7,20
22	or/3,21
23	(random* or double-blind*).tw.
24	placebo*.mp.
25	or/23-24
26	(meta analysis or systematic review or MEDLINE).tw.
27	or/25-26
28	and/22,27
29	28 not medline.cr.
30	29 not (exp animal/ not exp humans/)

#	Searches
31	30 not (Conference Abstract or Conference Review or Editorial).pt.

4. PsycINFO

Search interface: Ovid

- PsycINFO 1806 to April Week 2 2018

The following filters were adopted:

- Systematic review: Eady [117] – Best Specificity
- RCT: Eady [117] – Best Optimization of Sensitivity and Specificity

#	Searches
1	*Suicide Prevention/
2	Attempted Suicide/
3	*Suicidal Ideation/
4	((attempt* or ideation* or thought* or intention*) adj1 suicid*).ti,ab.
5	or/2-4
6	exp Intervention/
7	exp Psychotherapy/
8	Cognitive Therapy/
9	((brief* or postcard*) adj intervention*).ti,ab.
10	((group* or behavior* or behaviour* or cognitiv*) adj therapy*).ti,ab.
11	telephone*.ti.
12	problem solving*.ti,ab.
13	(prevent* adj4 suicid*).ti,ab.
14	(reduc* adj3 suicid*).ti,ab.
15	or/6-14
16	and/5,15
17	(double-blind or random* assigned or control).tw.
18	(meta-analysis or search*).tw.
19	or/17-18
20	(1 or 16) and 19

5. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews : Issue 4 of 12, April 2018
- Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2018

ID	Search
#1	MeSH descriptor: [Self-Injurious Behavior] this term only and with qualifier(s): [Prevention & control - PC]
#2	MeSH descriptor: [Suicide] explode all trees and with qualifier(s): [Prevention & control - PC]
#3	#1 or #2
#4	MeSH descriptor: [Suicide, Attempted] this term only
#5	MeSH descriptor: [Suicidal Ideation] this term only
#6	((attempt* or ideation* or thought* or intention*) near/1 suicid*):ti,ab
#7	#4 or #5 or #6
#8	MeSH descriptor: [Psychotherapy] explode all trees
#9	((brief* or postcard*) adj intervention*):ti,ab
#10	((group* or behavior* or behaviour* or cognitiv*) adj therapy*):ti,ab
#11	problem solving*:ti,ab
#12	telephone*:ti
#13	MeSH descriptor: [Suicide] this term only and with qualifier(s): [Prevention & control - PC]
#14	(prevent* near/4 suicid*):ti,ab
#15	(reduc* near/3 suicid*):ti,ab
#16	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17	(#7 and #16) or #3 in Cochrane Reviews (Reviews and Protocols) and Trials

6. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Self-Injurious Behavior WITH QUALIFIER PC
2	MeSH DESCRIPTOR Suicide EXPLODE ALL TREES WITH QUALIFIER PC
3	#1 OR #2
4	MeSH DESCRIPTOR Suicide, Attempted
5	MeSH DESCRIPTOR Suicidal Ideation
6	((attempt* OR ideation* OR thought* OR intention*) AND suicid*)
7	#4 OR #5 OR #6
8	MeSH DESCRIPTOR Psychotherapy EXPLODE ALL TREES
9	MeSH DESCRIPTOR Suicide WITH QUALIFIER PC
10	((brief* or postcard*) and Intervention*)

Line	Search
11	(((group* or behavior* or behaviour* or cognitiv*) and therapy*))
12	(problem solving*)
13	(telephone*):TI
14	(prevent* and suicid*)
15	(reduc* and suicid*)
16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	#7 AND #16
18	#3 OR #17
19	(#18) IN HTA

B.1.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategies
(suicide OR suicidal OR self-harm) [Condition]
(suicide OR suicidal OR self-harm) [Other terms] AND depression [Condition] AND (cognitive OR behavior OR behaviour OR behavioral OR behavioural OR group therapy OR problem-solving OR telephone OR brief intervention* OR prevention OR preventive OR prevent* OR postcard* OR psychotherapy OR reduc*) [Intervention]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategies
suicid* OR self-harm
cognitive AND depression OR behavior AND depression OR behaviour AND depression OR behavioral AND depression OR behavioural AND depression OR group AND therapy AND depression OR problem-solving AND depression OR telephone AND depression OR brief intervention* AND depression OR prevention AND depression OR preventive AND depression OR prevent* AND depression OR postcard* AND depression OR psychotherapy AND depression OR reduc* AND depression [The result of this search was filtered in EndNote for registry entries with the terms "suicid" or "self harm" in the outcome fields. According to the inclusion criteria, only these entries were evaluated].

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to April Week 1 2018
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 12, 2018
- Ovid MEDLINE(R) Daily Update April 12, 2018
- Ovid MEDLINE(R) Epub Ahead of Print April 12, 2018

The following filter was adopted:

- Glanville [118] – Emory University (Grady)

#	Searches
1	*Self-Injurious Behavior/pc
2	exp *Suicide/pc
3	or/1-2
4	Suicide, Attempted/
5	Suicidal Ideation/
6	((attempt* or ideation* or thought* or intention*) adj1 suicid*).ti,ab.
7	or/4-6
8	exp *Psychotherapy/
9	((brief* or postcard*) adj intervention*).ti,ab.
10	((group* or behavior* or behaviour* or cognitiv*) adj therapy*).ti,ab.
11	problem solving*.ti,ab.
12	telephone*.ti.
13	Suicide/pc
14	(prevent* adj4 suicid*).ti,ab.
15	(reduc* adj3 suicid*).ti,ab.
16	or/8-15
17	(economic* or cost*).ti.
18	cost benefit analysis/
19	treatment outcome/ and ec.fs.
20	or/17-19
21	animals/ not humans/
22	letter.pt.
23	or/21-22
24	20 not 23
25	(3 or 7 or 14 or 15) and 24
26	25 not (comment or editorial).pt.

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search (attempt* [TIAB] OR ideation* [TIAB] OR thought* [TIAB] OR intention* [TIAB]) AND suicid* [TIAB]
#2	Search (brief* [TIAB] OR postcard* [TIAB]) AND intervention* [TIAB]
#3	Search (group* [TIAB] OR behavior* [TIAB] OR behaviour* [TIAB] OR cognitiv* [TIAB]) AND therapy* [TIAB]
#4	Search problem solving*[TIAB]
#5	Search telephone*[TI]
#6	Search prevent* [TIAB] AND suicid* [TIAB]
#7	Search reduc* [TIAB] AND suicid* [TIAB]
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	Search economic*[tiab] OR cost*[tiab]
#10	Search (#1 OR #6 OR #7) AND #9
#11	Search #11 NOT Medline[SB]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 April 12

The following filter was adopted:

- Glanville [118] – Embase G

#	Searches
1	*automutilation/pc, th
2	exp *suicidal behavior/pc, th
3	or/1-2
4	*suicide attempt/
5	*suicidal ideation/
6	((attempt* or ideation* or thought* or Intention*) adj1 suicid*).ti,ab.
7	or/4-6
8	exp psychotherapy/
9	problem solving/

#	Searches
10	psychosocial care/
11	crisis intervention/
12	social support/
13	((brief* or postcard*) adj Intervention*).ti,ab.
14	((group* or behavior* or behaviour* or cognitiv*) adj therapy*).ti,ab.
15	problem solving*.ti,ab.
16	telephone*.ti.
17	exp suicidal behavior/pc, th
18	(prevent* adj4 suicid*).ti,ab.
19	(reduc* adj3 suicid*).ti,ab.
20	or/8-19
21	(Cost adj effectiveness).ab.
22	(Cost adj effectiveness).ti.
23	(Life adj years).ab.
24	(Life adj year).ab.
25	Qaly.ab.
26	(Cost or costs).ab. and controlled study/
27	(Cost and costs).ab.
28	or/21-27
29	(3 or 7 or 18 or 19) and 28
30	29 not medline.cr.
31	30 not (exp animal/ not exp humans/)
32	31 not (Conference Abstract or Conference Review or Editorial).pt.

4. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR Self-Injurious Behavior WITH QUALIFIER PC
2	MeSH DESCRIPTOR Suicide EXPLODE ALL TREES WITH QUALIFIER PC
3	#1 OR #2
4	MeSH DESCRIPTOR Suicide, Attempted
5	MeSH DESCRIPTOR Suicidal Ideation
6	((attempt* OR ideation* OR thought* OR intention*) AND suicid*)
7	#4 OR #5 OR #6
8	MeSH DESCRIPTOR Psychotherapy EXPLODE ALL TREES
9	MeSH DESCRIPTOR Suicide WITH QUALIFIER PC
10	((brief* or postcard*) and Intervention*)
11	(((group* or behavior* or behaviour* or cognitiv*) and therapy*))

Line	Search
12	(problem solving*)
13	(telephone*):TI
14	(prevent* and suicid*)
15	(reduc* and suicid*)
16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	#3 OR #7 OR #14 OR #15
18	(#17) IN HTA