IQWiG

ThemenCheck Medizin

Generalized anxiety disorder[1]

Do apps help people affected cope with their condition?

Health technology assessment commissioned by IQWiG

EXTRACT OF HTA REPORT

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The Institute for Quality and Efficiency in Health Care (IQWiG) was responsible for coordinating the project, conducting information retrieval for the domains “Benefit assessment“ and “Health economic evaluation”, and preparing the easy-to-understand summary (HTA kompakt).

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 A13 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the HTA report?

Insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies through "ThemenCheck Medizin" (Topic Check Medicine) to the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). The assessment is done in the form of a comprehensive Health Technology Assessment (HTA) report. Comprehensive HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

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

In September 2022, IQWiG commissioned a team of scientists led by the Austrian National Public Health Institute to investigate the selected topic of "HT22-02: Generalized anxiety disorder: Do apps help those affected to cope with their condition?". The team consisted of methodologists experienced in generating HTA reports, experts with knowledge and experience in health economic, ethical, social, legal, and organizational topics as well as two psychologists, one of whom female and one male.

Why is the HTA report important?

Generalized anxiety disorder is a common anxiety condition. It is estimated that around 5% of all people receive this diagnosis at some point in their lives. Women are affected about twice as often as men. Typically, onset of anxiety disorders occurs in mid-adulthood, but sometimes as early as during childhood or as late as during old age [2,3].

Generalized anxiety disorders can manifest themselves both psychologically and physically. Psychological complaints include persistent, unrealistic and exaggerated fears. The anxiety affects different areas of life. It is not a reaction to a threat and is not limited to certain things or situations. Physical symptoms include prolonged palpitations, shortness of breath, nervousness, or dizziness. Concentration and sleep disorders, trembling, sweating, muscle tension, or stomach problems are also common. Generalized anxiety disorder is diagnosed if fears and symptoms occur on most days for at least a period of 6 months and are experienced as uncontrollable and impairing [2].

In order to get a better grip on an anxiety disorder over time, psychological and psychotherapeutic treatments, especially cognitive behavioural therapy, are usually recommended. Such therapy should help to recognise and change thought patterns that trigger anxiety. It also involves consciously facing anxiety in order to gradually reduce it and change behaviour. Relaxation methods such as autogenic training or progressive muscle relaxation, medication (antidepressants) or self-help groups are also said to help those affected [2].

A large number of apps or browser-based applications (referred to in the report as digital interventions) can be found on the internet and in various app stores that claim to support those affected in the treatment of generalized anxiety disorder. They convey various contents and techniques in the form of text, audio or video files. They are mostly based on the principles of cognitive behavioural therapy. They may, for example, provide help in dealing with negative thoughts, sleep disorders, or structuring the day. They may also include guidance and exercises on relaxation techniques. Some apps also have a diary feature or provide reminders when it is time to do exercises. Some also offer the option of contacting a therapist if needed. The apps can be used as a stand-alone intervention or in conjunction with therapy.

In Germany, statutory health insurance covers the costs of apps that meet certain requirements in terms of safety, functionality, data protection and security, and quality – subject to a physician's prescription or approval by the health insurance company. These are referred to as digital health applications (DiGA) and are listed in the DiGA directory. This also includes 2 applications – velibra and Selfapy – for the treatment of generalized anxiety disorder (as of March 2024) [2].

Concerns of those proposing the topic

Those proposing the topic point out that since January 2021, physicians have been able to prescribe DiGA for the treatment of anxiety disorders. Against this backdrop, those proposing the topic ask whether it has been reliably proven that those affected can actually benefit from using an app to treat anxiety disorders.

Objective of the HTA report

To answer the suggesting party's question, the commissioned team of scientists took the different perspectives of an HTA report to investigate whether adolescents (14 years and older) and adults with generalized anxiety disorder can expect to benefit from apps. This would be the case, for example, if it were shown that using apps results in those affected having fewer mental and physical complaints, being able to cope better with everyday life, and having a higher quality of life.

Which questions are answered – and which are not?

Benefit assessment

The authors of the report were able to identify a total of 20 suitable studies investigating the use of apps for generalized anxiety disorder. They came to the following conclusion: When apps whose content is based on cognitive behavioural therapy (CBT) are compared with no treatment, there are indications of a benefit from the apps in terms of

- disease-related symptoms (data from 14 studies),
- quality of life (data from 6 studies), and
- everyday functions (data from 5 studies).

For the outcome "remission", there was no relevant difference between the intervention group and the control group for apps whose content is based solely on CBT. No data were reported in the studies on other outcomes such as mortality, risk of relapse, and self-efficacy.

The report does not provide separate evaluations of the two applications listed in Germany's DiGA directory. However, the results of the apps based in content on CBT also include the results of the Rubel 2024 study, based on which the Selfapy DiGA for the therapeutic indication of generalized anxiety disorder was permanently included in the DiGA directory. Statistically significant differences were reported for the patient-relevant outcomes of disease-related symptoms and health-related quality of life when comparing the app based on CBT with a control group of patients on a waiting list.

The present report also includes a study – Berger 2017 [4] – that justifies the permanent inclusion of the velibra DiGA for the therapeutic indication of generalized anxiety disorder into the DiGA directory. That study compared the usage of a DiGA based in content on CBT in combination with a cognitive bias modification (CBM) approach with a control group of patients on a waiting list. Both groups also received the usual care from their general practitioners. The study included patients with generalized anxiety disorder, social phobia, or panic disorder. The subgroup analysis reported in the study for patients with generalized anxiety disorder shows no statistically significant difference between the intervention group and the control group for the outcome of excessive, unrealistic worries as a central cognitive symptom of generalized anxiety disorder. However, a significant difference is reported for the outcome of remission based on the diagnosis of generalized anxiety disorder. Several symptoms from a corresponding symptom catalogue must be present to make this diagnosis.

Overall, however, the reported results must be interpreted with caution. The team of scientists points out that methodological standards were not always fully adhered to when conducting the studies. In addition, the authors of the report have found indications of a risk of bias due to unpublished study results. An author query by the team of scientists revealed,

for example, that the results of a study completed in 2019 according to the trial registry had not been published and that no significant effects had been found. In addition, they report that in 6 studies, the study authors had financial ties to the app manufacturing companies or that the studies were directly funded by said companies.

The studies fail to provide answers to other important questions: For example, similar to studies on face-to-face psychological interventions [5], adverse events are often not recorded or not recorded systematically. It therefore remains unclear what potential harm is associated with the use of apps for generalized anxiety disorder. Also, the duration of the studies was usually only 2 or 3 months. It is therefore not possible to say whether those affected will benefit from the use of apps beyond the intervention period. Furthermore, there were no studies investigating the use of apps by adolescents aged 14 years and older. It is also important to point out that no study has compared the use of apps with face-to-face psychotherapy or pharmacotherapy. However, this direct comparison would be important in order to be able to assess whether apps also represent an alternative to face-to-face therapies primarily recommended for generalized anxiety disorder.

Health economics

Conclusions about the costs of an app are hard to draw for various reasons. For example, development costs for applications vary and they incur costs for their technical provision. Additional costs arise where personal technical or therapeutic support is offered. Furthermore, if many of those affected use an app, the costs per user decrease because the development and provision costs are spread across a number or people. The authors of the report therefore refrain from naming the costs of the apps. They only point out that the providers of the two products that are listed in the German DiGA directory and can consequently be prescribed or applied for at the expense of the statutory health insurance funds, currently each receive around €230 for a period of use of 90 days. Prices were significantly higher when these products were first included in the DiGA directory.

The team of scientists also looked at the question of whether digital interventions for generalized anxiety disorder are cost-effective. They did find 2 studies investigating the cost-benefit ratio of apps and other therapies for generalized anxiety disorder. However, it is not possible to transfer the conclusions drawn in these publications to the German health care system.

Further aspects

A range of digital interventions can simplify access to health care services for those affected, for example when there are waiting times for a therapy place, and thus contribute to greater autonomy and self-determination. On the other hand, personal support is usually highly valued by those affected and face-to-face psychotherapy is often preferred to the use of an

app. In addition, not all those affected can actually be reached with digital interventions: Reasons for this may include severe mental illness, limited health literacy, insufficient language skills, or a low affinity for mobile-based interventions. In addition, the legal regulations on data protection and product safety are of particular importance for apps that process sensitive information about a mental disorder. For applications listed in the DiGA directory, the requirements are usually more stringent than for apps that are only offered in app stores. The authors of the report therefore recommend that those affected receive transparent information when deciding whether or not to use a digital intervention.

Classification by IQWiG

In comparison with no treatment, apps for the treatment of generalized anxiety disorder that are based on cognitive behavioural therapy can help those affected, at least in the short term. At the same time, however, many questions remain unanswered: There is a lack of results, for example in the adolescent age group, on possible adverse events, and on effects beyond the intervention period. Similarly, based on the available study results, it cannot be concluded that apps are better or worse than other therapies, such as face-to-face cognitive behavioural therapy. This would require studies that directly compare these interventions with each other. However, no such studies are currently available.

Therefore, studies of high methodological quality are needed in the adolescent age group, as well as studies with a sufficiently long follow-up period. Studies that directly compare apps for the treatment of generalized anxiety disorder with face-to-face cognitive behavioural therapy would also be desirable.

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HTA key statements

Research question of the HTA report

The following research questions arise:

- What is the benefit of digital health applications (DiGA, including apps) for the treatment of generalized anxiety disorder (GAD) in adolescents and adults of all sexes compared to sham treatment, other treatment, or a no-treatment approach in terms of patient-relevant outcomes?

- What are the direct costs of the assessed interventions from the perspective of the community of people insured by statutory health insurance?

- How does the cost-effectiveness of the intervention compare to the comparator intervention?

- What ethical, social, legal, and organizational aspects arise in connection with the selection and implementation of interventions?

Conclusion of the HTA report

The current study situation provides indications of **a benefit** of **digital interventions based on cognitive behavioural therapy** in comparison with no treatment in terms of disease-related symptoms, quality of life, and everyday functions. However, all included studies show a high risk of bias, which limits the certainty of the results. There is no hint of (greater or lesser) benefit for the outcome of GAD diagnosis (remission), and no data were reported for the outcomes of mortality, risk of relapse, and self-efficacy. There are also no hints regarding the potential for harm, as hardly any **adverse events** were recorded in the studies. For another intervention investigated – based on a mixture of cognitive behavioural therapy and cognitive bias modification – there was a hint of a benefit in terms of GAD diagnosis (remission), but not in terms of GAD-related symptoms (the other outcomes were not examined for this intervention). For all other comparisons – digital interventions based on cognitive bias modification in comparison with sham interventions and head-to-head comparisons between digital interventions with different designs – there are no hints of (greater or lesser) benefit in relation to any of the outcomes analysed.

In Germany, digital interventions without therapeutic support or with only rudimentary personal support are lower in **cost** than face-to-face individual psychotherapy, but, depending on the product, they can be more expensive than drug therapy. The 2 economic studies

identified do not allow conclusions to be derived on the **cost-effectiveness** of digital interventions for the German health care system.

From an **ethical** perspective, on the one hand there is the expectation that digital interventions can lead to improvements in access to health care services (e.g. during the waiting time for a therapy place) and generate gains in autonomy and self-determination if their effectiveness is sufficiently proven. On the other hand, these positive effects can only occur across different target groups if the implementation of appropriate accompanying measures is ensured and digital interventions are designed to suit the target group. In this context, accompanying (qualitative) research is important. Furthermore, **patient preferences** not only attach great importance to the individualization of the digital offering, but also to personal (i.e. non-digital) support. Not all affected individuals can be reached with digital interventions, and the individual and well-informed decision (for or against the use of a DI or for the selection of a specific digital intervention out of the available ones) is particularly important across different age groups and socioeconomic groups. This further emphasizes the need for transparent information about digital treatment options and their framework conditions, including the **legal** regulations on data protection and product safety, both for those affected and for healthcare professionals. Clarification is needed of the different legal frameworks that apply depending on whether a digital intervention is declared as a medical device or not. From an organizational point of view, it is relevant that a considerable proportion of physicians and psychotherapists rate their own knowledge of DiGA as insufficient.

Missing data

With most studies lasting 2–3 months, no data are available on **longer-term effects**. None of the randomized controlled trials included a **comparison with face-to-face psychotherapy** (individual or group setting) **or pharmacotherapy**, and none of the included studies examined **adolescents aged 14 years and older**. Very few studies recorded **adverse events**, and if they did, it was often not done systematically.

Need for research

Valuable further insights could come from high-quality studies that (1) conduct **longer-term** follow-up surveys in intervention and control groups, (2) that also systematically assess quality of life and, in particular, potential **adverse events**, and (3) that directly compare digital interventions based on cognitive behavioural therapy with **face-to-face** cognitive behavioural therapy. It is difficult or impossible to perform blinding and assess the outcomes objectively given the present research question. Therefore, a high risk of bias is also to be expected in future studies. This makes it all the more important to avoid further **risks of bias** – including deviations from study protocols and financial conflicts of interest of the authors in the studies included here.

In addition, the group of **(children and) adolescents** should be investigated in studies due to the prevalence and incidence of generalized anxiety disorder and the limited possibility of drug treatment.

A high number of ongoing studies is to be assumed.

Summary conclusion

Individuals with generalized anxiety disorder can benefit from digital interventions based on cognitive behavioural therapy, at least in the short term (average observation period 3 months). Meta-analyses with up to 14 studies provide indications of a benefit in reducing disease-related symptoms in comparison with no treatment as well as an improvement in quality of life and everyday functions. However, the current study situation does not allow any conclusions to be drawn about the long-term effects or possible adverse effects of digital interventions based on cognitive behavioural therapy. It is important for those affected and for health professionals that DIs are designed and used in a way that is appropriate for the target group, and that transparent and sufficient information is provided and disseminated about the treatment options and their framework conditions (including data protection and product safety regulations).

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List of abbreviations

Abbreviation	Meaning
ABM	Attention Bias Modification
AHRQ	Agency for Healthcare Research and Quality
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)
BMG	Bundesministerium für Gesundheit (Federal Ministry of Health)
CBM	Cognitive Bias Modification
CBT	cognitive behavioural therapy
CBT DI	Digital intervention(s) based on the principles and contents of cognitive behavioural therapy (CBT) and/or mindfulness
DI(s)	digital intervention(s)
DiGA	Digitale Gesundheitsanwendung(Elina) (digital health application[s])
DiGAV	Digitale Gesundheitsanwendungen-Verordnung (Digital Health Applications Ordinance)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DVG	Digitale-Versorgung-Gesetz (Digital Healtz Care Act)
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GAD	generalized anxiety disorder
HTA	health technology assessment
ICD	International Statistical Classification of Diseases and Related Health Problems
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NICE	National Institute for Health and Care Excellence
PDT	psychodynamic psychotherapy
RCT	Randomized controlled trial
RNT	Repetitive Negative Thinking
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
SMD	standardized mean difference
SSNRI(s)	serotonin-noradrenaline reuptake inhibitor(s)
SSRI(s)	selective serotonin reuptake inhibitor(s)

HTA overview

1 Background

1.1 Health policy background and commission

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

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

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

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

1.2 Medical background

1.2.1 Generalized anxiety disorder

Generalized anxiety disorder (GAD) (ICD-10: F41.1, DSM-5: 300.02) is a disorder from the spectrum of anxiety disorders. It is characterized by intense anxiety and worry, which can be triggered by a variety of things. Those affected suffer from the fact that they cannot control their anxiety and worry, and their ability to function in everyday life is significantly impaired as a result.

The 12-month prevalence of GAD varies between 0.2% and 2.9% and the lifetime prevalence between 2.8% and 6.2%. Women are affected about twice as often as men. While the onset of other anxiety disorders (e.g. phobias) occurs during childhood or adolescence, the average age at onset of GAD is 31 years [6]. Patients with GAD usually have other mental disorders as

well, often more than 2. These include specific phobias, social phobia, depression, and dysthymia [7].

The causes are not yet fully understood. According to current research, genetic predisposition appears to play only a minor role in GAD, as no specific hereditary pattern for this disorder has been found to date. However, a certain disposition to anxiety is inherited, and this, together with social learning experiences (e.g. behaviour modelled by important reference persons, ways of dealing with challenges) and stressful life events (e.g. job loss, separation, constant feeling of being overwhelmed), can trigger GAD [7].

The illness has a chronic course, albeit with fluctuations in intensity. Worry and anxiety are at the centre of the disorder. These are triggered by external (e.g. a conflict with a colleague at work) or internal stimuli (e.g. thoughts of the challenges ahead the next day). This leads to a perpetuating vicious circle: those affected try to suppress these worries, which may provide short-term relief, but in the long term increases the frequency and intensity of the worries. As a result, those affected experience their worries as uncontrollable [7]. In response to anxiety and worry, stress hormones are also produced, which affect various bodily functions. For example, patients experience palpitations, muscle tension, breathing difficulties, nervousness, drowsiness, concentration problems, or sleep disorders [8,9].

1.2.2 Diagnosis

The AWMF S3 guideline for the treatment of anxiety disorders [10] recommends a diagnostic process that includes a detailed medical history as well as an open and a structured interview. Questionnaires on specific content can also be used (e.g. Beck Anxiety Inventory [11]; Worry Domains Questionnaire [12]; Metacognitions Questionnaire [13]).

The collected information is then integrated and used to check whether the ICD-10 list of criteria has been met. All four criteria must be met to diagnose GAD [9]:

1) Feelings of predominant tension, worry, and anxiety about everyday events must be present most days for 6 months.
2) At least 4 of the following symptom groups must be present (including at least 1 vegetative symptom):

- Vegetative symptoms: tachycardia/tachypnoea, sweating, trembling, dry mouth
- Symptoms in the thorax or abdomen: breathing difficulties, tightness, chest pain, nausea, or tingling in the stomach
- Psychological symptoms: dizziness, derealization or depersonalization, fear of losing control, fear of dying
- General symptoms: hot flushes or cold shivers, numbness, or tingling sensations

- Symptoms of tension: muscle tension, restlessness, nervousness, lump in the throat, or difficulty swallowing
- Unspecific symptoms: increased anxiety, concentration problems, irritability, difficulty falling asleep

3) The criteria for panic disorder, phobic disorder, obsessive-compulsive disorder, and hypochondriasis must not be met.
4) The symptoms were not caused by an organic disease and/or by the consumption of psychotropic substances.

Alternatively, the 6 criteria of the DSM-5 can be used [8]:

1) Excessive anxiety and worry about various activities and events, occurring on most days for the past 6 months
2) Those affected have great difficulty controlling the worrying.
3) Anxiety and worry are associated with at least 3 other symptoms, with some of these symptoms occurring on most days for the past 6 months:

- Restlessness, nervousness, or excitement
- Being easily fatigued
- Difficulty in concentrating or mind going blank
- Irritability
- Increased muscle tension
- Sleep disorders (difficulty falling asleep or getting up, restless and unsatisfying sleep)

4) The anxiety, worry, or symptoms cause significant stress or impairment in social, professional, or other important areas of life.
5) The disorder cannot be attributed to the physiological effects of a substance (e.g. drug abuse, medication) or to other medical conditions (e.g. thyroid hyperfunction).
6) The disorder is not better explained by another mental disorder (e.g. panic attacks, social phobia, obsessive-compulsive disorders, separation from reference persons in the case of separation anxiety).

1.2.3 Therapy

Those affected usually do not seek psychological or therapeutic help until late, on average only 10 years after the onset of the disorder. According to the AWMF S3 guideline for the treatment of anxiety disorders, patients with GAD should be offered psychotherapy (primarily cognitive behavioural therapy [CBT]) or pharmacotherapy, taking into account the

"preference of the informed patient" [10]. If one of the two therapies was not sufficiently effective, the other or a combination can be offered [10].

Due to comorbidity and individual compliance, it is difficult to predict how many therapy sessions will be required.

The typical and promising therapy components of **CBT** for GAD are [7]:

- General information transfer: information about anxiety and GA, conditional model of the disorder (triggering and maintaining factors), self-observation via worry diaries
- Worry exposure in sensu: changing the strategies used by patients to reduce their worries
- Worry exposure in vivo: reducing avoidance and reassurance behaviour
- Cognitive therapy: learning cognitive techniques such as reality testing, decatastrophizing, or dealing with meta-worries (worries about worries)

Applied relaxation: teaching relaxation techniques that can be used to reduce anxiety

If CBT has proved ineffective, is not available, or if the patient has a preference in this regard, psychodynamic psychotherapy should be offered [10].

The following medications are recommended as part of **pharmacotherapy** [10]:

- Selective serotonin reuptake inhibitors (SSRIs): available as escitalopram and paroxetine
- Serotonin-noradrenaline reuptake inhibitors (SSNRIs): available as duloxetine and venlafaxine
- Calcium modulator: available as pregabalin
- Tricyclic anxiolytic: available as opipramol if SSRI, SSNRI and calcium modulator were ineffective or not tolerated
- Azapirone: offer of buspirone if SSRI, SSNRI and calcium modulator were ineffective or not tolerated

Digital interventions (DIs) (in the form of apps or browser-based applications) are now also being offered with the aim of supporting those affected in the treatment of their (generalized) anxiety disorder. They convey various contents and techniques in the form of text, audio or video files. Contents are often based on the principles of CBT. DIs for treating anxiety disorders can be based on other principles, such as:

- Cognitive Bias Modification (CBM): People with anxiety disorders tend to focus their attention on potentially threatening stimuli in their environment. Various CBM

procedures are therefore aimed at correcting this (faulty) information processing of threatening or ambivalent stimuli. These procedures involve the use of computer-based training tasks that are designed to encourage health-promoting processing when repeated [14].

- CBM is sometimes combined with RNT induction: Repetitive Negative Thinking (RNT; rumination) describes a strong focus of attention on stress and discomfort as well as their causes and consequences and makes it very difficult to deal with solutions and coping strategies [15]. Previous RNT induction is thought to enhance the effect of CBT.
- Mindfulness is a specific form of attention that is intentional, focussed on the present moment, and non-judgemental. Since worrying is concerned with future contents, mindfulness exercises help patients to focus on the present and free themselves from worry. In addition, these exercises establish an observational and non-judgemental attitude, which should also make it easier to cope with worrying [16].

Apps can also provide additional features. These include reminders when it is time to do exercises, exposure exercises, self-assessments accessible in the form of diaries, or contact options with a therapist as needed. The apps can be used as a stand-alone intervention or in conjunction with therapy. Other DIs can also be used to support people with GAD. The spectrum ranges from apps that send reminders to take medication to music streaming services and apps that remind users to exercise regularly.

The S3 guideline recommends "CBT-based interventions via the internet" for bridging the waiting period until therapy begins or in conjunction with therapy in the sense of a self-help guide. However, they should not be used as stand-alone treatment [10].

1.3 Health services situation

The availability of such DIs in Germany depends on the language or languages in which the application is available and, in the case of apps, also on the (regional) scope of the respective app store. There is a wide range of products on the market, tailored to different priorities and purposes (GAD-specific, anxiety disorders in general, mental health, meditation, therapy support, memory functions, etc.). In 2021, Stiftung Warentest tested 7 apps for anxiety disorders [17], 3 of which featured GAD as their therapeutic indication.

Reimbursement of certain digital health applications by statutory health insurance (SHI) was regulated as part of the Act for Better Care through Digitalisation and Innovation (Digital Health Care Act [18] and Digital Health Applications Ordinance [19]), which came into force in Germany in 2019. If it is not yet possible to provide proof of positive effects on care, a digital health application can be provisionally reimbursed by the statutory health insurance for 1 year if a plausible justification of its contribution to improving care is presented and after an examination of various aspects such as safety, functionality, and quality. The period of

provisional reimbursement can be extended by 1 year if necessary. After this time at the latest, the manufacturer must demonstrate that the application has a medical benefit or contributes to patient-relevant structural and procedural improvements and thus offers a "positive effect on care" [19]. According to Section 33a of Social Code Book (SGB) V , certification as a medical device of risk class I or IIa is also a prerequisite[2], the main function of the application must be essentially based on digital technologies and it must support the "detection, monitoring, treatment, or alleviation of diseases or the detection, treatment, alleviation, or compensation of injuries or disabilities" [20]. One or more indications according to ICD-10 must be specified. The "Directory for digital applications" (DiGA directory) maintained by the Federal Institute for Drugs and Medical Devices lists the reimbursable digital health applications; for GAD, 2 applications are included as of July 2023, both indicating a minimum age of 18 years for patients [21].

To be able to use a DI, those affected usually need internet access and an end device. The two applications listed in the DiGA directory [22,23], for example, are available as web applications, with Selfapy also being available as an app. From the service providers' point of view, there are basically no requirements, unless an application provides for direct interaction with the service providers – in which case the same technical requirements apply to them as to those affected.

Concrete usage rates are only documented for the reimbursable DI: the first applications were included in the DiGA directory at the end of September 2020. By September 2022, the number of DiGA prescriptions had risen to a total of around 200,000, and the activation code sent (which is required to start the app) was actually redeemed for around 160,000 of them during this period (report by the National Association of Statutory Health Insurance Funds [24]). The most frequently used application reached 28,000 redemptions, while the velibra and Selfapy apps listed for GAD reached around 5,000 and 2,000 redemptions respectively [24] (as of September 2021, there were 1,400 and 200 redemptions respectively [25]). In terms of DiGA utilization by age and sex, the analysis shows a high proportion of women (70%) and the highest usage rate in the 55 to 60 age group [24]. The two GAD apps tend to be slightly above average in terms of the proportion of women and slightly below average in terms of usage by age [26].

1.4 Concerns of those proposing the topic

Those proposing the topic point out that apps for the treatment of anxiety disorders can be prescribed since January 2021. Costs for the apps are covered by statutory health insurance if

[2] On 30 August 2023, the Federal Cabinet adopted the Digital Act (DigiG), which provides for the DiGA provisions to be extended to medical devices in risk class IIb (https://www.bundesgesundheitsministerium.de/ministerium/gesetze-und-verordnungen/guv-20-lp/digig.html).

prescribed by a physician. Against this backdrop, those proposing the topic ask in general whether it has been reliably proven that those affected can benefit from using an app to treat anxiety disorders.

2 Research questions

The following research questions arise:

- What is the benefit of digital applications (including apps) for the treatment of generalized anxiety disorder in adolescents and adults of all sexes compared to sham treatment, other treatment, or a no-treatment approach in terms of patient-relevant outcomes?
- What are the direct costs of the assessed interventions from the perspective of the community of people insured by statutory health insurance?
- How does the cost-effectiveness of the intervention compare to the comparator intervention?
- What ethical, social, legal, and organizational aspects arise in connection with the selection and implementation of interventions?

3 Methods

3.1 Methods – benefit assessment

The target population of the benefit assessment consisted of adolescents (14 years and older) and adults of all sexes with GAD (ICD-10: F41.1, DSM-5: 300.02). The experimental intervention was either a stand-alone treatment or a supplementary treatment – to another therapy – using an app or digital application. The requirements for intervention shown in Table 3 of the full report apply. There were no limitations regarding the comparator intervention. However, the comparator intervention was only allowed to differ from the intervention with respect to the absence of the app/digital intervention or its replacement with a placebo (accordingly, studies investigating, for example, psychotherapy in combination with an app versus a control group of patients on a waiting list were excluded).

The following patient-relevant outcomes were taken into account in the investigation:

- Morbidity such as
  - Symptom reduction (change in anxiety symptoms and/or accompanying psychosomatic complaints; GAD diagnosis [remission]),

  - Risk of relapse[3]
- Self-efficacy
- Activities of daily living/everyday functioning
- Health-related social functioning, including occupational and social participation
- Health-related quality of life
- Adverse events
- All-cause mortality

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

In parallel to the preparation of the HTA report protocol, a search for systematic reviews was conducted in the MEDLINE databases (which includes the Cochrane Database of Systematic Reviews) and the HTA database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was ascertained whether at least 1 high-quality, current systematic review existed whose information retrieval was a suitable basis for the assessment (hereinafter: basic SR).

If that was the case, a 2nd step followed, where a supplementary search was conducted for studies for the time period not covered by the basic SR(s). Otherwise, the search for studies was carried out without time restriction.

A systematic literature search for studies was conducted in the following databases: MEDLINE, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials.

In addition, the following information sources and search techniques were taken into account: trial registries, publicly accessible documents from regulatory authorities, the screening of reference lists, and author queries.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, risk of bias criteria across outcomes and outcome-specific risk of bias criteria were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were described according to outcomes.

[3] Proportion of patients who were in remission from GAD after treatment and are diagnosed again at a later date or exceed a corresponding symptom cut-off

In addition to the comparison of the individual studies' results, meta-analyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was drawn regarding the evidence base for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: There was either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or none of those 3 situations. The latter was the case if no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

For the outcome of GAD-related symptoms, 3 distinct data collection instruments were combined that had been sufficiently tested and validated with regard to their suitability as screening instruments for GAD. For the outcome of quality of life, 6 different data collection instruments were combined that measure quality of life and/or mental well-being. For the outcome of everyday functions, 2 different data collection instruments were combined that measure functional limitations in different domains of life (for details, see Section A3).

Bayesian meta-analyses were conducted. The risk ratio was used for binary outcomes (remission) and the standardized mean difference (SMD) for continuous outcomes. Markov Chain Monte Carlo methods were used for the calculations, using the package "brms" [27], which in turn uses "Stan" [28]. 16,000 iterations were performed and "adapt_alpha" was set to 0.99999. The prior for the mean effect (intercept) was "Normal(0, 1)" and "Half_Cauchy(0, 0.5)" was used for τ. Metaregressions with categorical predictors were used to model the effects of the subgroups. A prior of "normal(0, 0.25)" was assumed for the effects of these predictors as well as for the effect of time (intervention duration), age and sex (proportion of women) in the corresponding meta-regressions.

All calculations and visualizations were carried out using the programming language R (v 4.2.2). The "tidyverse" package [29] was used for data processing and visualizations. In addition, the package "tidybayes" [30] was used to extract and manipulate the posterior draws. The "metaHelper" package [31] was used to convert the statistical results. The packages "ggridges" [32] and "glue" [33] were also used to create graphics.

The SMD calculated in the meta-analyses were approximately converted into changes on the GAD-7 scale for contextualization. For this purpose, the SMD were multiplied by the standard deviation (SD) of the GAD-7 scale. An averaged SD of the values at baseline was calculated in the total populations of the studies included in the meta-analysis (reported in 9 of the 14

studies). This averaged SD (4.23) corresponds approximately to the SD reported in the validation study of the GAD-7 scale (4.8) [34].

3.2 Methods – health economic assessment

To calculate intervention costs, the average resources required directly when performing the experimental and comparator intervention were estimated. For this purpose, the services directly associated with the intervention as well as the experimental and comparator intervention were taken into account. The relevant regulated or negotiated prices of these services were used wherever possible. As this is usually a long-term or continuous therapy, the costs incurred per patient per year were stated. The frequency and duration of use was based on the information in the respective remuneration catalogues and the recommendations of the S3 guideline [10]. Reimbursable costs were listed separately from non-reimbursable costs.

The systematic overview of health economic studies included searching for cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses in German or English. The systematic focused literature search was carried out in the MEDLINE and Embase databases and in the HTA database. The identified references were selected by 1 person, with a 2nd person doing quality assurance. The data extraction into standardized tables as well as the evaluation of the report quality and the assessment of the transferability of the results – both based on predefined criteria – were carried out by one person each. The results of the individual studies were comparatively described as part of the information synthesis.

3.3 Methods – ethical aspects

To obtain information, the first step was to collect and list possible ethically relevant arguments and aspects using the structured collection of questions on the ethical domain of the EUnetHTA Core Model of the European Network for Health Technology Assessment (EUnetHTA) [35]. Subsequently, orientating research was carried out in the following information sources:

- Ethics in Medicine (ETHMED)
- MEDLINE
- Laws, regulations, or guidelines
- Interest-dependent sources of information, e.g. Websites of professional associations or self-help groups

Additionally, the following documents were checked for potential ethical arguments and aspects:

- Studies included in the benefit assessment

- Studies included in the health economic assessment
- The protocol for documenting the discussion with the surveyed affected people

As an additional source of information, the reflective thoughts method, i.e. reflection informed by the authors' knowledge regarding potential ethical arguments and aspects, was applied [36].

One reviewer screened the sources from all information sources employed for the scoping searches or all other documents for statements on ethical arguments and aspects of the technology to be investigated. A 2nd person assured the quality of the result. The processing and presentation of results was again based on the collection of questions on the ethical domain of the EUnetHTA Core Model [35] and aspects already collected in the first step were taken up and refined in an iterative process.

3.4 Methods – social, legal, and organizational aspects

For the analysis of social, legal, and organizational aspects, scoping searches were conducted in the following information sources:

- MEDLINE
- Social Sciences Citation Index (SSCI)
- Laws, regulations, or guidelines
- Interest-based sources of information, e.g. websites of associations or self-help groups

Additionally, the following documents were checked for potential social, legal, and/or organizational arguments and aspects:

- Studies included in the benefit assessment
- The protocol for documenting the discussion with the surveyed affected people

As an additional source of information, the reflective thoughts method, i.e. reflection informed by the authors' knowledge regarding potential ethical and social arguments and aspects, was applied [36].

One reviewer screened the information from all sources employed in the scoping searches or all other documents for statements on social, legal, and organizational arguments and aspects of the technology to be investigated. A 2nd person assured the quality of the result.

The preparation of information on social aspects was based on the conceptual framework proposed by Mozygemba 2016 [37]; in addition, the checklist from the EUnetHTA Core Model [35] was examined. The preparation of information on legal aspects was based on the guidelines developed by Brönneke 2016 [38] for identifying legal aspects, while the

information on organizational aspects was based on the grid proposed by Perleth 2014 [39] for assessing the organizational consequences of examination and treatment methods.

3.5 Interviews with affected people

In order to gain an impression of how patients (or their relatives) experience the disease, what treatment experiences they have had, and what they would like from treatment, affected persons were involved. Affected people were understood here to mean only people with GAD, although affected people can also be family members, for example. The interviews were conducted in the form of individual telephone interviews using a structured interview guide. The interview recordings were transcribed and processed in tabular form (see section A12).

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

One systematic review was rated as being current and of high quality and was included as basic SR for the identification of primary studies [40].

The information retrieval revealed 23 randomized controlled trials relevant to the research question, 20 of which were considered for the benefit assessment (see also Table 1). One completed study without reported results was found (see Table 13 of the full report). No search for planned or ongoing studies was carried out (the search results from the trial registries were only screened to identify (further) completed studies).

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 21 December 2022.

Table 1: Study pool of the benefit assessment

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / Result report from trial registries**	**Study report from author queries**	**Other Documents**
Considered in benefit assessment				
Andersson 2012	Yes [41]	No	No	No
Berger 2017	Yes [4]	Yes	No	DiGA directory entry [42]
Carl 2020	Yes [43]	Yes	No	No
Dahlin 2016	Yes [44]	Yes	No	No
Dahlin 2022	Yes [45]	Yes	No	No
Dear 2015	Yes [46]	Yes	No	No
Hirsch 2018	Yes [47]	Yes	No	No
Hirsch 2020	Yes [48]	No	No	No
Hirsch 2021	Yes [49]	Yes	No	No
Jones 2016	Yes [50]	Yes	No	No
Loughnan 2019	Yes [51]	Yes	No	No
Newman 2021	Yes [52]	No	No	No
Paxling 2011	Yes [53]	No	No	No
Richards 2016	Yes [54]	Yes	No	No
Robinson 2010	Yes [55]	Yes	No	No
Roy 2021	Yes [56]	No	No	No
Rubel 2024	Yes [57]	Yes	Yes	DiGA directory entry [58]
Schneider 2020	Yes [59]	No	No	No
Titov 2009 / Lorian 2011	Yes [60,61]	Yes	No	No
Titov 2010	ja [62]	Yes	No	No
Not considered in the benefit assessment (due to a discontinuation rate of over 30%)				
Amir 2019	Yes [63]	Yes	No	No
Christensen 2014	Yes [64]	No	No	No
Mason 2023	Yes [65]	No	No	No

4.2 Characteristics of the studies included in the assessment

Two studies were conducted with students and therefore included younger populations: Newman 2021 [52] with a mean age of 21 years and Richards 2016 [54] with a mean age of 23 years. The Jones 2016 study [50] was conducted on an older population with a mean age of 65 years. The mean age in the remaining studies ranged from 29 years in Hirsch 2018 [47] to 58 years in Schneider 2020 [59]. In all studies, a minimum age of 18 years was an inclusion

criterion. No studies with adolescents between 14 and 18 years of age were identified that met the inclusion criteria of the present report.

The Loughnan 2019 study [51] was conducted on women in the postpartum period (up to 12 months after giving birth). In the remaining studies, the proportion of women ranged from 58% for Schneider 2020 to 90.5% for Roy 2021 [56]. The option to specify sex as 'other' was available in three studies, with 2% of participants choosing this option in Carl 2020 [43], 2% in Roy 2021, and 1% in Rubel 2024 [57] .

In 16 studies, a diagnosis of GAD by a medically trained person was an inclusion criterion; in 6 studies, a threshold value on a survey instrument validated for GAD screening (e.g. GAD-7) was used instead. In the Jones 2016 study, one of these two criteria had to be met. In all studies except Carl 2020 and Roy 2021, severe depression and/or suicidal thoughts were an exclusion criterion.

The details of the interventions analysed in the studies (content/elements, access, design, support, duration/units) are described in Table 16 and Table 17 of the full report. Most studies (14) investigated the effectiveness of digital interventions (DI) based on the principles and content of cognitive behavioural therapy (CBT) and/or mindfulness (CBT DI[4]) compared to a control group that received no active treatment. In 11 of the 14 studies, a waiting list design was used in which the participants in the control group also received the intervention after the last comparative outcome survey. In 3 studies, the control group received no treatment at all, although in two of these studies the term 'standard treatment' was used (Loughnan 2019, Roy 2021), which did not, however, involve any treatments provided as part of the study. In 3 studies, the contents of the intervention were tailored to specific populations: to older people in Jones 2016, to women in the postpartum period in Loughnan 2019, and to people who had suffered from acute heart disease in the past (e.g. unstable angina or heart attack) in Schneider 2020. The duration of the interventions in these 14 studies ranged from 4 weeks to 12 weeks, the mean duration being 8 weeks. In all 14 studies, some form of in-person support was provided in the course of CBT DI. However, this support varied greatly between studies, including in terms of the people providing it (e.g. psychologists or psychotherapists, coaches, administrative staff), extent, frequency, mode of communication, and focus (therapeutic or technical questions). The descriptions varied in level of detail, and no clear groups could be identified. In the presentation of results (see Section 4.5), a distinction is made between "technical" and "therapeutic" support for the sake of simplicity.

[4] The contents of CBT and mindfulness partly overlap. Only 2 of the included studies used only the term mindfulness in the description of the intervention and not the term CBT. For ease of reading, the abbreviation "CBT DI" is therefore used for the entire group.

In 2 studies (Dear 2015 [46] and Dahlin 2022 [45]) and in 1 study, which is also included in the above-mentioned study pool (CBT DI versus no treatment) (Robinson 2010 [55]), CBT DI was investigated in various forms in head-to-head comparisons. In 3 studies, interventions based on the principle of cognitive bias modification (CBM) were investigated in comparison with a sham application or in different designs in head-to-head comparisons: Hirsch 2018, Hirsch 2020 [48] and Hirsch 2021 [49]. The Berger 2017 study [4] investigated CBT DI in combination with CBM in comparison with a waiting list. In 1 study, which is also included in the above-mentioned study pool (CBT DI versus no treatment), the comparison of CBT DI with a DI based on psychodynamic psychotherapy (PDT) was also investigated (Andersson 2012 [41]).

In 3 other studies, the discontinuation rates were over 30%. These studies were therefore not included in the benefit assessment, although they met the inclusion criteria. They investigated the comparisons of Attention Bias Modification (ABM) versus waiting list (Amir 2019 [63]), CBT DI versus psychoeducation or versus sertraline medication (Christensen 2014 [64][5]) and 1 head-to-head comparison of 2 different CBT DIs (Mason 2023 [65]).

4.3 Overview of patient-relevant outcomes

From 20 studies, it was possible to extract data on patient-relevant outcomes.

Table 2 presents an overview of the data available on patient-relevant outcomes from the included studies. In all 20 studies, data on the outcome of GAD-related symptoms were reported, in 7 studies data on the outcome of quality of life, in 5 studies data on the outcome of everyday functions and in 6 studies data on the outcome of adverse events (however, only in 2 studies systematically with predefined questionnaires). In 3 studies, data on the outcome of GAD diagnosis (remission) were reported, in 1 further study (Paxling 2011 [53]) these data were not reported, although their collection was specified in the study methodology. No data were reported on the outcomes of risk of relapse, mortality, and self-efficacy in any of the studies.

[5] In this study, the statistical power was also inadequate: the plan was to recruit 120 people, but only 21 were actually recruited. The authors stated that this gave them 8% power to detect an effect of >2. However, the effects of the studies included in the benefit assessment tend to be in the range of 0.5 to 1.5. Of this very small number of participants, a total of just under 30% discontinued the study before the first survey date. Due to the discontinuation rates in these study arms, the authors did not calculate the effect for the comparison of CBT DI vs. sertraline.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes							
		Morbidity						
	All-cause mortality/overall survival	GAD-related symptoms	GAD diagnosis (remission)	Risk of relapse	Everyday functions	Health-related quality of life or level of social functioning	Self-efficacy	Adverse events
CBT DI versus no treatment[a]								
Andersson 2012	-	●	●	-	-	●	-	-
Carl 2020	-	●	-	-	-	●	-	●
Dahlin 2016	-	●	-	-	-	●	-	-
Jones 2016	-	●	-	-	-	●	-	-
Loughnan 2019	-	●	-	-	-	-	-	-
Newman 2021	-	●	-	-	-	-	-	-
Paxling 2011	-	●	x	-	-	●	-	-
Richards 2016	-	●	-	-	●	-	-	-
Robinson 2010	-	●	-	-	●	-	-	-
Roy 2021	-	●	-	-	-	-	-	●
Rubel 2024	-	●	-	-	●	●	-	●
Schneider 2020	-	●	-	-	-	-	-	-
Titov 2009 / Lorian 2011	-	●	-	-	●	-	-	-
Titov 2010	-	●	-	-	-	-	-	-
CBT DI: head-to-head comparisons								
Dahlin 2022	-	●	-	-	-	●	-	●
Dear 2015	-	●	●	-	-	-	-	-
Mason 2023	-	○	x	-	-	-	-	-
Robinson 2010	-	●	-	-	●	-	-	-
CBM versus sham								
Hirsch 2018	-	●	-	-	-	-	-	●
Hirsch 2020	-	●	-	-	-	-	-	●
Hirsch 2021	-	●	-	-	-	-	-	●
CBM head-to-head comparisons								
Hirsch 2018	-	●	-	-	-	-	-	●
Hirsch 2020	-	●	-	-	-	-	-	●
Hirsch 2021	-	●	-	-	-	-	-	●
CBT DI + CBM versus waiting list								
Berger 2017	-	●	●	-	-	-[b]	-	-

Study	Outcomes							
		Morbidity						
	All-cause mortality/overall survival	GAD-related symptoms	GAD diagnosis (remission)	Risk of relapse	Everyday functions	Health-related quality of life or level of social functioning	Self-efficacy	Adverse events
CBT DI versus other interventions								
Andersson 2012	-	●	●	-	-	●	-	-
Christensen 2014 (CBT DI versus health information)	-	○	-	-	-	-	-	-
Christensen 2014 (CBT DI versus sertraline)	-	x	-	-	-	-	-	-
ABM + applied relaxation + psychoeducation versus waiting list								
Amir 2019	-	○	-	-	○	-	-	-

●: Data were reported and usable.
○ Data were reported but not usable for the benefit assessment.
X: Data were not reported despite the collection of these data being pre-specified.
-: No data were reported (no further information). / The outcome was not surveyed.

a: Waiting list/untreated/standard treatment.
b: Data reported, but not separately for GAD subgroup.

ABM: Attention Bias Modification; CBM: Cognitive Bias Modification; DI: digital intervention; GAD: generalized anxiety disorder; CBT: cognitive behavioural therapy

4.4 Assessment of the risk of bias of the results

The risk of bias across outcomes was rated as high for all 20 studies. This was mainly due to the lack of blinding in connection with subjective outcome recording. Further methodological shortcomings in several studies were differences in or insufficient information on baseline characteristics and deviations from the study protocols. In some studies, the masking of group allocation was also insufficiently described. In addition, there were financial conflicts of interest among the authors in 8 studies (see Table 22 of the full report for details).

4.5 Results on patient-relevant outcomes

Below, the results on patient-relevant outcomes are presented separately by investigated comparison. Detailed results of the meta-analyses are presented in Section A3.3 of the full report.

4.5.1 Results on GAD-related symptoms

CBT DI versus no treatment

Data on GAD-related symptoms were reported in 14 studies comparing CBT DI with no treatment (see Table 2). The meta-analysis of these studies shows a moderate to strong effect of CBT DI in reducing GAD-related symptoms (SMD = -0.76; 95% confidence interval: [-1.01; -0.51]; n = 293; see Figure 2 of the full report). This corresponds approximately to a reduction in GAD-related symptoms by 3.2 points on the GAD-7 scale. The effects are in the same direction across the studies, but differ in their magnitude, as the observed statistical heterogeneity also shows (Tau = 0.38).

A meta-regression showed that the age of the subjects had an influence on the effect of CBT DI. For each additional year of age of the subjects, the effect increased by -0.02 (95% confidence interval: [-0.04; 0.00]; Tau = 0.27; see Figure 3 of the full report). Further subgroup analyses and meta-regressions showed no influence of the factors of sex, intervention duration, control group (waiting list versus untreated), GAD status (diagnosis versus threshold on survey instrument), theoretical focus (CBT or mindfulness), or content focus (general or tailored to specific target population). It was not possible to conduct the analysis of a possible effect modification by the factor of concomitant illnesses (co-morbidities) provided for in the report protocol, since co-morbidities were rarely or inconsistently reported in the included studies.

The 95% confidence interval of the SMD (Cohen's d) lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. These results are based exclusively on studies with a high risk of bias, so there is an indication of a benefit of CBT DI compared to no treatment.

CBM RNT versus sham

In 3 studies, CBM in combination with an initial induction of rumination (Repetitive Negative Thinking, RNT) was compared with a sham application and data on GAD-related symptoms were reported (Hirsch 2018, Hirsch 2020 and Hirsch 2021). The meta-analysis of these studies shows a minor effect of CBT RNT in reducing CAD-related symptoms (SMD = -0.34; 95% confidence interval: [-0.7; 0.03]; n = 350; see Figure 7 of the full report). This corresponds approximately to a reduction in GAD-related symptoms by 1.4 points on the GAD-7 scale.

The results of the meta-analysis are based exclusively on studies with a high risk of bias and the 95% confidence interval of the calculated effect overlaps the null effect, therefore there is no evidence of a benefit of CBM RNT in comparison with sham application.

CBM: head-to-head comparisons

In 2 of the above-mentioned studies, head-to-head comparisons of different designs of CBM were also examined: Hirsch 2018 provides a comparison of CBM RNT versus CBM without RNT, and Hirsch 2020 a comparison of CBM RNT alone versus in addition to a one-time "mental imagery" training. The results reported for these comparisons showed no significant differences.

There is no hint of greater or lesser benefit of the different designs of CBM analysed in these studies in comparison with each other.

CBT DI + CBM versus waiting list

The Berger 2017 study investigated CBT DI in combination with CBM in comparison with a waiting list. In the subgroup of participants with GAD included in the present report, no statistically significant difference was reported between the two study arms (Cohen's d = 0.34; 95% CI: [-0.17; 0.86]; n = 58).

There is no hint of a benefit from CBT DI + CBM in comparison with waiting list.

CBT DI: head-to-head comparisons

In the Dahlin 2022 study, a comparison was made between weekly support and on-demand support on the one hand, and between a focus on the topic of anxiety and a broader and more individualized focus on content on the other hand. The Dear 2015 study analysed the comparison of therapeutic support with no support on the one hand, and the comparison of a content focus specifically on GAD with a transdiagnostic focus (content more generally on anxiety and depressed mood) on the other hand. The Robinson 2010 study analysed the comparison of therapeutic support with technical support.

Dear 2015 reported a statistically significant advantage of transdiagnostic content targeting over GAD targeting at the last survey time point (24 months) (Cohen's d = 0.48; 95% CI: [0.24; 0.71]; $p < 0.001$). According to the authors, the other time points analysed in this comparison (2, 3 and 12 months) and all other comparisons in the aforementioned studies showed no significant differences (data not reported in detail).

The authors of the Dear 2015 study assessed the observed differences between CBT DI with a transdiagnostic content focus compared to CBT DI with a content focus specifically on GAD as small. They also pointed out that the relevance of these differences was unclear, as no significant differences were found at the other survey times or for other outcomes or in other groups of people analysed.

There is no hint of greater or lesser benefit of the different designs of CBT DI analysed in these studies in comparison with each other.

CBT DI versus PDT DI

The Andersson 2012 study investigated the comparison of CBT DI versus DI based on psychodynamic psychotherapy (PDT) and reported no significant differences in the outcome of GAD-related symptoms.

There is no hint of greater or lesser benefit of CBT DI in comparison with PDT DI.

4.5.2 Results on quality of life

CBT DI versus no treatment

Data on quality of life were reported in 6 studies comparing CBT DI with no treatment (see Table 2). The meta-analysis of these studies shows a minor to moderate effect of CBT DI in improving everyday functions (SMD = 0.45; 95% confidence interval: [0.24; 0.66]; n = 699; see Figure 8 of the full report).

The 95% confidence interval of the SMD (Cohen's d) lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. These results are based exclusively on studies with a high risk of bias, so there is an indication of a benefit of CBT DI compared to no treatment.

CBT DI: head-to-head comparisons

In the Dahlin 2022 study, a comparison was made between weekly support and on-demand support on the one hand, and between a focus on the topic of anxiety and a broader and more individualized focus on content on the other hand; no significant differences were reported for the outcome of quality of life.

There is no hint of greater or lesser benefit of the different designs of CBT DI analysed in this study in comparison with each other.

CBT DI versus other interventions

The Andersson 2012 study investigated the comparison of CBT DI versus DI based on psychodynamic psychotherapy (PDT) and reported no significant differences in the outcome of quality of life.

There is no hint of greater or lesser benefit of CBT DI in comparison with PDT DI.

4.5.3 Results on everyday functions

CBT DI versus no treatment

Data on everyday functions were reported in 4 studies comparing CBT DI with no treatment (see Table 2). The meta-analysis of these studies shows a moderate effect of CBT DI in

improving everyday functions (SMD = 0.58; 95% confidence interval: [0.21; 0.93]; n = 699; see Figure 9 of the full report).

The 95% confidence interval of the SMD (Cohen's d) lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. These results are based exclusively on studies with a high risk of bias, so there is an indication of a benefit of CBT DI compared to no treatment.

CBT DI: head-to-head comparisons

In the Robinson 2010 study, the comparison of therapeutic support with technical support was investigated and no significant differences were reported for the outcome of everyday functions.

There is no hint of greater or lesser benefit of the different designs of CBT DI analysed in this study in comparison with each other.

4.5.4 Results on GAD diagnosis (remission)

CBT DI versus no treatment

The Andersson 2012 study compared CBT DI with a waiting list and reported data on GAD diagnosis (remission). A higher remission rate was reported in the CBT DI group than in the waiting list group (35% versus 16%). The statistical significance of the results was not reported.

There is no hint of a benefit of CBT DI in comparison with waiting list.

CBT DI + CBM versus waiting list

The Berger 2017 study investigated CBT DI in combination with CBM in comparison with a waiting list. In the subgroup of participants with GAD included in this report, remission rates of 44.8% (13/29) were reported in the intervention group and 0% (0/29) in the control group ($p < 0{,}001$).

As the assessment of the clinical relevance of the symptoms is part of the diagnostic process, this result is interpreted as a relevant effect. There is no hint of a benefit of CBT DI + CBM in comparison with no treatment.

CBT DI: head-to-head comparisons

The Dear 2015 study analysed the comparison of therapeutic support with no support on the one hand, and the comparison of a content focus on GAD with a transdiagnostic focus on the other hand. The authors stated that the remission rates were the same across the different groups.

There is no hint of greater or lesser benefit of the different designs of CBT DI analysed in this study in comparison with each other.

CBT DI versus other interventions

The Andersson 2012 study compared CBT DI versus DI based on psychodynamic psychotherapy (PDT). A lower remission rate was reported in the CBT DI group than in the PDT DI group (35% versus 54.5%). The statistical significance of the results was not reported.

There is no hint of greater or lesser benefit of CBT DI in comparison with PDT DI.

4.5.5 Results on adverse events

CBT DI versus no treatment

In the Carl 2020 study, adverse events were systematically recorded using a predefined questionnaire. The adverse events recorded occurred more frequently in the waiting list group than in the CBT DI group, and some of the differences were statistically significant (see Table 30 of the full report). In the Rubel 2024 study, negative effects were recorded at the end of the intervention period using the Negative Effects Questionnaire (NEQ). Statistically significantly fewer negative effects were reported in the waiting list group than in the CBT DI group ($p = 0.005$). Adverse events were reported in the Roy 2021 study (anxiety and back pain, in each case only in the CBT DI group), but were not systematically recorded using a predefined questionnaire or were not reported accordingly. In addition, a large proportion of the outcomes recorded in the three studies fall within the spectrum of GAD-related symptoms, so a clear distinction between adverse events and GAD-related symptoms is not possible.

Since the available results each come from a single study with a high risk of bias and the interpretation of the measured parameters is unclear, there is no hint of harm from CBT DI in comparison with no treatment.

CBM versus sham and head-to-head comparisons

In the Hirsch 2018, Hirsch 2020 and Hirsch 2021 studies, it was reported that no adverse events occurred in any of the groups studied (CBM in various forms and sham applications). However, the survey was not carried out systematically using a predefined questionnaire or was not reported accordingly.

There is no hint of harm from CBT in comparison with a sham application.

CBT DI: head-to-head comparisons

In the Dahlin 2022 study, adverse events were systematically recorded using a predefined questionnaire. The proportion of participants per group who had at least one adverse event

was reported: 63% in the group with weekly support and 54% in the group with on-demand support, 58% in the group with a content focus on anxiety and 59% in the group with a broader and individualized content focus. The most frequently reported adverse events across all groups were: stress (47.7%), unpleasant memories (30.8%), increased anxiety (24.6%), not understanding the treatment[6] (24.6%), and unpleasant feelings (21.5%). The authors reported that no significant differences were found between the groups.

There is no hint of greater or lesser harm from the different designs of CBT DI analysed in this study in comparison with each other.

4.6 Overall evaluation of the results

Evidence map

The following shows the evidence map regarding patient-relevant outcomes.

[6] in the untranslated text: "reporting of not understanding the treatment"

Table 3: Evidence map regarding patient-relevant outcomes

Study	Outcomes							
		Morbidity						
	All-cause mortality/overall survival	GAD-related symptoms	GAD diagnosis (remission)	Risk of relapse	Everyday functions	Health-related quality of life or level of social functioning	Self-efficacy	Adverse events
CBT DI versus no treatmenta	-	⇑	⇔	-	⇑	⇑	-	⇔
CBM versus sham	-	⇔	-	-	-	-	-	⇔
CBM: head-to-head comparisons	-	⇔	-	-	-	-	-	⇔
CBT DI + CBM versus waiting list (Berger 2017)	-	⇔	⇗	-	-	-	-	-
CBT DI versus PDT DI (Andersson 2012)	-	⇔	⇔	-	-	⇔	-	-
CBT DI: head-to-head comparisons								
Dahlin 2022 (weekly support versus on-demand support)	-	⇔	-	-	-	⇔	-	⇔
Dahlin 2022 (content: anxiety versus content: individualized)	-	⇔	-	-	-	⇔	-	⇔
Dear 2015 (focus: GAD versus focus: transdiagnostic)	-	⇔	⇔	-	-	-	-	-
Dear 2015 (therapeutic support versus no support)	-	⇔	⇔	-	-	-	-	-

⇑: indication of benefit
⇗: hint of benefit
⇔: no hint, indication or proof, homogeneous result
-: no data reported

a: (Waiting list/untreated/standard treatment.)
CBM: cognitive bias modification; DI: digital intervention; GAD: generalized anxiety disorder; CBT: cognitive behavioural therapy; PDT: psychodynamic therapy

Assessment of the volume of unpublished data

One study was identified in registries which, according to the registry entry, is completed and should report potentially relevant results (see Table 13 of the full report). A query to the

responsible author revealed that the study was not published due to the results (non-significant effect of DI) and that a follow-up study was considered necessary due to what was perceived as limited patient selection. Since intended studies are not always registered (see also Table 22 of the full report), it is not possible to assess whether a similar approach was taken in further studies. An additional risk of bias due to unpublished study results can therefore not be ruled out, particularly in view of the fact that the authors of many of the published studies had financial conflicts of interest.

Weighing of benefits versus harms

The results of the meta-analyses show **moderate effects** in reducing GAD-related symptoms (14 studies) and improving quality of life (6 studies) and everyday functions (5 studies) with CBT DI compared to no treatment. The effects are the same across all studies, but the observed statistical heterogeneity shows differences in effect size. The results on GAD-related symptoms showed an effect modification by the age factor: stronger effects of DI were reported in the studies with older populations. Other potential effect modifiers analysed showed no influence. However, due to the lack of blinding and subjective outcome recording, the included studies all have a high **risk of bias**, which limits the certainty of the results. In addition, a **waiting list design** was used for the control group in 11 of the 14 studies. This study design can lead to overestimation of effects [66]. In addition, in 6 of the 14 included studies there are conflicts of interest due to financial connections of the authors to the manufacturing companies or direct financing of the studies by the manufacturing companies.

The outcomes used in the meta-analyses comparing CBT DI versus no treatment were surveyed on average about 3 months (between 1.5 and 9 months) after the start of the intervention. These results therefore do not provide any information on long-term effects. In 8 of 14 studies, an additional follow-up survey of the outcome “GAD-related symptoms” was conducted in the intervention group on average 10 months (between 3 and 36 months) after the start of the intervention. Table 24 of the full report provides an overview of the reported pre-post effects in the intervention groups. However, as there was no longer a control group in the follow-up survey due to the study design, it is not possible to determine whether these results are attributable to effects of the interventions or not.

Only a few of the included studies (systematically) recorded and reported adverse events: 3 of the 14 studies that compared CBT DI with no treatment and 4 of the other studies. In addition, some aspects were recorded as adverse events that coincide with GAD-related symptoms (e.g. anxiety, stress). Whether and, if so, how these could be distinguished from GAD-related symptoms was not discussed in the studies. Therefore, no conclusions can be drawn regarding the **potential for harm** from the interventions analysed.

5 Results: Health economic evaluation

5.1 Intervention costs

The costs of DIs are about as heterogeneous as the interventions themselves and partly depend on the number of users. The two applications analysed in the RCTs of the benefit assessment [4,58] and listed in the German DiGA directory and therefore eligible for reimbursement are reported to cost around €230 for 90 days. An extension option is available, resulting in costs of around €460 for six months of use and around €910 for a full year of use. Others offers analysed in the RCTs [41,43-56,59-65] that are currently available in Germany (at least in English) range in price from €0 to about €200 for a one-year period of use. This is to be seen as an example; a search for other DIs that may be available and their costs was not carried out for the purposes of this report. In the case of DIs that systematically include psychological support or that are used in conjunction with therapy, additional costs for psychological specialists/psychotherapy are incurred.

Face-to-face **psychotherapy** carried out in accordance with the psychotherapy guideline – using the example of behavioural therapy in an individual setting – costs a rounded minimum of €1510 for 12 appointments (corresponding to the short-term therapy according to the guideline). Long-term therapy with 60 appointments can cost over €7,000.[7] For group therapy, prices decrease progressively depending on the number of participants (with 9 being the maximum group size, the costs for therapy sessions are about 40% lower [67]).

For the two SSRIs escitalopram and paroxetine as a comparator **drug** intervention, the costs for a 6- to 12-month therapy with the cheapest preparation in each case remain in the range of (rounded) €30 to €110 for escitalopram and €40 to €210 for paroxetine. However, if at the beginning of the therapy the dosage has to be adjusted to the patient, the costs are higher due to (initially) smaller package sizes and the corresponding medical monitoring. According to the Summary of Product Characteristics (SPC), close monitoring is recommended in general or at least in cases of high suicide risk.

For all interventions, it was assumed that doctor's visits for clarification, diagnosis and prescription of therapy would take place. Costs for these visits were not factored into the calculations. Moreover, the DI generally requires patients to have an internet-enabled end device and internet access.

[7] As the guideline distinguishes between short-term and long-term therapy and also provides for ranges in the number of reimbursable sessions, the two figures are to be understood as minimum and maximum values (see also section A.4.1 of the full report).

5.2 Systematic review of health economic evaluations

5.2.1 Results of the information retrieval

The various search steps found a total of 2 relevant studies: Jankovic 2022 [68] and Kumar 2018 [69]. The search strategies for bibliographic databases are found in the appendix.

Table 4: Study pool of the health economic assessment

Study	Available documents [reference]
Jankovic 2022	[68], supplemented by: [70,71]
Kumar 2018	[69]

5.2.2 Characteristics of the studies included in the assessment

Both studies are heath economic analyses that use Markov modelling and include costs from the perspective of the public payers. Kumar 2018 also takes the social perspective into account. Both are based on a patient population of adults with GAD, whereby the proportion of people with a value ≥ 10 on the GAD-7 scale is 100% for Kumar 2018 and 82% for Jankovic 2022 (and of these, the largest proportion with a GAD-7 score between 10 and 14). Kumar et al. 2018 compare a CBT-based, coach-facilitated DI with individual CBT therapy and "treatment as usual" for the US health care system. They assume an intervention period of 3 months in each case. Based on a network meta-analysis, Jankovic et al. 2022 compare different strategies for the UK health care system: accompanied/unaccompanied DI, accompanied/unaccompanied digital control group (e.g. sham intervention), drug therapy (SSRI, sertraline), group therapy (CBT/mindfulness training), "treatment as usual" (incl. waiting list). Again, the intervention duration is assumed to be about 3 months, but for the SSRI, the costs of a 5-year therapy are included, which the authors consider a conservative assumption.

5.2.3 Results and limitations of the health economic evaluations

Kumar 2018 conclude that the CBT DI examined results in both a higher number of quality-adjusted life years (QALYs) and lower overall costs compared to CBT and also compared to “treatment as usual”. It is assumed that 70% of DI participants and 42% of CBT participants will improve by at least one of the three GAD-7 health states[8] as a result of the treatment. Only with a CBT response rate of 76% or more, as calculated by the team of authors in the sensitivity analysis, does CBT become cost-effective compared to CBT DI[9]. However, a major limitation is that the effect data come from completely different sources, for DI from a single-

[8] 5-9, 10-14, and 15-21 on the GAD-7 scale, see also Appendix Table 39 in the full report.

[9] The publication does not contain any numerical data.

arm, (apparently) unpublished pilot study and for CBT from a Cochrane Review (Hunot 2007, cited in Kumar 2018 [69]). Moreover, only univariate sensitivity analyses are carried out.

In contrast, Jankovic 2022 come to the conclusion that SSRIs are a dominant strategy compared to all other strategies, as they are associated with both a higher gain in QALYs and lower costs. Group therapy follows in 2nd place in the ranking (and is dominant over all strategies except SSRI). For their part, the two DIs are dominant compared to the two control groups (accompanied/unaccompanied digital control group) and compared to "treatment as usual"[10]. However, the certainty of the results is very low (wide, overlapping confidence intervals/low probability values in the probabilistic sensitivity analysis[11]). For the SSRI strategy, only the effect data of a very small triple-arm RCT comparing CBT-based DI with a control intervention and sertraline were included in the network meta-analysis (Christensen 2014 [64]), and for group therapy those of 2 studies (Navarro-Haro et al. 2019 and Topper et al. 2017, both cited in Saramago et al. 2021 [71]). Christensen 2014 was not considered for the benefit assessment in the present report due to high discontinuation rates[12], the other two studies were excluded from this report due to other criteria (see Section A9.1.2). The authors themselves note that the high level of uncertainty of results does not allow any reliable conclusions to be drawn. Another limiting factor is that although the SSRI strategy included a very long treatment duration and relatively close monitoring in line with British guidelines, as far as can be seen no assumptions were made regarding the inclusion of adverse effects.

The quality of the economic evaluation by Kumar 2018, which was financially supported by the CBT DI manufacturer, is considered low due to the limitations in the effect data and the lack of transparency in the presentation of the sensitivity analysis. From the outset, the authors describe their study as a case study or an application study in the context of developing a model and analytical framework to assess the cost-effectiveness of CBT DI for individuals with GAD. The quality of the economic evaluation of Jankovic 2022 is largely good, although it should be criticized that the quality of the SSRI effect data and the question of the inclusion of adverse effects are not addressed. Incremental results are only presented for the comparison of all (other) interventions versus the dominant intervention SSRI. However, the fact that the DIs are included in the model with a zero-cost assumption is particularly restrictive for the research question of the present report. According to the authors, a threshold analysis for intervention costs > 0 was planned but then not conducted due to the result (SSRI dominant compared to all other interventions). Thus, for the comparison of the

[10] However, it should be noted that the DIs were included in this modelling with a zero-cost assumption (i.e. only costs for therapeutic support for the accompanied DIs were included). A threshold analysis was planned, but was not carried out for this comparison (DI versus control) due to the overall result.

[11] For SSRIs, the team of authors calculated a probability of (only) 43% of the intervention actually being cost-effective assuming a willingness to pay £15,000 per QALY.

[12] In addition, their statistical power was insufficient (see Section 4.2).

two DIs (accompanied and unaccompanied) with the control groups (such as sham intervention, waiting list or "treatment as usual"), it can only be said that the DIs are a dominant strategy if they come at no cost. However, it is unclear up to what amount of intervention costs they remain a dominant intervention here or are still cost-effective assuming a willingness to pay £15,000 per QALY.

The transferability of the two studies to the research question to be analysed in this report is limited with regard to the level of the cost inputs used, and possible adverse events are not considered as an outcome in either study, and the effect data for Kumar 2018 were obtained from a single-arm pilot study. The Lantern intervention analysed in Kumar 2018 is no longer available as the company has ceased operations [52].

It is not possible to draw conclusions for the German health care context regarding the cost-effectiveness of DIs in GAD on the basis of the two included studies.

6 Results: Ethical, social, legal and organizational aspects

6.1 Results on ethical aspects

Individuals with GAD often experience significant psychological strain (see Section 1.2.1). Digital health interventions are generally considered to have great potential in terms of access to and use of health care services. This also applies to their use in connection with mental disorders [72-76]. At the same time, there is a broad body of literature that addresses ethical challenges in connection with digital health technologies. When addressing ethical aspects related to digital health interventions and mental disorders, the literature largely lacks a differentiation between different mental disorders, albeit anxiety disorders are explicitly mentioned [74,77,78]. Similarly, the literature found on ethical aspects of digital health interventions largely fails to differentiate ethically between browser-based and app-based approaches or between specifically guided and non-guided interventions or stand-alone solutions [77,79]. While the ethical challenges of the various applications are very similar, it can be assumed that some ethical issues are even more pressing in the case of stand-alone solutions.

Below, the identified ethical aspects are summarized along the principles of Beauchamp and Childress [27].

The literature sees the potential of DIs for mental disorders in **promoting patient well-being by providing low-threshold access to psychiatric and psychotherapeutic health care services.** It is assumed that patient groups that have more difficulty accessing appropriate health care services, for example due to geographical distance, fear of stigmatization due to a mental illness [72,73 2119,74,75,77], or because they are waiting for a therapy place [74,77].

The literature emphasizes a further advantage of DI for mental disorders: an **increase in autonomy and self-determination** for users [73,74,77]. Opportunities for autonomy are increased to the extent that users can decide for themselves when and at what pace they use the offers of the (app) programme and are thus enabled to make better use of their individual resources for self-determined action. By enabling independent learning, the sense of "self-efficacy" and self-control can be enhanced [73,74,77]. In order to support users' autonomy, medical and therapeutic professionals need sound knowledge of the possibilities and limitations of apps [74]. Self-determined decisions in this context also require evidence-based, participatory, process-oriented and transparent education. According to Rubeis and Steger, however, the form and quality of adequate education have rarely been discussed in the literature [74].

Facilitating access to psychiatric and psychotherapeutic health care services through DIs and strengthening the autonomy of users in claiming it are also linked to the expectation that **existing inequalities in health care can be levelled out**. At the same time, (international) studies show that digital health technologies are generally used more in urban areas, by people with a higher level of education and a higher economic status, and by younger people, and less by members of ethnic minorities and people with language barriers [76,80]. Furthermore, Rubeis and Ketteler state in their article that people with severe and recurrent mental disorders may not benefit to the desired extent. This also applies to people with limited health, reading, writing and media skills and a low affinity for web-based or mobile-based interventions [77]. **Existing inequalities can thus be exacerbated** if digital care services are introduced across the board with the aim of filling existing gaps in health care, but without taking into account the needs and characteristics of those patient groups that cannot benefit from digital services for the reasons mentioned. In addition, **new barriers to accessing** health care services can arise due to the cost of end devices or apps that are not affordable for socially disadvantaged people or for people who live in regions with poor internet connections or network density [72,73].

To ensure equality in acceptance and use, the digital health care services used in the treatment of GAD must also have a **truly user-friendly and participatory design** [80]. In addition, resources and time must be made available for **well thought-out dissemination and implementation strategies,** and **sufficient technical support** must be guaranteed for users [80].

In terms of distributive justice, it is important to focus on **vulnerable groups**, including **children and adolescents**. The WHO estimates that around 20% of children and adolescents worldwide are affected by a mental illness, which is almost double the rate of the general population. Anxiety disorders are the most common mental disorders in childhood and adolescence [75,79,81,82]. The present report analyses adults and adolescents aged 14 and

older; however, no relevant study for the group of adolescents with GAD could be identified. There are also highly vulnerable groups with special health care needs among refugees [83]. **Refugees** have a high prevalence of mental disorders, including anxiety disorders [84]. In their study, Wirz et al. point out that the effectiveness of digital interventions for refugees with mental disorders has not been sufficiently investigated to date, and they address the fact that refugees show a high discontinuation rate in existing online services related to mental health [83].

DIs are considered to have the potential to keep the health care system efficient despite the increasing demand for health care services [74,77,78]. Groß and Schmidt point out that DIs are **not integrated into established health structures, especially as a stand-alone solution**, and that they are currently not systematically embedded in concepts for providing health care services [73].

In order to comply with the **principle of non-maleficence**, several authors call for **uniform quality criteria** for digital health applications, as well as a **generally accepted method for their ethical evaluation and classification** [81,85,86]. In addition, Rubeis and Steiger point out that medical devices are subject to fewer requirements for market launch than medicinal products [74]. Likewise, **matters of liability and the handling of patient data** must be taken into account [73,78,87]. While guidelines regarding these points are laid down in the Digital Health Applications Ordinance (DiGAV) for products in the DiGA directory, questions remain unanswered for products that are available outside the DiGA directory. To avoid harm, **more emphasis should be placed on accompanying research** [73]. **Greater attention should be paid to adverse effects** and it must also be asked which patient groups do not benefit from the use of DIs and in which cases their use has a harmful effect on patient well-being [76-78]. Last but not least, questions about the ethical implications of non-guided applications need to be investigated more closely [74].

6.2 Results on social aspects

To analyse social aspects, studies were used in particular that examined the perspectives of users and experts on topics such as preferences, acceptance, conditions of use and challenges in connection with GAD and web-based or mobile-based interventions. The results of the survey of those affected were also used (see sections 3.5 and A12 of the full report). The results of the five interviews are not in competition with the results of the included studies; rather, the experiences of the interviewees serve to clarify or substantiate various aspects that are presented in studies at a higher level of abstraction.

The literature often points out that taking into account the personal situation, the different abilities and technical skills of users and their treatment preferences can increase patient satisfaction, effectiveness, acceptance and adherence to therapy [88-91]. As a **treatment**

preference, the included studies often emphasise personal contact (**face-to-face therapy**) with the therapist [89,92-95]. This preference is also reflected in the survey of those affected.

Aspects such as expectations, trust in the effectiveness, motivation and adherence to therapy are interwoven and important for successful treatment, even with web-based and mobile-based interventions. Huckvale et al [96] address in their study what was also expressed in the survey of those affected: A high variability of mood in people affected by GAD as well as temporarily emerging feelings of crisis and the heterogeneity of symptoms on an individual level pose major challenges for adherence to therapy. According to Huckvale et al., these challenges make it difficult to provide a "one-size-fits-all" app that is relevant to a particular person at a particular time [96]. A similar aspect is highlighted by Weisel et al. in their study, that in addition to being **overwhelmed by the content and pace, the lack of individualization** of the programme also represents an **obstacle to its use** [97]. This aspect was also mentioned several times in the survey of those affected. One of the interviewees put it this way in the interview: "The app was too broadly based: depression, suicidal thoughts, anxiety disorders, et cetera. The suggested measures were lacking in credibility. I thought to myself, I don't think they know what they're talking about. I realized straight away that they couldn't help me at all." Another interviewee said that the apps she used did not reflect the reality of her life in the situation at all. All but 1 of the respondents had quickly lost confidence in the effectiveness of the app programmes they were using and did not feel that they could help them. The fact that the **constant presence of apps can also be a hindering factor** is addressed by Schütz and Urban [78]. In the survey of those affected, several people also mentioned that this affected their motivation and commitment. The reminders and requests for action associated with the app programmes were sometimes perceived as stressful and disruptive or triggered the feeling of becoming dependent. One affected person did not perceive the reminders as negative, but tended to ignore them over time, so that they also lost their impact.

In the survey of those affected, one person cited the cost of the app as a **reason for discontinuing**, another person cited the end of the research project, and three people cited a lack of effectiveness and the associated negative feelings and perceived worsening of symptoms. One affected person said: “I felt that being confronted with the things I cannot manage made my condition worse”’ Another affected person said that "this good-humoured talking" made her feel even worse and that the fact that the app had no effect triggered the feeling: “How terrible I am.”

It should also be mentioned that key aspects for adherence to therapy with an app include the **commitment and enthusiasm of therapists** for the intervention, **or** a clear **recommendation** to this effect [98,99] (survey of those affected, see Section A12 of the full report).

The fact that there are sociodemographic and socioeconomic differences regarding the usage and benefits of web-based and mobile-based health interventions has already been

explained in the results on the ethical aspects. **The elderly** show a marked preference for non-digital treatment when it comes to mental health [89,100,101]. Nevertheless, digital interventions can prove successful for this target group as well, provided that they are user-friendly and tailored to the needs of the target group, as Riadi et al. [101] show in their systematic review.

Smart et al. show that while **adolescents** aged between 8 and 17 years appreciate the convenience of online sessions, they still prefer face-to-face sessions [102]. In their study, Dewa et al. analyse the evidence and impact of high-quality social relationships in the context of DIs in the treatment of anxiety and depression in **adolescents** aged between 14 and 24 years. They conclude that high-quality social relationships are an important and often underestimated component that can support the effectiveness of DIs for depression and anxiety in young people. Based on their research, they emphasize that high-quality relationships are characterized, among other things, by a sense of connection, confidentiality and belonging, while disconnection from the real world and a lack of awareness of body language are perceived as hindering [103].

Culturally sensitive services and competences on the part of the practitioners are necessary because members of **migrant communities and refugees** show a high prevalence of mental disorders and at the same time face barriers to accessing adequate health care services [77,83,84]. A study from Australia shows that migrants must also be perceived as a heterogeneous group when it comes to the use and benefits of web-based and mobile-based interventions for anxiety disorders: the results of the intervention are positive and comparable to autochthonous groups when the migrants have a high level of formal education [104].

6.3 Results on legal aspects

In Germany, the Digital Healthcare Act (DVG) created a legal basis for the prescription and reimbursement of DIs after scientific evaluation and inclusion in the DiGA directory. Inclusion in the DiGA directory is only possible for Class I or IIa medical devices[13]. These are defined as DIs intended for the "detection, prevention, monitoring, treatment or alleviation of disease" [105]. However, this purpose is based on the manufacturer's own definition. In principle, a DI with similar content to the DIs examined in this report (principles and elements of CBT, CBM, PDT) may or may not be classified as a medical device. In addition to the requirement for certification as a Class I or IIa medical device, further provisions in accordance with the DiGAV apply when applying for authorisation in the DiGA directory, in particular with regard to safety,

[13] On 30 August 2023, the Federal Cabinet adopted the Digital Act (DigiG), which provides for the DiGA provisions to be extended to medical devices in risk class IIb (https://www.bundesgesundheitsministerium.de/ministerium/gesetze-und-verordnungen/guv-20-lp/digig.html).

functionality, data protection, interoperability, user-friendliness and freedom from advertising [19].

DiGAs are reimbursed by the SHI if a corresponding application has been submitted to the Federal Institute for Drugs and Medical Devices (BfARM) and the product has been included in the DiGA directory. This requires a prescription from a physician or psychotherapist, or an existing diagnosis. Other DIs must usually be paid for privately.

Various laws and regulations apply to DIs not included in the DiGA directory. These include the Medical Devices Implementation Act (MPDG) for the corresponding purpose. In this case, DIs must obtain a CE marking in order to be distributed on the German market. Regardless of their classification as a medical device, all DIs are subject to data protection regulations under the GDPR. In addition, DIs claiming or advertising medical or therapeutic effects are subject to the provisions of the German Act on the Advertising of Medicinal Products (Heilmittelwerbegesetz, HWG) [106]. Manufacturers of DIs that are offered as apps agree to comply with certain guidelines in a distribution agreement with the respective app store [107-110]. These include provisions on data protection, inappropriate content, deception, intellectual property, unwanted software and malware, but are not identical across the various app stores. It is not possible to assess whether, and if so how, compliance with these guidelines is verified.

6.4 Results on organizational aspects

From an organizational perspective, digital interventions represent an opportunity to alleviate gaps or bottlenecks in psychotherapeutic health care either as a bridging solution or as an alternative to face-to-face therapy. Accordingly, in a survey conducted in 2021, around two thirds of German physicians and therapists surveyed rated the prescribability of DIs via the DiGA directory as positive. In the same survey, however, almost 90% of respondents rated their own DiGA knowledge as insufficient [111].

7 Discussion

7.1 HTA report compared with other publications

For the UK health care system, an HTA report (Gega 2022 [70]) was published in 2022, which is based on the systematic review used as the basis for this report (basic SR, Saramago 2021 [71]) and which also conducted a search for economic evaluations and a separate economic evaluation (Jankovic 2022, see Section A4.2.2). The authors of the basic SR (Saramago 2021) did not derive any benefit conclusions from their network meta-analyses, as the calculated confidence intervals were very wide and included the null effect. One exception was the comparison with drug therapy (sertraline). However, this was based on only one single RCT [64], which had to be excluded from the present report due to insufficient statistical power

and high discontinuation rates (see Section 4.2). When looking at the HTA report as a whole, Gega et al. 2022 also point to the low certainty of results and limitations. Having said this, however, they see a possible trend that DIs could take on a role as a "treatment of first choice" over no treatment or pure monitoring (but not over other therapeutic interventions).

The results of the benefit assessment of the present report differ significantly from Saramago 2021: In the benefit assessment of this report, a moderate effect of CBT DI in comparison with no treatment was calculated. The results of the individual studies are homogeneous, but the certainty of the results of the benefit conclusion is limited by the fact that all studies have a high risk of bias. These differences can be explained by a very different study pool: on the one hand due to the more recent search (about half of the included studies were published after the last search date of the basic SR), on the other hand due to stricter inclusion criteria regarding the population (6 studies that were included in the basic SR did not fulfil the inclusion criteria of the present report regarding the participants' GAD status).

7.2 HTA report compared with guidelines

The S3 guideline published in 2021 [10] explicitly endorses CBT-based internet interventions to bridge the gap or to accompany therapy, but not as a stand-alone treatment. In the context of the current results, this could possibly be differentiated or extended to other treatment and therapy methods such as mindfulness. However, there is no direct contradiction to this conclusion.

7.3 Critical reflection on the approach used

For the outcome of GAD-related symptoms, various instruments were combined in the present report that had been sufficiently tested and validated with regard to their suitability as screening instruments for GAD (see sections 3.1 and A3 of the full report). In addition to these instruments, a number of **other instruments** were used in the included studies to measure anxiety or worry; these were not considered in the present report. However, it can be assumed that the instruments validated for GAD screening are better suited to measure the relevant effects and that the other instruments used would not have provided any additional information. Furthermore, a number of instruments were used that assess various other symptoms (e.g. depressiveness). These additional results are not considered in the present report.

The search for literature in trial registries mainly serves the additional identification of completed studies and results. Since an unrestricted search returned too many hits, the hits were restricted to studies with results in order to obtain results with the greatest possible efficiency. It is therefore not possible to conclude which outcomes or parameters could yield (further) research results in the coming years.

7.4 Characteristics of the intervention and the comparator interventions

The intervention allows a **variety of different design options** at content, technical and organizational/personal level: over half of the studies were based on CBT and/or mindfulness principles, while some others used CBM principles, for example, or were tailored to specific subgroups. The majority of the DIs (where indicated) provided the intervention via a website, only a few via an app. Some of the DIs were offered with and some without (personal) support, whereby the type and role of support – a factor with high relevance for costs and care planning – varied greatly.

Despite these possible differentiations, the results of the meta-analysis were homogeneous in the benefit assessment and various subgroup analyses showed no differences (see Section 4.5). However, it was not possible to statistically analyse possible effects on the effectiveness of DIs, particularly with regard to the **extent and design of the accompanying support**. The descriptions in the study publications were too different in their level of detail to make a meaningful classification for subgroup analyses. Only the Dear 2015 study directly compared CBT-DI with and without support. It reported no significant differences. However, the results of this individual study with a high risk of bias are insufficient to derive a benefit conclusion.

Some authors [96,97], as well as those interviewed, mention the importance of a wide range of customization options with regard to the intervention, whereas a "one-size-fits-all app" is not considered suitable for this target group.

In most cases, the DIs in the studies are compared with untreated control groups or waiting lists, sometimes (in all compared groups) with concomitant medication. However, there are no meaningful **comparisons of DIs with face-to-face CBT or pharmacotherapy**. This could be partly due to the fact that the DIs make no claim of substituting these therapeutic options. Systematic reviews that examined the effectiveness of face-to-face CBT for anxiety disorders in general or for GAD in particular in reducing anxiety symptoms compared to no treatment reported pooled effects similar in size to the effect calculated in the present report [112,113]. However, in view of the frequently encountered hope that DIs can counteract unequal access to (psychotherapeutic) health care services – unequal, for example, due to staff shortages, geographical gaps in health care or fear of stigmatization/direct personal confrontation – a direct comparison with face-to-face CBT at least would be important.

7.5 Implementation in the health care system

In general, the summarized view makes it clear that several requirements must be taken into account for the successful implementation of DIs in the health care system. Some important points are regulated for the reimbursement sector (DiGA directory): clear declaration of the intended purpose of the product and certification as a medical device, availability of a

German-language version or a tested/validated German-language translation, easily accessible information on available DIs, on the underlying evidence, and on its place in the treatment process, questions of legal protection, for example with regard to data protection. Outside the reimbursement sector, the market is very heterogeneous and less regulated – for example, for DIs developed abroad or obtained via foreign websites. At the same time, DIs can be accessed easily compared to many other health interventions, and in some cases they even offer a "playful" approach. Sufficient dissemination of the above-mentioned information is important both for those affected and for therapeutic/medical staff in order to obtain a reliable overview of available services.

A stakeholder survey at Gega 2022 revealed that in practical experience, DIs contribute significantly less to disease recovery than reported in research results. It is possible that motivation and adherence play a different role in practice than in the study setting. The waiting list design used in many studies for the control group can also lead to an overestimation of effects [66]. However, ethical and social aspects also make it clear that Di design is driven not only by the general requirement for high user-friendliness, but also by the need to address target groups differentiated by age and ethnic/cultural background. Transferability of the study results to practice may also be relative due to the fact that there is often a pronounced preference for personal contact among those affected (see Section 6.2).[14]

8 Conclusion

The current study situation provides indications of **a benefit** of **digital interventions based on cognitive behavioural therapy** in comparison with no treatment in terms of disease-related symptoms, quality of life, and everyday functions. However, all included studies show a high risk of bias, which limits the certainty of the results. There is no hint of (greater or lesser) benefit for the outcome of GAD diagnosis (remission), and no data were reported for the outcomes of mortality, risk of relapse, and self-efficacy. There are also no hints regarding the potential for harm, as hardly any **adverse events** were recorded in the studies. For another intervention investigated – based on a mixture of cognitive behavioural therapy and cognitive bias modification – there was a hint of a benefit in terms of GAD diagnosis (remission), but not in terms of GAD-related symptoms (the other outcomes were not examined for this intervention). For all other comparisons – digital interventions based on cognitive bias modification in comparison with sham interventions and head-to-head comparisons between

[14] The DigiG Act (adopted by the Federal Cabinet on 30 August 2023) now provides for an application-accompanying performance measurement, the results of which are to be published in the DiGA directory [114].

digital interventions with different designs – there are no hints of (greater or lesser) benefit in relation to any of the outcomes analysed.

In Germany, digital interventions without therapeutic support or with only rudimentary personal support are lower in **cost** than face-to-face individual psychotherapy, but, depending on the product, they can be more expensive than drug therapy. The 2 economic studies identified do not allow conclusions to be derived on the **cost-effectiveness** of digital interventions for the German health care system.

From an **ethical** perspective, on the one hand there is the expectation that digital interventions can lead to improvements in access to health care services (e.g. during the waiting time for a therapy place) and generate gains in autonomy and self-determination if their effectiveness is sufficiently proven. On the other hand, these positive effects can only occur across different target groups if the implementation of appropriate accompanying measures is ensured and digital interventions are designed to suit the target group. In this context, accompanying (qualitative) research is important. Furthermore, **patient preferences** not only attach great importance to the individualization of the digital offering, but also to personal (i.e. non-digital) support. Not all affected individuals can be reached with digital interventions, and the individual and well-informed decision (for or against the use of a DI or for the selection of a specific DI out of the available ones) is particularly important across different age groups and socioeconomic groups. This further emphasizes the need for transparent information about digital treatment options and their framework conditions, including the **legal** regulations on data protection and product safety, both for those affected and for healthcare professionals. Clarification is needed of the different legal frameworks that apply depending on whether a digital intervention is declared as a medical device or not. From an organizational point of view, it is relevant that a considerable proportion of physicians and psychotherapists rate their own knowledge of DiGA as insufficient.

Missing data

With most studies lasting 2–3 months, no data are available on **longer-term effects**. None of the randomized controlled trials included a **comparison with face-to-face psychotherapy** (individual or group setting) **or pharmacotherapy**, and none of the included studies examined **adolescents aged 14 years and older**. Very few studies recorded **adverse events**, and if they did, it was often not done systematically.

Need for research

Valuable further insights could come from high-quality studies that (1) conduct **longer-term** follow-up surveys in intervention and control groups, (2) that also systematically assess quality of life and, in particular, potential **adverse events**, and (3) that directly compare digital interventions based on cognitive behavioural therapy with **face-to-face** cognitive behavioural

therapy. It is difficult or impossible to perform blinding and assess the outcomes objectively given the present research question. Therefore, a high risk of bias is also to be expected in future studies. This makes it all the more important to avoid further **risks of bias** – including deviations from study protocols and financial conflicts of interest of the authors in the studies included here.

In addition, the group of **(children and) adolescents** should be investigated in studies due to the prevalence and incidence of generalized anxiety disorder and the limited possibility of drug treatment.

A high number of ongoing studies is to be assumed.

Summary conclusion

Individuals with generalized anxiety disorder can benefit from digital interventions based on cognitive behavioural therapy, at least in the short term (average observation period 3 months). Meta-analyses with up to 14 studies provide indications of a benefit in reducing disease-related symptoms in comparison with no treatment as well as an improvement in quality of life and everyday functions. However, the current study situation does not allow any conclusions to be drawn about the long-term effects or possible adverse effects of digital interventions based on cognitive behavioural therapy. It is important for those affected and for health professionals that DIs are designed and used in a way that is appropriate for the target group, and that transparent and sufficient information is provided and disseminated about the treatment options and their framework conditions (including data protection and product safety regulations).

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Please see full HTA report for the full reference list.

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109. Apple. Apple Developer Program License Agreement [online]. 2023 [Accessed: 05.10.2023]. URL: https://developer.apple.com/support/terms/apple-developer-program-license-agreement/#ui-data-privacy

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The full HTA report (German version) is published under
https://www.iqwig.de/sich-einbringen/themencheck-medizin/berichte/ht22-02.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 [35] 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, the following overview indicates where the relevant information can be found (see Table 5). 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 6.2
Legal aspects (LEG)	**Legal aspects** Section 3.4; Section 6.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.4; Section 6.4

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1 – Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to November 02, 2022

The following filter was adopted:

- Systematic review: Wong [115] – High specificity strategy

#	Searches
1	exp Anxiety Disorders/
2	(anxiety* adj disorder*).ti,ab.
3	or/1-2
4	tele*.hw.
5	exp internet/
6	video games/
7	exp telephone/
8	exp microcomputers/
9	exp wearable electronic devices/
10	((web* or computer* or internet* or tele* or online* or remot*) adj3 (assisted* or based* or delivered* or supervised* or program* or intervention*)).ti,ab.
11	((video* adj1 (gam* or chat*)) or exergam* or telerehabilitation* or computeri#ed* or phone* or accelerometer* or app? or digital* or smart*).ti,ab.
12	or/4-11
13	cochrane database of systematic reviews.jn.
14	(search or MEDLINE or systematic review).tw.
15	meta analysis.pt.
16	or/13-15
17	exp animals/ not humans.sh.
18	16 not 17
19	3 and 12 and 18
20	19 and (english or german or multilingual or undetermined).lg.
21	..l/ 20 yr=2012-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"Anxiety Disorders"[mhe]
2	anxiety disorder*
3	#2 OR #1
4	* FROM 2012 TO 2022
5	#4 AND #3

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to December 21, 2022

The following filter was adopted:

- RCT: Lefebvre [116] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	exp Anxiety Disorders/
2	*Anxiety/
3	(anxiety* adj disorder*).ti,ab.
4	or/1-3
5	tele*.hw.
6	exp internet/
7	video games/
8	exp telephone/
9	exp microcomputers/
10	exp wearable electronic devices/
11	((web* or computer* or internet* or tele* or online* or remot*) adj3 (assisted* or based* or delivered* or supervised* or program* or intervention*)).ti,ab.
12	((video* adj1 (gam* or chat*)) or exergam* or telerehabilitation* or computeri#ed* or phone* or accelerometer* or app? or digital* or smart*).ti,ab.
13	or/5-12
14	randomized controlled trial.pt.
15	controlled clinical trial.pt.
16	(randomized or placebo or randomly or trial or groups).ab.
17	drug therapy.fs.

#	Searches
18	or/14-17
19	18 not (exp animals/ not humans.sh.)
20	and/4,13,19
21	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
22	hi.fs. or case report.mp.
23	or/21-22
24	20 not 23
25	24 and (english or german or multilingual or undetermined).lg.
26	25 and 20190601:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2022 December 21

The following filter was adopted:

- RCT: Wong [115] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	anxiety disorder/ or generalized anxiety disorder/
2	(anxiety* adj disorder*).ti,ab.
3	or/1-2
4	(internet* or tele* or game* or smart* or tracker* or wearable*).hw.
5	videoconferencing/
6	exp personal computer/
7	accelerometer/
8	((web* or computer* or internet* or tele* or online* or remot*) adj3 (assisted* or based* or delivered* or supervised* or program* or intervention*)).ti,ab.
9	((video* adj1 (gam* or chat*)) or exergam* or telerehabilitation* or computeri#ed* or phone* or accelerometer* or app? or digital* or smart*).ti,ab.
10	or/4-9
11	(random* or double-blind*).tw.
12	placebo*.mp.
13	or/11-12
14	and/3,10,13
15	14 not medline.cr.
16	15 not (exp animal/ not exp human/)
17	16 not (Conference Abstract or Conference Review or Editorial).pt.

#	Searches
18	17 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.
19	18 and 20190601:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 12 of 12, December 2022

#	Searches
#1	[mh "Anxiety Disorders"]
#2	[mh ^"Anxiety"]
#3	(anxiet* near/1 disorder*):ti,ab
#4	#1 or #2 or #3
#5	tele*:kw
#6	[mh internet]
#7	[mh ^"video games"]
#8	[mh telephone]
#9	[mh microcomputers]
#10	[mh "wearable electronic devices"]
#11	((web* or computer* or internet* or tele* or online* or remot*) near/3 (assisted* or based* or delivered* or supervised* or program* or intervention*)):ti,ab
#12	((video* near/1 (gam* or chat*)) or exergam* or telerehabilitation* or computeri?ed* or phone* or accelerometer* or app? or digital* or smart*):ti,ab
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14	#4 and #13
#15	#14 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#16	#15 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#17	#16 with Cochrane Library publication date Between Jun 2019 and Dec 2022, in Trials

4. PsycInfo

Search interface: Ovid

- APA PsycInfo 1806 to December Week 2 2022

The following filter was adopted:

- RCT: Eady [117] – combination of terms – small drop in specificity with a substantive gain in sensitivity

#	Searches
1	exp Anxiety Disorders/
2	*Anxiety/
3	(anxiety* adj disorder*).ti,ab.
4	or/1-3
5	tele*.hw.
6	exp internet/
7	video games/
8	exp Computer Assisted Therapy/
9	exp microcomputers/
10	((web* or computer* or internet* or tele* or online* or remot*) adj3 (assisted* or based* or delivered* or supervised* or program* or intervention*)).ti,ab.
11	((video* adj1 (gam* or chat*)) or exergam* or telerehabilitation* or computeri#ed* or phone* or accelerometer* or app? or digital* or smart*).ti,ab.
12	or/5-11
13	(double-blind or randomized or randomly assigned).tw.
14	and/4,12-13
15	14 not ((albanian or arabic or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or estonian or farsi iranian or finnish or french or georgian or german or greek or hebrew or hindi or hungarian or italian or japanese or korean or lithuanian or malaysian or nonenglish or norwegian or polish or portuguese or romanian or russian or serbian or serbo croatian or slovak or slovene or spanish or swedish or turkish or ukrainian or urdu) not (english or german)).lg.
16	15 and 20190601:3000.(up).

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: Expert Search

Search strategy
(web OR internet OR computer OR computerised OR computerized OR telerehabilitation OR telehealth OR telephone OR online OR remote OR video chat OR accelerometer OR app OR smart OR smartphone OR smartwatch) AND AREA[ResultsFirstSubmitDate] NOT MISSING AND AREA[ConditionSearch] Anxiety Disorder

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

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

Search strategy
anxiety AND (web OR internet OR computer OR computerised OR computerized OR telerehabilitation OR telehealth OR telephone OR online OR remote OR remotely OR game OR gaming OR video chat OR exergame OR exergames OR exergaming OR accelerometer OR app OR smart OR smartphone OR smartwatch) with results

B.1.3 Further information sources and search techniques

Web of Science (Thomson Reuters)

Suchtechnik
Citation Tracking: „Times Cited"

Pubmed

Suchtechnik
„Similar Articles“

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to January 26, 2023

The following filter was adopted:

- Gesundheitsökonomische Studie: Glanville [118] – Emory University (Grady)

#	Searches
1	exp Anxiety Disorders/
2	*Anxiety/
3	(anxiety* adj disorder*).ti,ab.
4	or/1-3
5	tele*.hw.
6	exp internet/
7	video games/
8	exp telephone/
9	exp microcomputers/
10	exp wearable electronic devices/
11	((web* or computer* or internet* or tele* or online* or remot*) adj3 (assisted* or based* or delivered* or supervised* or program* or intervention*)).ti,ab.
12	((video* adj1 (gam* or chat*)) or exergam* or telerehabilitation* or computeri#ed* or phone* or accelerometer* or app? or digital* or smart*).ti,ab.
13	or/5-12
14	(economic$ or cost$).ti.
15	cost benefit analysis/
16	treatment outcome/ and ec.fs.
17	or/14-16
18	17 not ((animals/ not humans/) or letter.pt.)
19	and/4,13,18
20	19 not (comment or editorial).pt.
21	20 and (english or german).lg.
22	21 and 20181101:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2023 January 26

The following filter was adopted:

- Gesundheitsökonomische Studie: Glanville [118] – Emory University (Grady)

#	Searches
1	anxiety disorder/ or generalized anxiety disorder/
2	(anxiety* adj disorder*).ti,ab.
3	or/1-2
4	(internet* or tele* or game* or smart* or tracker* or wearable*).hw.
5	videoconferencing/
6	exp personal computer/
7	accelerometer/
8	((web* or computer* or internet* or tele* or online* or remot*) adj3 (assisted* or based* or delivered* or supervised* or program* or intervention*)).ti,ab.
9	((video* adj1 (gam* or chat*)) or exergam* or telerehabilitation* or computeri#ed* or phone* or accelerometer* or app? or digital* or smart*).ti,ab.
10	or/4-9
11	(cost adj effectiveness).ab.
12	(cost adj effectiveness).ti.
13	(life adj years).ab.
14	(life adj year).ab.
15	qaly.ab.
16	(cost or costs).ab. and controlled study/
17	(cost and costs).ab.
18	or/11-17
19	and/3,10,18
20	19 not medline.cr.
21	20 not (exp animal/ not exp human/)
22	21 not (Conference Abstract or Conference Review or Editorial).pt.
23	22 and (english or german).lg.
24	23 and 20181101:3000.(dc).

3. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	"Anxiety Disorders"[mhe]
2	"Anxiety"[mh]
3	anxiety disorder*
4	#3 OR #2 OR #1
5	tele*
6	"Internet"[mhe]
7	"video games"[mh]
8	"telephone"[mhe]
9	"microcomputers"[mhe]
10	"wearable electronic devices"[mhe]
11	((web* or computer* or internet* or tele* or online* or remot*) AND (assisted* or based* or delivered* or supervised* or program* or intervention*))
12	((video* AND (gam* or chat*)) or exergam* or telerehabilitation* or computeri#ed* or phone* or accelerometer* or app? or digital* or smart*)
13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
14	#13 AND #4
15	(*) FROM 2018 TO 2023
16	#15 AND #14