ThemenCheck Medizin

Extract of HTA report

Developmental vision disorders[1]

Do children and adolescents benefit from active vision training?

Health technology assessment commissioned by IQWiG

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[1] Translation of Chapters 1 to 8 of the HTA report H21-03 *Entwicklungsbedingte Sehstörungen: Profitieren Kinder und Jugendliche von aktivem Sehtraining?* (Version 1.0; Status: 1 December 2022 [German original], 25 July 2023 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers.

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IQWiG coordinated the project, conducted the literature search for the domains “Benefit assessment“ and “Health economic evaluation”, and prepared the easily understandable summary (HTA compact).

Keywords: Orthoptics, Amblyopia, Refractive Errors, Strabismus, Benefit Assessment, Systematic Review, Technology Assessment – Biomedical

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

Publisher's comment

What is the background of the HTA report?

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

In a 2-step selection procedure, which also involves the public, up to 5 new topics are selected each year from among all submitted proposals. According to the legal mandate, these topics 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 the summer of 2021, IQWiG commissioned a team of scientists under the leadership of the Institute for Evidence in Medicine at Freiburg University to investigate the selected topic "HT21-03: Developmental vision impairment: Do children and adolescents benefit from active vision training?". 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 an ophthalmologist.

Why is the HTA report important?

Many children and adolescents are affected by developmental visual impairments, e.g. amblyopia, nearsightedness, and farsightedness. Amblyopia affects about 3.7% of the population in Europe [2]. In Germany, 11.4% of all children and adolescents aged 0 to 17 years are affected by myopia corrected with visual aids [3]. If treated too late or not at all, amblyopia is associated with lifelong functional impairment and reduced quality of life [4].

It is therefore important for developmental visual impairments to be treated early. In case of myopia or hyperopia, this is usually done with eyeglass lenses or contact lenses.

Amblyopia is often treated with occlusion therapy, where the unaffected, stronger eye is covered for certain periods of time, e.g. using a patch. In this way, the brain is stimulated to increase the visual acuity of the weaker eye. This is an established procedure for early amblyopia treatment in children [5].

Additionally, various vision training options are available for the treatment of developmental visual impairments: Optometrists, for instance, offer "visual training" in which different aspects of vision, e.g. fixation, focusing, eye movements, and visual perception, are specifically trained in multiple sessions to improve overall vision.

Some vision training programmes are carried out digitally on a computer or using virtual reality glasses. For instance, patients with amblyopia are shown "separate" images for the stronger and the weaker eye in an effort to improve both the visual acuity of the amblyopic eye and binocular vision (binocular training). Monocular procedures use background stimulation via moving sinusoidal gratings, which are intended to provide neurosensory stimulation to the weaker eye.

Concerns of those proposing the topic

A relative of the person proposing the topic had been offered vision training – a programme in which affected individuals perform various visual exercises regularly every 1 to 2 weeks over a period of 6 to 12 months under professional guidance. In light of this offer, the person proposing the topic wanted to know in which situations children and adolescents with vision problems may benefit from vision training.

Objective of the HTA report

In light of the interest expressed by the person proposing the topic, the commissioned team of experts investigated from the different perspectives of an HTA report whether children and adolescents suffering from a developmental visual impairment can be successfully treated with active vision training – i.e. vision training which requires regular and attentive participation of the affected persons. This would be the case, in particular, if it were demonstrated that active vision training results in a relevant improvement of visual acuity and binocular vision.

Which questions are answered – and which are not?

The external experts, led by the Institute for Evidence in Medicine, Freiburg, Germany, were able to identify a total of 17 studies which investigated vision training for developmental visual impairments. However, all of these studies focused on digital vision training for amblyopia. Neither studies examining vision training for the treatment of other developmental visual impairments nor studies investigating non-digital training were found.

The results found in the 17 studies of digital vision training for amblyopia are somewhat sobering. All studies report results on the outcome of "best-corrected visual acuity of the amblyopic eye." However, while some of the studies report small effects in favour of digital vision training, the external experts deem the effects too small to presume a benefit for those

affected. Likewise, none of the results found for all other outcomes, e.g. binocular vision or adverse events, showed any benefit of vision training.

When interpreting the results, it should be noted that the studies' treatment durations were often limited to only a few weeks, whereas the treatment of amblyopia usually takes several months or even years. Another problem plaguing the studies was the frequently low treatment adherence: The application of the digital vision training may be problematic, e.g. because younger children are overwhelmed by the digital training or adolescents are insufficiently challenged because the contents are too simple.

In Germany, digital vision training is used only as an add-on to occlusion therapy in the treatment of amblyopia. Therefore, the cost of digital vision training is incurred on top of the costs of standard treatment. For example, a 3-month treatment with a monocular vision training programme available in Germany costs €380 [6]. While statutory health insurance (SHI) usually covers the costs of occlusion therapy, it typically does not cover additional vision training. In addition, other free and paid training courses are offered on the Internet. Non-digital vision training courses exist as well, in which various vision exercises are performed under professional guidance. This HTA report does not provide any example costs of non-digital vision training.

The external experts also addressed the question of whether vision training for developmental vision impairments may be cost-effective. The authors of the HTA report did not find any studies investigating the cost-effectiveness of vision training. However, due to the lack of evidence of benefit, it appears that digital vision training is not cost-effective.

Undergoing occlusion therapy can be stressful for adolescents and their families, e.g. if the temporary covering of an eye leads to stigmatization of the affected person and subsequently to a rejection of therapy. If digital training were to replace or at least shorten occlusion therapy, it could potentially help relieve the burden on sufferers. But at present, digital vision training does not represent an alternative or suitable add-on due to the lack of evidence of benefit. Moreover, digital vision training may indirectly further the often already high consumption of digital media among children and adolescents.

What's the next step?

It is important to note the external experts' finding that there is currently no evidence showing any benefit of digital vision training for children and adolescents with amblyopia.

In addition, the person proposing the topic is particularly interested in the question of whether non-digital vision training may help individuals with amblyopia or other developmental vision impairments. However, no studies investigating non-digital training were found. In Germany, non-digital vision training (visual training) is offered by optometrists, for example. The costs

for such visual training may exceed €1,000 for 10 training units. These costs have to be borne out of pocket by the patients or their parents [7]. It would be desirable for expensive vision training courses to be offered only after their benefit has been demonstrated in studies.

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HTA key statements

Research question of the HTA report

The aims of this investigation are to

- assess the benefit of treatment with active vision training versus treatment without active vision training in children and adolescents with deficits in visual developmental in terms of patient-relevant outcomes

- determine the costs (intervention costs) and assess the cost-effectiveness of treatment with active vision training versus treatment without active vision training in children and adolescents with deficits in visual development as well as

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

Conclusion of the HTA report

A total of 17 randomized trials evaluating active digital vision training in children and adolescents were included in the present health technology assessment (HTA). The identified studies focused on patients with amblyopia (from anisometropia and/or strabismus). To date, no results from randomized trials have been published on other relevant deficits in visual development (refractive anomalies or eye misalignment) or on vision training interventions which are not digitally delivered.

Of the 17 included studies, 11 studies (with N = 1138 children and adolescents) evaluated the benefit of dichoptic (binocular) vision training, while 6 studies (with N = 165 children and adolescents) investigated the benefit of monocular vision training.

Dichoptic training was compared with (A) no training, (B) sham training, or (C) conventional treatment (occlusion). Treatment was provided at home in all but 1 study, where children and adolescents attended an outpatient clinic. In total, 2 studies evaluated children with amblyopia induced exclusively by anisometropia (refractive amblyopia). The remaining studies included amblyopia from anisometropia and/or strabismus. The age of the children and adolescents in the 11 studies on dichoptic training ranged from 3 to 17 years, and the proportion of those who had received prior treatment ranged from 26% to 96%. In 10 studies, dichoptic training was performed using a video game (e.g. Tetris), while in 1 study, participants watched films or series. The image separation required during dichoptic training was achieved via anaglyph glasses (8 studies), shutter glasses (1 study), or virtual reality glasses (2 studies).

Except in the 2 studies using virtual reality glasses, training was conducted on a computer or tablet.

In total, 6 studies investigated the benefit of monocular vision training compared with (A) no training or (B) sham training. In 4 studies, monocular training, where the stronger eye is occluded, was performed on an outpatient basis. Two studies evaluated only refractive amblyopia, and 4 studies investigated only 2- to 10-year-old children who had received their initial diagnosis. While monocular training involved playing a video game on a computer or tablet in 5 studies, 1 study asked children and adolescents to trace images which were presented digitally. Three studies used special background stimulation (a moving sinusoidal grating for neural stimulation) during monocular training. The remaining 3 studies did not use this background stimulation.

All studies reported data for the outcome "best-corrected visual acuity of the amblyopic eye". (A) Comparing active digital vision training with no training, significant effects were found in favour of active vision training – both dichoptic and monocular. The available study pool fails to show whether the additional occlusion treatment (which some studies used as add-on treatment in both intervention arms) enhances the effect of digital training. (B) When comparing vision training versus sham training, 1 of 6 studies described a statistically significant effect in favour of the investigated intervention. The missing effects in this comparison category could be due to the fact that the respective sham intervention (which was also based on vision training) showed the same effect as the experimental intervention. (C) Only studies on dichoptic training investigated digital vision training in the form of monotherapy versus occlusion treatment alone. Except for 1 study (with a treatment duration of only 2 weeks), no studies showed any statistically significant effects in favour of vision training – on the contrary, the effect estimators were in favour of occlusion treatment.

Although isolated studies suggest a statistically significant effect in favour of active vision training compared to no training or sham training for the outcome "best-corrected visual acuity of the amblyopic eye", the differences measured in these comparisons cannot be assumed to be clinically relevant. Most studies with statistically significant results do not meet a clinical relevance threshold of -0.05 logMAR (improvement by +0.5 lines) for the outcome "best-corrected visual acuity of the amblyopic eye". Only in 1 study, which compared monocular vision training versus no training, was the clinical relevance threshold exceeded at 1 of 4 measurement time points: The upper and lower limits (95% CIs) of measured mean differences after 9 weeks of treatment were -0.24 logMAR (+2.4 lines) and -0.06 logMAR (+0.6 lines), respectively.

In summary, for the outcome "best-corrected visual acuity of the amblyopic eye," no hint of (greater) benefit of digital dichoptic or monocular vision training was found in any of the comparisons: neither compared to no training nor to sham training or occlusion treatment.

For the patient-relevant outcome of binocular vision, none of the studies showed a hint of greater benefit of digital training – neither compared to no training nor to sham training or occlusion treatment.

In the present study pool, the number of reported adverse events was rather low, and no study showed any hint of an increased risk of such events – neither with digital training nor in the control group. However, it must be noted that the rather small number of study participants precludes drawing a reliable conclusion with regard to adverse events. No data are available on other patient-relevant outcomes.

In Germany, vision training is currently used only as an add-on to occlusion treatment. The average total costs per person for occlusion treatment in the 1st year of treatment are between €606 and €646, which is largely covered by the statutory health insurance (SHI); 2/3 of the costs are for the aids used in the treatment. In addition to these costs, 3 months of treatment with the monocular vision training offered in Germany by the company Caterna Vision GmbH would cost €380. Some health insurance funds cover the costs for the vision training within the framework of selective contracts. Apart from the costs presented for monocular visual training by Caterna Vision GmbH, no further data were available from which a reliable cost estimate for active vision training might be derived. In summary, for vision training to be cost-effective, the additional costs must be associated with either greater benefit (in the form of better treatment outcomes) or savings in conventional treatment (e.g. through reduced treatment times for the same benefit). Since neither of these conditions is currently met, the cost-effectiveness of active vision training in amblyopia cannot be conclusively assessed. Given that no studies were found on other relevant developmental vision impairments or on other non-digitally delivered vision training, extending the economic evaluations to other therapeutic indications or interventions was not deemed useful.

When making decisions regarding digital training, the early and risk-associated access to digital media and the increased media consumption associated with such therapy must be considered critically from ethical and social perspectives. In terms of adherence to the prescribed therapy, study data additionally show that problems and treatment discontinuations repeatedly occur in practice. These are often due to a lack of understanding of the video game and/or patients being overchallenged (especially younger children) or underchallenged (especially older children and adolescents) because the 'health games' offered are typically video games with a simple design (e.g. Tetris). With regard to the home therapy concept, retaining attention therefore plays a critical role in active vision training.

Overall, the available evidence does not allow drawing a final conclusion on the benefit of active vision training in children and adolescents with amblyopia. Alongside the frequent lack of treatment adherence, it is important to note that the studies' treatment duration was set to only a few weeks, while amblyopia treatment is often required for many years.

Furthermore, it was impossible to deduce from the heterogeneous study pool whether children with refractive amblyopia achieve better results than children with amblyopia from strabismus. Such results would be important for the benefit assessment of digital therapies, however, in order to better assess which patients benefit most from such therapy. In addition, further studies are needed to determine whether more interesting (possibly also non-digital) games or vision training interventions lead to better treatment adherence and possibly also show greater benefit with regard to patient-relevant outcomes – especially in older children. Overall, it can be concluded that the outcomes of the new therapies were not superior.

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List of abbreviations

Abbreviation	Meaning
BGB	Bürgerliches Gesetzbuch (German Civil Code)
CAM	Cambridge Vision Stimulator
CI	confidence interval
DVG	Digitale-Versorgung-Gesetz (Digital Health Care Act)
ETHMED	Ethics in Medicine
EUnetHTA	European Network for Health Technology Assessment
GDPR	General Data Protection Regulation
HTA	Health Technology Assessment
ICD	International Classification of Diseases
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAR	minimum angle of resolution
MBO	Muster-Berufsordnung für Ärzte (Model Medical Code of Practice)
MD	mean difference
MDR	Medical Device Regulation
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance
SSCI	Social Science Citation Index
VR	virtual reality
WHO	World Health Organization

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 to patient care.

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

IQWiG disseminates HTA reports to German institutions, for instance, those deciding about healthcare services and structures. The HTA report will be made available to the professional community through the 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 Differentiation of the clinical picture

Diseases of the eye include a wide spectrum of different disorders and/or impairments (ICD-10-WHO, H00-H59) [1]. The developmental vision disorders (deficits in visual development) described below occur frequently in children and adolescents [2-8] and are therefore deemed relevant for the research question of the HTA.

Amblyopia

Amblyopia (lazy eye) is due to abnormal visual development in early childhood. Amblyopia often results from severe, uncorrected (unilateral) refractive anomalies. In the presence of such refractive errors, only blurred image contours are imaged on the retina, which precludes optimal development of visual acuity. In addition to uncorrected refractive anomalies,

misalignment of the eyes (e.g. strabismus or crossed eyes) can also lead to amblyopia. This is especially true if such a defect is already present in infancy or childhood. In this case, both eyes are physically healthy, but different "images" are received on the respective sites of sharpest vision (*foveae centrales*) as well as on other corresponding retinal sites. To avoid such double images, the visual system suppresses the visual impression from 1 eye. During the particularly sensitive phase of visual development, which lasts approximately until the 6th year of life [7], this suppression means that the corresponding eye cannot develop sufficient visual capacity [9]. Deprivation triggered, for example, by congenital upper eyelid ptosis (drooping upper eyelid) or cataract can also cause amblyopia [5].

A systematic review from 2018 which evaluated data from 73 international studies reported a worldwide amblyopia prevalence of 1.8% (95% confidence interval [CI]: 1.6%; 1.9%) [6]. The highest prevalence was found in Europe at 3.7% (95% CI: 2.9%; 4.5%). In an analysis stratified by age, the authors also reported a prevalence of 3.8% (95% CI: 2.9%; 4.6%) in children and 3.3% (95% CI: 0.6%; 6.0%) in adults. The main cause of amblyopia was anisometropia (different refractive power in the right versus left eye) (in about 62% of patients) [6].

However, studies on the prevalence of amblyopia often exhibit limited inter-study comparability because the definitions of amblyopia often differ due to the absence of an internationally accepted agreement. For example, according to Bangerter, preschool children are said to have mild amblyopia at visual acuity values of 0.8 to 0.4, moderate amblyopia at values of 0.3 to 0.1, and severe amblyopia at values < 0.1 [10]. These data refer to visual acuity measured with the Snellen chart (single optotypes). In general, amblyopia is suspected if visual acuity is more than one decadic logarithmic step below the expected normal visual acuity for the patient's age. The normal visual acuity expected based on age can be found in the guideline of the German Ophthalmological Association (BVA) and the German Ophthalmological Society (DOG) [5].

Refractive anomalies

Like hyperopia (farsightedness), myopia (nearsightedness) is a refractive anomaly. This vision defect is characterized by a mismatch between the axial length of the eyeball and the refractive power of the eye. In myopes, the focal point of the incident light rays is in front of the retina, while in hyperopes, it is behind it. Astigmatism (corneal curvature) can occur alone or in combination with myopia or hyperopia. A difference in the refractive power of the 2 eyes is called anisometropia.

It is estimated that myopia affected approximately 1.5 billion people (about 1/4 of the total population) in 2014 [4]. The German Child and Adolescent Health Survey (KiGGS) suggests a myopia prevalence of 11.4% (95% CI: 10.7%; 12.2%) among children and adolescents aged 0 to 17 years (surveyed between 2014 and 2017) [11]. According to studies, the proportion of

myopic individuals in the overall population is increasing but varies widely internationally [4]. For example, in Southeast Asian metropolitan areas, the prevalence rate increased from 20% in 1940 to 80% in 2015 [12]. Hyperopia prevalence (with values of +2 dioptre or higher) was reported to be 4.8% in an English cohort study evaluating 7825 children aged 7 years (surveyed between 1998 and 2000) [2].

Eye misalignment

Strabismus or crossed eyes refers to a disorder of ocular mobility that is often associated with amblyopia (see above) and impaired binocular vision. Strabismus is divided into 3 groups [7]: (i) heterophoria (latent strabismus); (ii) manifest strabismus (e.g. concomitant strabismus of one eye or alternately of both eyes or microstrabismus); and (iii) acquired strabismus (due to damage to the brain nuclei, nerves, or muscles). While heterophoria can usually be compensated and is present in about 70% to 80% of all people, manifest strabismus affects about 1% of the Central European population [13]. Acquired strabismus is found mainly in adults, typically as a consequence of a localized lesion (stroke) and requires neurological evaluation.

1.2.2 Burden of disease

Visual deficits are associated with a high burden of disease. For example, myopia has been ranked by the World Health Organization (WHO) as one of the leading causes of blindness and visual impairment. It is also one of the top 5 diseases of the eye, and its control is a high priority. In particular, in addition to the age factor, pronounced myopia is the main risk factor for degenerative eye diseases such as cataract, glaucoma, retinal detachment, and myopic macular degeneration [14,15]. Thus, reducing myopia progression in childhood and adolescence is of particular importance. In addition to refractive anomalies, which are usually correctable by optical aids (such as glasses or contact lenses), amblyopia plays a major role in childhood. This visual impairment is acquired in childhood and – if treated too late or not at all – is associated with lifelong functional impairment and reduced quality of life [16]. In addition, conventional occlusion therapy, which is commonly used for the treatment of amblyopia, is associated with a reduced quality of life for adolescents and their families [17]. Furthermore, individuals with unilateral amblyopia are at 2 to 3 times higher risk of bilateral visual impairment than those without amblyopia. Furthermore, the cumulative lifetime risk of bilateral visual impairment in a population-based Dutch study was estimated to be 18% in the presence of unilateral amblyopia and 10% in nonamblyopic individuals [18].

1.2.3 Treatment

Amblyopia

Conservative (conventional) amblyopia treatment consists of refraction correction or occlusion treatment or a combination of both [5]. Occlusion involves periodically taping the

unaffected (stronger or dominant) eye (for a fixed duration) using a patch or film. Forcing fixation with the weaker eye encourages the visual centre to take into account the visual impression from the amblyopic eye. This measure is intended to improve visual acuity. In addition to occlusion treatment, atropine penalization ("nebulization") of the stronger eye is used to increase the visual acuity of the amblyopic eye [19]. However, this treatment method is not (or only very rarely) used in Germany, because – as with myopia treatment – this drug has not been officially approved for amblyopia treatment.

In addition to conventional treatment methods based on suppressing the stronger eye for a certain period of time using a patch or film, new (mainly digital) training methods, often based on perceptual learning methods, have been developed in recent years [20-23].

Dichoptic (binocular) training is a therapy method based on image separation. In addition to improving the visual acuity of the amblyopic eye, it is intended to improve binocular vision (including stereopsis) [20,21]. The 2 eyes are presented with "separate" images. While the stronger (dominant) eye is presented with image components (stimuli) at reduced contrast (including brightness-reduced and/or blurred components), the amblyopic eye is presented with high-contrast image components. For this visual training, various interactive video games or films have been developed or edited to include different high-contrast image components. For example, in order to be successful in a dichoptic video game, both eyes must perceive the appropriate image components (contrast elements) and solve the presented tasks, which in turn is only possible in the presence of sufficient fusion of the image components. In the course of the treatment (as soon as the function of the amblyopic eye improves), the contrast of the image component perceived by the dominant eye is increased. This process is continued until, ideally, fusion ability is achieved with image components having the same contrast. Image separation in dichoptic training can be accomplished using a variety of techniques. Often, colour separation using anaglyph glasses (red-green glasses) is used. Yet image separation can also be achieved using shutter glasses (liquid crystal-coated glasses which can be electronically switched between transparent and opaque). In addition, various headsets in the form of virtual reality (VR) glasses are used.

In addition to dichoptic training methods, digital monocular vision training methods are available. In the monocular methods, background stimulation (through moving sinusoidal gratings) is combined with an interactive computer game in the foreground. While the computer game serves to increase motivation, the weaker eye receives neurosensory stimulation through the drifting sinusoidal grating with the aim of improving visual acuity. In Germany, for example, interactive monocular vision training devised by Caterna Vision GmbH on the basis of such a stimulation procedure is used as a supplement to conventional occlusion treatment [24].

Refractive anomalies

With the help of eyeglass or contact lenses (optical aids), sharp vision can usually be restored in children and adolescents with refractive anomalies. Myopia usually begins at elementary school age and, on average, stops progressing after puberty; particularly in this therapeutic indication, therefore, various procedures are used to counteract progression or even to achieve a decrease in the existing refractive error. Besides experimental optical interventions (e.g. multifocal lenses), pharmacological treatments such as atropine are used [3]. In Germany, however, this pharmacological treatment has not been officially approved (off-label treatment). A 2000 review also describes various vision training interventions (referred to in the paper as visual training), e.g. the "Bates method", "biofeedback", and other eye relaxation and movement exercises [25].

Eye misalignment

In case of eye misalignment, the primary treatment goal is to minimize unfavourable effects on the visual capacity of the affected eye and to increase the quality of binocular vision (see above, amblyopia treatment). In addition, surgical procedures are used to correct the misalignment.

1.3 Health services situation

In Germany, a dense network of outpatient and inpatient ophthalmologic facilities exists for the care of patients with eye diseases. At the end of 2020, a total of 10 862 ophthalmology specialists were registered with the medical associations [26]. Ophthalmologists are often assisted by orthoptists [27]. This is an allied health profession in the field of ophthalmology. In particular, orthoptics encompasses the prevention, diagnosis, and therapy of developmental visual deficits, e.g. strabismus and visual impairment.

To ensure appropriate care for patients with eye diseases, several guidelines have been written by the Professional Association of German Ophthalmologists and the German Ophthalmology Society. Several guidelines exist in addition to a relatively recent S2k guideline (guideline with formal consensus) from 2017 on visual perception disorders, which involved not only the German Ophthalmology Society but also other non-ophthalmological professional societies [7]. Most notable among these are the guidelines on basic ophthalmic diagnosis in children, recommendations on the optical correction of refractive errors, and recommendations on strabismus and amblyopia [28].

The monocular training offered by Caterna Vision GmbH [24] and performed in combination with occlusion treatment has been prescribed in about 350 ophthalmic practices or clinics in Germany (as of 2020). The approximate costs of €380 for the treatment, which the manufacturer reported to have been performed more than 1800 times thus far, was covered by 36 statutory health insurers (SHIs) and 4 private health insurances as part of selective

contracts in 2020 [29]. Treatment coverage requires that the adolescents be between 4 and 16 years of age, have a functional visual impairment (amblyopia), have been unsuccessfully treated with occlusion in the form of monotherapy, and use the Caterna app under medical supervision [30]. In addition to a medical prescription, a computer, laptop or tablet, and an Internet connection are required for therapy at home.

In addition to this computer-based therapy explicitly developed for amblyopia, a wide variety of offers – both paid and free – can be found on various German-language websites [31,32] to train vision.

1.4 Concerns of those proposing the topic

A relative of the person proposing the topic was offered vision training – a programme in which affected individuals perform various visual exercises regularly every 1 to 2 weeks over a period of 6 to 12 months under professional guidance. Against this background, the person proposing the topic asks in which situations children and adolescents with vision problems may benefit from vision training and whether the costs for such training are covered by SHI.

2 Research questions

The aims of this investigation are to

- assess the benefit of treatment with active vision training versus treatment without active vision training in children and adolescents with deficits in visual developmental in terms of patient-relevant outcomes
- determine the costs (intervention costs) and assess the cost-effectiveness of treatment with active vision training versus treatment without active vision training in children and adolescents with deficits in visual development as well as
- review ethical, social, legal, and organizational aspects associated with the medical intervention.

3 Methods

3.1 Methods – benefit assessment

The target population of the benefit assessment consists of children and adolescents up to the age of 18 who suffer from a monocular or binocular deficit in visual development (amblyopia, refractive anomaly, eye misalignment according to Section 1.2.1). The experimental intervention was active vision training guided by an appropriately qualified person. The comparator intervention was sham training, standard treatment (e.g. occlusion treatment for amblyopia), surgical intervention, drug treatment, no vision training (no treatment).

The following patient-relevant outcomes were taken into account for the assessment:

- Morbidity, defined as visual acuity
  - visual acuity, binocular vision, refraction value, strabismus angle
  - where the outcome of “visual acuity” is dependent on the existing visual deficit in accordance with Section 1.2.1.
- Adverse events
- Health-related quality of life
- Health-related social and educational functioning, e.g.
  - stigmatization and school failure

In addition, treatment adherence, intervention-related and disease-related effort, and satisfaction of the children and adolescents with the treatment were taken into account. Based on these outcomes alone, (greater) benefit was not found.

In studies which used different methods to assess vision, data were extracted for the method which was most frequently used by the other studies. In the present study pool, visual acuity was mostly reported as minimum angle of resolution (MAR). This is the reciprocal of visual acuity, and the logarithm of MAR (logMAR) was used for averaging the resolution.

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 database (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.

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 systematic review(s). Otherwise, the search for studies was carried out without time restriction.

A systematic literature search for primary studies was conducted in the following databases:

- MEDLINE, Embase, Cochrane Central Register of Controlled Trials

The following sources of information and search techniques were also used:

- study registries, viewing of reference lists, 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, outcome-specific and study-level criteria for the risk of bias were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were described in the order of outcomes.

In addition to the comparison of the individual studies' results, the plan also called for metaanalyses and sensitivity analyses and for investigating effect modifiers, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was drawn regarding the evidence 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 neither of the above 3. The latter was the case if either 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.

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, in addition to the experimental and comparator interventions, the services directly associated with the intervention were taken into account. The relevant regulated or negotiated prices of these services were used wherever possible. Where a therapy took more than 1 year, the average annual cost per patient was reported. Reimbursable costs were listed separately from non-reimbursable costs.

Comparative studies drawing conclusions on cost-effectiveness (cost-effectiveness analyses or efficacy analyses, cost–utility analyses, cost–benefit analyses) of the experimental

intervention were to be included in the systematic review of health economic studies. In the event that no such studies were found, studies with a comparison limited to the costs of the experimental intervention and the comparator intervention (cost-cost analyses) were to be analysed. Further criteria for study inclusion were the availability of a full publication in German or English and the contextual relation to Germany or another high-income economy.

The search for suitable health economic studies was conducted systematically via a focused information retrieval in the following databases:

- MEDLINE, Embase, HTA Database

Reference lists of the identified systematic reviews were taken into account as additional sources of information.

The publications found in the search were selected by 1 reviewer, and quality assurance was performed by a 2nd reviewer.

In the event that appropriate studies had been identified, the following steps were to be taken: data extraction into standardized tables, assessment of reporting quality, assessment of transferability of results, and a comparative description of the results of each study as part of an information synthesis.

3.3 Methods – ethical, social, legal, and organizational aspects

The target population relevant for this HTA report (children and adolescents) is generally more vulnerable due to their age, since they themselves cannot give consent to treatment or can do so only to a limited extent. Given their role in therapeutic decision-making, parents and legal guardians of affected children and adolescents are therefore included in the analyses of ethical, social, legal, and organizational aspects.

3.3.1 Ethical aspects

The ethical analysis and evaluation is based on the framework for public health interventions developed by Marckmann 2015 [33].

In a 1st step, the normative framework for the ethical analysis was identified and modified to fit the specific question. In a 2nd step, scientific literature as well as other non-scientific sources of information were used for the content analysis and supplemented by the results of the other domains. Finally, in the 3rd step, the survey of affected people as well as the "reflective thoughts" of the authors of the report were used.

The normative framework of the ethical analysis is fundamentally based on the well-known principles of medical ethics: beneficence, nonmaleficence, and respect for autonomy and

justice [34]. Through the included public health perspective, however, the framework goes beyond the individual and requires appropriate justification for the intervention(s) under investigation [35].

For the analysis of ethical aspects, scoping searches were conducted in the following databases:

- Ethics in Medicine (ETHMED) and Philosopher's Index and Social Science Citation Index (SSCI)

In addition, national registries, laws, regulations, and websites of relevant institutions, providers, and stakeholders were screened for further ethical aspects. To put potential benefits and harms as well as cost-effectiveness into concrete terms, the results of the HTA domains "benefit assessment" and "economic assessment" were used. In addition, relevant contents of the social, legal, and organizational aspects were integrated. Furthermore, the results of the stakeholder survey and "reflective thoughts", i.e. reflective thinking about possible ethical arguments and aspects based on the knowledge of the report authors, were used as sources of information [36].

One person checked the documents for conclusions on ethical arguments and aspects of the technology to be investigated, and quality was assured by a 2nd person.

All arguments and aspects necessary for information processing were extracted into tables.

3.3.2 Social aspects

In the HTA, social and sociocultural aspects address the mutual interactions between examination/treatment methods and the social environment (e.g. resource distribution in society, access to technologies, patient preferences, social norms, and values). The information processing on social aspects was based on the comprehensive conceptional framework proposed by Mozygemba 2016 [37].

For the analysis of social aspects, scoping searches were conducted in the following databases:

- MEDLINE and SSCI

These searches were supplemented by website-based searches. In addition, the studies included in the benefit assessment and the patient interview protocols were reviewed for social aspects. Furthermore, "reflective thoughts", i.e. reflective thinking based on the knowledge of the report authors, were used [36].

One person checked the documents for conclusions on social arguments and aspects of the technology to be investigated, and quality was assured by a 2nd person.

All arguments and aspects necessary for information processing were extracted into tables.

3.3.3 Legal aspects

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

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

- databases (Federal Court of Justice [BGH], Federal Legal Information System, "Juris" and "Beckonline"), national and regional registers, laws, regulations or guidelines, interest-based information sources (for example, websites of interest groups).

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

The check of the documents for statements on legal arguments and aspects of the technology to be investigated was conducted by 1 person. A 2nd person assured the quality of the result.

All arguments and aspects necessary for information processing were extracted into tables.

3.3.4 Organizational aspects

Organizational aspects comprise the interactions resulting from a treatment method with the organization of care.

The information processing of organizational aspects followed the grid template proposed by Perleth 2014 [39] for the assessment of the organizational consequences of treatment methods.

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

- Medline and the guideline database of the Association of the Scientific Medical Societies in Germany (AWMF)

This search was supplemented by website-based searches. In addition, studies which were included in the benefit assessment were screened for organizational aspects. Furthermore,

the protocols of the stakeholder interviews were screened for organizational aspects, and reflective thoughts were used [36].

The review of documents for statements on organizational aspects of the investigated technology was done by 1 person. A 2nd person assured the quality of the result.

All arguments and aspects necessary for information processing were extracted into tables.

3.4 Interviews with affected people

During the generation of the HTA, patient-relevant aspects, relevant subgroups as well as relevant ethical, social, legal, and organizational aspects were discussed with affected people. For this purpose, one-on-one interviews were conducted with the mothers of 2 affected children using an interview guide that was provided to the families in advance and discussed with the children within the family. The aspects reported by the patients' mothers were used for the preparation of the HTA (especially for the definition of patient-relevant outcomes, but also for the ethical, social, legal, and organizational aspects).

4 Results: Benefit assessment

4.1 Results of the comprehensive information retrieval

No systematic reviews were rated as being current and of high quality and included for the identification of primary studies.

The information retrieval found 17 RCTs relevant to the research question (21 publications, including 2 design publications) which examined digital vision training in children and adolescents with amblyopia. No RCTs were identified for other relevant developmental vision disorders (refractive anomalies or eye misalignment) or vision training interventions which were not digital.

In addition, 3 planned studies (each for the therapeutic indication of amblyopia) and 14 ongoing studies (amblyopia N = 13, eye misalignment N = 1) were identified. Furthermore, 15 studies of unclear status (amblyopia N = 8, refractive anomalies N = 3, eye misalignment N = 4) as well as 1 discontinued and 2 completed studies (each for the therapeutic indication of amblyopia) without reported results were found. Table 10 of the full report lists the above studies together with their status of planned, ongoing, discontinued or completed, or unpublished.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search in bibliographic databases was conducted on 28 October 2021, while the last search in study registries was on 1 December 2021.

Table 1: Study pool of the benefit assessment

Study	**Available documents**		
	Full publication	**Registry entry**	**Other documents**
Dichoptic training			
Dichoptic training vs. no training			
Without additive occlusion			
Holmes (2019)	Yes [40]	Yes [NCT02983552] [41]	No
Xiao (2022)	Yes [42]	Yes [NCT03608150] [43]	No
With additive occlusion			
Rajavi (2016)	Yes [44]	Yes [NCT02740725] [45]	No
Yao (2020)	Yes [46]	Yes [NCT02200211] [47]	No
Dichoptic training versus sham training			
Herbison (2016) Foss (2013)	Yes [48] Yes [50]	Yes [NCT01702727] [49]	1 study (2 publications, including 1 design publication [50])
Gao (2018) Gao (2021)	Yes [51] Yes [54]	Yes [ACTRN12613001004752] [52]	1 study

Guo (2016)	Yes [53]		(3 publications, including 1 design publication [53])
Dichoptic training versus occlusion			
Holmes (2016)	Yes [55]	Yes [NCT02200211] [47]	No
Manh (2018)	Yes [56]	Yes [NCT02200211] [47]	No
Rajavi(2019)	Yes [57]	Yes [NCT03940222] [58]	No
Birch (2020) Kelly (2016)	Yes [59] Yes [61]	Yes [NCT02365090] [60]	1 study (2 publications)
Yao (2020)	Yes [46]	Yes [NCT02200211] [47]	No
Rajavi (2021)	Yes [62]	Yes [NCT04261868] [63]	No
Study	**Available documents**		
	Full publication	**Registry entry**	**Other documents**
Monocular training			
Monocular training vs. no training			
Without additive occlusion			
Iwata (2018)	Yes [64]	No	No
With additive occlusion			
Dadeya (2016)	Yes [65]	No	No
Monocular training vs. sham training (digital vs. non-digital)			
Jukes (2019)	Yes [66]	No	No
Monocular training vs. sham training (with stimulation vs. without stimulation)			
Kämpf (2001)	Yes [67]	No	No
Bau (2012)	Yes [68]	No	No
Yeh (2021)	Yes [69]	Yes [NCT04213066] [70]	No
vs.: versus Yao2020 is a 3-arm study and is shown twice in the table.			

4.2 Characteristics of the studies included in the assessment

Table 2 shows the relevant study pool for the therapeutic indication of amblyopia, stratified by intervention (dichoptic training or monocular training) and comparator treatment (no training, sham training, occlusion). Because no studies were identified for other developmental vision disorders, these therapeutic indications are not further discussed in the results section of the benefit assessment.

Dichoptic training

A total of 11 studies (15 publications [40,42,44,46,48,50,51,53-57,59,61,62], including 2 design publications [50,53]) examined the benefit of dichoptic training compared with (a) no training [40,42,44,46], (b) sham training [48,51], or (c) standard treatment (occlusion) [46,55-57,59,62]. In this regard, the study by Yao 2020 [46] reported 2 comparisons: dichoptic

training versus no training (each combined with occlusion treatment) and dichoptic training versus occlusion treatment (each as monotherapy). Training took place at home in all studies, except the study by Herbison 2016 [48], which provided treatment on an outpatient basis.

In total, 2 studies evaluated children with amblyopia induced exclusively by anisometropia (refractive amblyopia) [44,46]. The remaining studies included amblyopia caused by anisometropia and/or strabismus. Furthermore, non-pretreated patients were evaluated alongside pretreated patients. The proportion of the pretreated population ranged from 26% [46] to 96% [40] in the 11 studies.

In 10 studies, dichoptic training was conducted using a video game (such as Tetris or Dig Rush), while 1 study involved watching films or series [42]. Except for Rajavi 2021 [62] and Xiao 2022 [42], which used a head-mounted headset, the studies involved training on a computer or tablet. For image separation, anaglyph glasses were used in 8 studies [40,44,46,51,55-57,59], shutter glasses in 1 study [48], and VR glasses in 2 studies [42,62].

Dichoptic training versus no training

Two studies (enrolling 243 randomized children from the United States) compared dichoptic training versus no training [40,42]. Patients in both the intervention group and the control group were fitted with optical correction (glasses) (if necessary). While Holmes 2019 [40] evaluated school children between 7 and 12 years of age, Xiao 2022 [42] enrolled younger children between 4 and 7 years of age. Both studies included amblyopia caused by anisometropia and/or strabismus. The studies' treatment durations were 8 weeks [40] and 12 weeks [42]. In Holmes 2019 [40], children played a video game a total of 5 times per week for 1 hour per day (planned training duration of 40 hours). In the study by Xiao 2022 [42], preschoolers were given a choice of different films and series via VR glasses, to be watched 6 times per week for 1 hour each (planned training duration of 72 hours).

Two other studies (involving 117 randomized patients from Iran [44] and China [46]) compared dichoptic training in combination with occlusion treatment versus occlusion treatment alone. The studies enrolled children with refractive amblyopia between the ages of 3 and 10 [44] and 3 and 13 years [46], respectively. The studies' treatment duration was 4 weeks [44] and 12 weeks [46]. In the study by Rajavi 2016 [44], dichoptic training was conducted in the form of a video game 5 times per week for 0.5 hours each time (planned training duration of 10 hours). In Yao 2020 [46], training was conducted 7 times per week for 0.75 hours each time (planned training duration of 63 hours). Occlusion treatment was conducted daily (7 times per week) in both groups and was scheduled for longer than dichoptic training. In Rajavi 2016 [44], the recommended occlusion time was 2 hours per day (planned occlusion duration of 56 hours), and in Yao 2020 [46], it was between 2 and 6 hours

per day (depending on the severity of amblyopia, planned occlusion duration of 168 to 504 hours).

Dichoptic training versus sham training

Two studies (enrolling 113 randomized children and adolescents) from Australia, New Zealand, China, and Canada compared dichoptic training versus sham training [48,51]. In both studies, patients wore special glasses (anaglyph glasses or shutter glasses) which produced image separation during both dichoptic and sham training. Unlike the dichoptic video game, the placebo game did not incorporate any elements with different contrast. While Gao 2018 [51] evaluated children and adolescents between 7 and 17 years of age (reporting results stratified for 7- to 12-year-olds and 13- to 17-year-olds), Herbison 2016 [48] included children between 4 and 8 years of age. Both studies included amblyopia caused by anisometropia and/or strabismus. The treatment duration was 6 weeks in both studies; Herbison 2016 [48] additionally reported data after 10 weeks of follow-up. In Gao 2018 [51], training was conducted daily (7 times per week) for 1 to 2 hours (planned training duration of 42 to 84 hours). In Herbison 2016 [48], the recommended training time was 0.5 hours once weekly (planned training duration of 3 hours). Identical training times were used for sham training.

Dichoptic training versus occlusion

A total of 6 studies (with 703 randomized children and adolescents from Iran [57,62], China [46], and the USA [55,56,59]) compared dichoptic training versus occlusion treatment. In 5 studies, both interventions were used as monotherapy. Rajavi 2019 [57] compared dichoptic training in the form of monotherapy versus occlusion treatment and additional sham training [57]. The sham training was identical to the dichoptic training, but without anaglyph glasses (without image separation). The study by Manh 2018 [56] was the only one to focus on adolescents between 13 and 16 years of age. The other 5 studies included preschool and school-aged children between 3 and 13 years of age. While Yao 2020 took into account only refractive amblyopia, the other studies did not apply any restrictions with regard to the cause of amblyopia. The studies' treatment duration ranged from 2 weeks [59] to 4 weeks [57,62], 12 weeks [46], and a maximum of 16 weeks [55,56]. Dichoptic training was conducted either 5 or 7 times per week for 0.50, 0.75, or 1 hour (planned training duration between 10 hours [57,59] and 112 hours [55,56]). Occlusion treatment, which applied only to the control group, was conducted 7 times per week for a minimum of 2 and a maximum of 6 hours each (depending on the severity of amblyopia, planned occlusion duration between 28 hours [59] and 504 hours [46]).

Monocular training

In total, 6 studies (6 publications [64-69]) investigated the benefit of monocular vision training compared to (a) no training [64,65] and (b) sham training [66-69]. In contrast to dichoptic

training, monocular training was conducted on an outpatient basis in the majority of studies [64,65,67,68].

Two studies [64,69] enrolled only children with refractive amblyopia. In addition, 4 studies evaluated children who had recently been initially diagnosed (without prior treatment) [64-66,68].

Monocular training was performed using a video game [64-68], or patients were asked to trace images presented digitally [69]. In 2 studies [67,68] which used video games and in 1 study [69] where images were presented digitally for tracing, training was conducted in front of a moving sinusoidal grating (which served as background stimulation). The 3 other studies [64-66] did not use (additional) background stimulation.

During monocular training, the dominant eye was occluded, and training was conducted on a personal computer or tablet. Only the Iwata 2018 study [64] investigated a special electronic device ("OccluPad"), and study participants were not occluded with a patch, but equipped with Polaroid glasses. While the amblyopic eye followed the video game, the dominant eye perceived only a white background (which is similar to occlusion).

Monocular training versus no training

The Japanese study by Iwata 2018 [64] compared outpatient treatment using the "OccluPad" (based on a video game) versus no training in 3- to 8-year-olds. The 46 children had not received any prior treatment and suffered from amblyopia due to anisometropia. Patients in both the intervention and control groups were fitted with optical correction (glasses). The study's treatment duration was 24 weeks. The children in the intervention group trained twice a week for 0.5 hours each (planned training duration of 24 hours). Instead of occlusion by a patch, Polaroid glasses were worn during training in the study.

Another study (with 40 randomized children from India [65]) compared vision training in the form of a video game in combination with occlusion treatment versus occlusion treatment alone. The study included non-pretreated children between 4 and 7 years of age with unilateral amblyopia caused by anisometropia and/or strabismus. The treatment duration was 12 weeks. Monocular vision training was performed once weekly for 0.5 hours in addition to occlusion treatment (planned training duration of 6 hours). In contrast to the digital training, occlusion treatment took place 4 to 6 times per week, for the whole day (planned occlusion duration of a maximum of 576 hours per group).

Monocular training versus sham training

When comparing monocular training versus sham training, the 2 comparisons were analysed separately due to the different intervention approaches:

Monocular training versus sham training (digital versus non-digital).

One study (with 20 randomized children from the United Kingdom [66]) compared digital vision training versus near work (sham training). The study conducted occlusion treatment in addition to vision training (in both groups). The enrolled children were between 2 and 7 years old and non-pretreated, and the amblyopia was due to anisometropia and/or strabismus. The children in the intervention group were handed a list of age-appropriate video games, while the control group was instructed to perform non-computer-based near work (such as painting or crafting). The training was conducted 7 times per week for 1 hour each (over a period of 7 weeks) during the occlusion period under the supervision of parents or legal guardians at home (planned training duration of 49 hours per group). Occlusion was likewise applied 7 times per week in both groups, but for 2 hours each (planned occlusion duration of 98 hours per group).

Monocular training versus sham training (with versus without stimulation)

A total of 3 studies (with 58 randomized children from Germany [67,68] and Taiwan [69]) compared monocular computer-based vision training with background stimulation versus sham training (without background stimulation). The studies provided occlusion treatment in addition to vision training. In 2 studies, the age of the children ranged from 4 to 10 years [68,69]. In Kämpf [67], the children were slightly older (between 6 and 13 years). While Yeh 2021 [69] included only children with refractive amblyopia, the other 2 studies involved no restrictions with regard to the cause of amblyopia. Bau 2012 [68] differed from the other 2 studies in that only children with an initial diagnosis were included. Bau 2012 [68] and Kämpf [67] evaluated the Caterna monocular training, which is in use in Germany. Yeh 2021 [69] used the Cambridge Vision Stimulator (CAM), which, like Caterna, employs background stimulation. In contrast to Caterna, however, CAM does not show an interactive video game in the foreground but asks children to trace the images presented in the foreground on a tablet. The studies' treatment durations were 2 weeks [67], 4 weeks [68], and 24 weeks [69]. Training was conducted 5 times per week for 0.75 hours [67,68] and 0.25 hours [69], respectively (planned training duration of 7.5 hours [67], 15 hours [68], and 30 hours [69], respectively). The training and occlusion durations were identical in Bau 2012 [68] and Yeh 2021 [69] (15 hours [68] and 30 hours [69], respectively). In Kämpf 2001 [67], children in both comparison groups were occluded beyond the training period (planned occlusion duration of 80 hours per group).

4.3 Overview of patient-relevant outcomes

Table 2 shows the overview of available data on patient-relevant outcomes, stratified by intervention or comparator intervention.

From each of the 17 included studies, it was possible to extract and use data on the patient-relevant outcome of best-corrected visual acuity of the amblyopic eye. For the binocular vision

outcome, a total of 9 studies reported results (including 1 study [68] which examined monocular training). The outcome was not reported in 6 studies. Two other studies reported data, but their data were either incomplete [65] or not reported stratified by age [51] and thus unusable. Data on the adverse events outcome were available from 10 studies (including 7 studies investigating dichoptic training and 3 studies investigating monocular training). Six studies did not report adverse events, and in 1 study [51], the data were unusable (no age-specific data).

No data were reported on other relevant vision-related outcomes. This is due to the fact that the present HTA found only studies on the therapeutic indication of amblyopia. No studies on other relevant developmental visual disorders (refractive anomalies or strabismus), from which data for other relevant outcomes (e.g. myopia progression) might have been derived, have been published so far.

Furthermore, the existing study pool shows no reported data on the outcomes of health-related quality of life or health-related social and educational functioning.

Due to heterogeneity in terms of the intervention, comparator intervention, age of the included population, and other study characteristics (see Table 11 of the full report), study results were not pooled per outcome for any of the comparisons presented in Table 2. For study results, see Table 14 through Table 17 of the full report.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes					
	Best corrected visual acuity of the amblyopic eye	Binocular vision	Other vision outcomes	Adverse events	Health-related quality of life	Health-related social functioning
Therapeutic indication: amblyopia						
Dichoptic training						
Dichoptic training vs. no training						
Without additive occlusion						
Holmes (2019)	●	●	NR	●	-	-
Xiao (2022)	●	●	NR	●	-	-
With additive occlusion						
Rajavi (2016)	●	-	NR	●	-	-
Yao (2020)	●	●	NR	●	-	-
Dichoptic training vs. sham training						
Herbison (2016)	●	●	NR	●	-	-
Gao (2018)	●	○	NR	○	-	-
Dichoptic training vs. occlusion						
Holmes (2016)	●	●	NR	●	-	-
	●	●	NR	●	-	-
Rajavi (2019)	●	●	NR	-	-	-
Birch (2020)	●	●	NR	-	-	-
Yao (2020)	●	●	NR	●	-	-
Rajavi (2021)	●	-	NR	-		-
Monocular training						
Monocular training vs. no training						
Without additive occlusion						
Iwata (2018)	●	-	-	-	-	-
With additive occlusion						
Dadeya (2016)	●	○	NR	●	-	-

Table 2: Matrix of patient-relevant outcomes (continued)

Study	Outcomes					
	Best corrected visual acuity of the amblyopic eye	Binocular vision	Other vision outcomes	Adverse events	Health-related quality of life	Health-related social functioning level
Monocular training vs. sham training (digital vs. non-digital)						
Jukes (2019)	●	-	NR	●	-	-
Monocular training vs. sham training (with stimulation vs. without stimulation)						
Kämpf (2001)	●	-	NR	-	-	-
Bau (2012)	●	●	NR	●	-	-
Yeh (2021)	●	-	NR	-	-	-
Therapeutic indication of refractive anomaly: No studies identified						
Therapeutic indication of strabismus: No studies identified						

NR: not relevant for the therapeutic indication of amblyopia; vs.: versus

Yao 2020 is a 3-arm study and is presented twice in the table.

The phrase "with or without additive occlusion" when comparing dichoptic training versus no training and monocular training versus no training provides information about the add-on treatment (concomitant treatment). Since this add-on treatment was used either in both groups or in neither of them, these details have not been analysed separately in the interpretation of results.

For monocular training, Kämpf 2001, Bau 2012, and Yeh 2021 employed a digital system which uses background neural stimulation.

● Data were reported and were usable.

○ Data were reported but unusable for the benefit assessment.

- No data were reported.

4.4 Assessment of the risk of bias of the results

The risk of bias across outcomes was rated as low for 1 study [51] and as high for the other 16 studies. High risk of bias is primarily due to lack of blinding of the treatment provider, patients, and outcome recorders (mostly caused by the treatment principle evidently differing between intervention and control groups). The monocular treatment methods suffered not only from bias caused by lack of blinding, but also from ambiguities concerning the randomization method and group allocation. In 5 of 6 studies evaluating monocular vision

training, it was furthermore impossible to rule out reporting bias (due to missing study protocols or study registrations).

The high risk of bias at the study level was also reflected by the risk of bias at outcome level (except in Gao 2018 [51]). Details on the risk of bias at study and outcome levels for each study are found in Sections A3.2 to A3.3 of the full benefit assessment.

4.5 Results on patient-relevant outcomes

Table 3 shows the results of each study with regard to patient-relevant outcomes, stratified by intervention and comparator intervention for the longest observation period.

Table 3: Overview of effects with regard to reported patient-relevant outcomes at the individual study level

Study	Morbidity[a]		Adverse events[a]									
	Best corrected visual acuity of the amblyopic eye (logMAR)	Binocular vision (log angular sec)	Double vision	Asthenopia and headache	Decreased visual acuity		Strabismus (newly diagnosed)	Nausea, dizziness	Eye blinking	Nightmares	Conjunctivitis	Skin irritation
					Amblyopic eye	Dominant eye						
Therapeutic indication: amblyopia												
Dichoptic training												
Dichoptic training vs. no training												
Without additive occlusion												
Holmes (2019)	↔	↔	↔	-	-	-	↔	-	-	-	-	-
Xiao (2022)	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	-	↔
With additive occlusion												
Rajavi (2016)	↑	-	-	-	↔	-	-	-	-	-	-	-
Yao (2020)	↔	↑	-	-	-	-	-	-	-	-	-	↔
Dichoptic training vs. sham training												
Herbison (2016)	↔	↔	↔	-	↔	-	-	-	-	-	↔	-
Gao (2018)	↔	-[b]	-	-[b]	-	-	-	-	-	-	-	-
Dichoptic training vs. occlusion												
Holmes (2016)[c]	↓	↔	↔	-	-	-	↔	-	-	-	-	↔
Manh (2018)	↔	↔	↔	-	-	-	↔	-	-	-	-	↔

(continued)

Table 3: Overview of effects with regard to reported patient-relevant outcomes at the individual study level (continued)

Study	Morbidity[a]		Adverse events[a]									
	Best corrected visual acuity of the amblyopic eye (logMAR)	Binocular vision (log angular sec)	Double vision	Asthenopia and headache	Decreased visual acuity		Strabismus (newly diagnosed)	Nausea, dizziness	Eye blinking	Nightmares	Conjunctivitis	Skin irritation
					Amblyopic eye	Dominant eye						
Rajavi (2019)	↔	↔	-	-	-	-	-	-	-	-	-	-
Birch (2020)	↑	↔	-	-	-	-	-	-	-	-	-	-
Yao (2020)	↔	↔	-	-	-	-	-	-	-	-	-	↔
Rajavi (2021)	↔	-	-	-	-	-	-	-	-	-	-	-
Monocular training												
Monocular training vs. no training												
Without additive occlusion												
Iwata (2018)	↑	-	-	-	-	-	-	-	-	-	-	-
With additive occlusion												
Dadeya (2016)	↑	-[b]	-	-	-	-	-	-	-	-	-	↔
Monocular training vs. sham training (digital vs. non-digital)												
Jukes (2019)[d]	↔	-	-	-	-	-	-	-	-	-	-	-
Monocular training vs. sham training (with vs. without stimulation)												
Kämpf (2001)	↔	-	-	-	-	-	-	-	-	-	-	-
Bau (2012)[d]	↔	↔	-	-	-	-	-	-	-	-	-	-
Yeh (2021)	↑	-	-	-	-	-	-	-	-	-	-	-
Therapeutic indication: Refractive anomaly: No studies found												
Therapeutic indication: Strabismus: No studies found												

(continued)

Table 3: Overview of effects with regard to reported patient-relevant outcomes at the individual study level (continued)

ang sec: angular second; CI: confidence interval; logMAR: logarithm of the minimum angle of resolution; ND: no data; vs.: versus

Yao 2020 is a 3-arm study and is presented twice in the table.

The phrase "with or without additive occlusion" when comparing dichoptic training versus no training and monocular training versus no training provides information about the add-on treatment (concomitant treatment). Since this add-on treatment was used either in both groups or in neither of them, these details have not been analysed separately in the interpretation of results.

During monocular training, Kämpf (2001), Bau (2012), and Yeh (2021) employed a digital system which uses background neural stimulation.

↑: Statistically significant effect in favour of the intervention

↓: Statistically significant effect in favour of the control

↔ No statistically significant difference

-: No data reported

[a] Effects shown are for the longest treatment or observation period (observation period applies to studies where treatment completion does not coincide with study end).

[b] In the Gao 2018 and Dadeya 2016 studies, the outcome data marked with footnote b are unusable for the benefit assessment. In Gao 2018, the outcome was not reported on an age-specific basis, while in the Dadeya 2016 study, outcome reporting is inadequate.

[c] In the Holmes 2016 study, the effect is shown for the 5- to 12-year-old age group. The effects present in the other age-stratified groups point in the same direction.

[d] Bau 2012 and Jukes 2019 generally report that no adverse effects (adverse outcomes) were found in the studies, with individual events not being reported.

4.5.1 Best corrected visual acuity of the amblyopic eye

Dichoptic training

The benefit assessment for the outcome of best-corrected visual acuity of the amblyopic eye included the results from a total of 11 studies (12 comparisons, with the 3-arm study by Yao 2020 [46] being listed twice) which evaluated dichoptic training versus different comparator interventions. Due to the frequently small number of studies per comparator category, heterogeneous patient populations, differences in treatment procedures and durations, and statistical heterogeneity, a meta-analytic summary was deliberately omitted. Detailed results are presented in Table 16 in Section A3.3 of the full report.

Dichoptic training versus no training

Two studies [40,42] compared dichoptic training versus no training. Participants in both groups were additionally fitted with optical correction. In Holmes 2019 [40], which evaluated children between 7 and 12 years of age, no significant differences between the intervention and control groups were found at any measurement time point (mean difference [MD] in logMAR at 8 weeks: 0.0; 95% CI not stated; p = 0.71; N = 138). In Xiao 2022 [42], conducted with younger children (4- to 7-year-olds), there was a significant difference between intervention and control groups in favour of dichoptic training at both 4 weeks and 12 weeks (but not 8 weeks) (MD in logMAR at 12 weeks: -0.10; 95% CI -0.16 to -0.04; N = 90).

Two studies [44,46] compared dichoptic training as an add-on to occlusion treatment versus occlusion treatment alone. In Rajavi 2016's study [44] on 3- to 10-year-olds, there was a significant difference between the intervention and control groups in favour of the intervention (MD in logMAR at 4 weeks: -0.11; 95% CI -0.17 to -0.05; N = 50). In Yao 2020 [46], which evaluated children aged 3 to 13 years, the effect estimate pointed in the same direction (in favour of the intervention), but the difference was not statistically significant (MD in logMAR after 12 weeks: -0.02; 95% CI -0.14 to +0.10; N = 52).

Dichoptic training versus sham training

Two studies [48,51] compared dichoptic training versus sham training. In Herbison 2016 [48], which evaluated 4- to 8-year-olds, there was no statistically significant difference between dichoptic training and sham training at any of the measurement time points (3, 6, 10 weeks) after statistically controlling for baseline visual acuity (MD in logMAR at end of study [10 weeks]: -0.01; 95% CI -0.08 to +0.06; N = 50). Similarly, the Gao 2018 study, after adjusting for baseline visual acuity, found no significant difference between the intervention and control groups, neither in the 7- to 12-year-olds (MD in logMAR at 6 weeks: +0.06; 95% CI -0.02 to +0.14; N = 45) nor in the 13- to 17-year-olds (MD in logMAR at 6 weeks: -0.01; 95% CI -0.08 to +0.06; N = 17).

Dichoptic training versus occlusion

A total of 6 studies [46,55-57,59,62] compared dichoptic training in the form of monotherapy versus standard treatment (occlusion). Of the 6 studies, 1 study [59] with 4- to 10-year-old children showed a significant difference in favour of dichoptic training (MD in logMAR at 2 weeks: -0.08; 95% CI -0.13 to -0.03; N = 47). In contrast, the Holmes 2016 study [55], which evaluated 5- to 12-year-old children, showed an effect in favour of occlusion treatment (MD in logMAR after 16 weeks: +0.03; 95% CI >0.00 to +0.05; N = 385). The subgroup effects in 5- to 6-year-olds and 7- to 12-year-olds pointed in the same direction (in favour of occlusion) but were not significant [55]. In addition, the studies by Manh 2018 [56] (13- to 16-year-olds, 16 weeks), Rajavi 2021 [62] (4- to 10-year-olds, 4 weeks), Rajavi 2019 [57] (3- to 10-year-olds, 4 weeks), and Yao 2020 [46] (3- to 13-year-olds, 12 weeks) likewise showed effect estimates in favour of occlusion treatment which were not statistically significant.

Monocular training

The benefit assessment for the outcome of best-corrected visual acuity of the amblyopic eye included the results from a total of 6 studies which evaluated monocular training versus various comparator interventions. Due to the small number of studies in each comparator category, the heterogeneous patient population, and the differences in treatment procedures and durations, a meta-analytic summary was intentionally omitted. Detailed results are presented in Table 16 in Section A3.3 of the full report.

Monocular training versus no training

Iwata 2018 [64] evaluated 3- to 8-year-old children, comparing monocular training (without specific background stimulation) versus no training. In both groups, children additionally received optical correction. At both 12 and 24 weeks, a statistically significant difference was found between monocular training versus no training (MD in logMAR at 24 weeks: -0.11; 95% CI not reported; $p < 0.0001$; N = 26).

Dadeya 2016 [65] compared monocular training (without specific background stimulation) in combination with occlusion treatment versus occlusion treatment alone in 4- to 10-year-olds over several weeks (3, 6, 9, and 12 weeks). At all measurement time points, the combination treatment was superior to occlusion therapy alone (MD in logMAR at 12 weeks: -0.13; 95% CI -0.20 to -0.03; N = 40).

Monocular training versus sham training

When comparing monocular training versus sham training, the 2 comparisons were analysed separately due to the different intervention approaches:

Monocular training versus sham training (digital versus non-digital)

Jukes 2019 [66] evaluated 2- to 7-year-old preschoolers, comparing video games (without specific background stimulation) versus a non-digital near task. It found no statistically significant difference between the interventions (MD in logMAR at 7 weeks: +0.03; 95% CI -0.11 to +0.18; N = 18).

Monocular training versus sham training (digital with versus without stimulation)

Three studies [67-69] investigated monocular training with specific background stimulation compared with training without background stimulation. The children in both groups simultaneously received occlusion treatment. Kämpf 2001 [67] (6- to 14-year-olds) and Bau 2012 [68] (4- to 10-year-olds) each used Caterna vision training. Kämpf 2001 [67] reported a non-significant effect in favour of the intervention group (p = 0.109, no logMAR values reported). In Bau 2012 [68], the effect pointed in the same direction (MD in logMAR after 4 weeks: -0.02; 95% CI -0.20 to +0.16; N = 15). According to the authors, the Yeh 2021 study [69] investigating children between 4 and 8 years of age found a "statistically significant difference in favour of the intervention group" after 24 weeks. However, no numerical values were reported in this study.

4.5.2 Binocular vision

Results from a total of 9 studies [40,42,46,48,55-57,59,68] were included in the benefit assessment for the binocular vision outcome. The small number of studies per comparator category precluded a metaanalytic summary. Detailed results are presented in Table 17 in Section A3.3 of the full report.

Dichoptic training

Dichoptic training versus no training

In total, 3 studies [40,42,46] reported binocular vision data for this comparison. Among them, only the study by Yao 2020 [46] with 3- to 13-year-old children showed a significant effect estimate in favour of dichoptic training compared with no training (MD in log angular seconds after 12 weeks: +0.38; 95% CI +0.06 to +0.70; N = 52).

Dichoptic training versus sham training

Only Herbison 2016 [48] provided data on this outcome in this comparator category. However, no numerical values were reported. The study's authors concluded that there was no statistically significant difference between the groups.

Dichoptic training versus occlusion

A total of 5 studies [46,55-57,59] reported on data evaluating this comparison. Only 1 study [46] reported an effect estimate in this regard (MD in log angular seconds at 12 weeks:

+0.20; 95% CI -0.10 to +0.50; N = 12). The other studies concluded that there were "no differences between groups".

Monocular training

Monocular training versus sham training (with versus without stimulation)

The Bau 2012 study [68] likewise reported no differences between monocular training (with background stimulation) versus digital training without background stimulation. As was the case in the majority of studies reporting on this outcome, exact numerical values were missing in this study.

4.5.3 Other vision outcomes

No data were reported on other relevant outcomes related to vision.

4.5.4 Adverse events

The results from a total of 10 studies [40,42,44,46,48,55,56,65,66,68] were included in the benefit assessment for the adverse events outcome. Two [66,68] of the studies only generally reported that no adverse effects (adverse events) occurred. Therefore, these two studies are omitted from Table 18 in Section A3.3 of the full report.

A description stratified by intervention was deliberately omitted for this outcome because the different vision training methods are not expected to differ with regard to adverse effects, and adverse events were observed only sporadically.

In addition to temporary double vision (5 studies [40,42,48,55,56]), the studies reported skin irritation caused by occlusion (5 studies [40,42,44,46,48,55,56,65,66,68]) and new-onset strabismus (4 studies [40,42,55,56]).

Isolated studies also reported on other adverse events such as asthenopia and headache, decreases in visual acuity of the dominant eye as well as the amblyopic eye, nausea or dizziness, increased eye blinking, nightmares, and conjunctivitis.

However, the adverse events were rather few overall, often reversible, and did not differ significantly between the comparison groups.

4.5.5 Health-related quality of life

No data were reported for the outcome of health-related quality of life.

4.5.6 Health-related social and educational functioning

No data were reported for the outcome of health-related social and educational functioning.

4.5.7 Supplementary outcomes

Treatment adherence

A total of 12 studies [39, 41-48, 51, 54, 58] reported data on treatment adherence. Detailed results are presented in Table 19 in Section A3.3.8 of the full report.

The electronically recorded data on treatment adherence for digital training ranged from 13% [56] to 100% [62,65]. The 100% adherence rate in the Dadeya 2016 study [52] was achieved through the constant presence of the investigator. In studies which recorded both objective and subjective treatment adherence, the subjective rates were between 10% and 50% higher than those recorded electronically.

In contrast, data for conventional therapy were based solely on subjective information (self-reports) and ranged from 75% [56] to 100% [42,59,62]).

When interpreting the reported data on treatment adherence, it must be noted that for dichoptic training, the extent to which patients actually used the anaglyph glasses (for image separation) was not recorded. In addition, it is mostly unclear whether the planned training times were adhered to, since in many cases, only the number of logins was recorded. How often the trainees' gaze wandered from the screen (due to distraction or lack of concentration) is another factor that is not measurable with current digital methods (except with VR glasses).

Satisfaction with treatment

One study [48] descriptively reported that >90% (no precise numerical data available) of children aged 4 to 8 years were satisfied with the digital training.

The studies did not provide further data on supplementary outcomes.

4.6 Overall evaluation of results

Evidence map

Table 4 below shows the evidence map regarding patient-relevant outcomes, stratified by intervention and comparator treatment and taking into account clinical relevance.

Table 4: Evidence map regarding patient-relevant outcomes

	Morbidity			**Adverse events**	**Health-related quality of life**	**Health-related social functioning level**
	Best corrected visual acuity of the amblyopic eye	Binocular vision	Other vision outcomes			
Therapeutic indication of amblyopia						
Dichoptic training						
Dichoptic training vs. no training	⇔	⇔	NR	⇔	-	-
Dichoptic training vs. sham training	⇔	⇔	NR	⇔	-	-
Dichoptic training vs. occlusion	⇑⇓	⇔	NR	⇔	-	-
Monocular training						
Monocular training vs. no training	⇔	-	NR	⇔	-	-
Monocular training vs. sham training (digital vs. non-digital)	⇔	-	NR	⇔[a]	-	-
Monocular training vs. sham training (with vs. without stimulation)	⇔	⇔	NR	⇔	-	-
Therapeutic indication of refractive anomaly: No studies available						
Therapeutic indication of strabismus: No studies available						
NR: not relevant for the therapeutic indication of amblyopia; vs.: versus ⇔ no hint, indication, or proof; homogeneous result. ⇑⇓ no hint, indication, or proof, heterogeneous results - no data reported						

[a] Bau 2012 and Jukes 2019 generally report that no adverse effects were identified in the studies.

Assessment of the volume of unpublished data

Due to the heterogeneity of the published studies and the small number of studies in each comparator category (<10 studies), it proved impractical to quantify publication bias (estimate the true number of published studies).

Overall, the registry search identified 2 studies which had been completed but not published [71,72]. The study from Taiwan evaluated children with refractive amblyopia and was completed as early as 2007, according to the registry entry. However, results are available neither in the registry nor in the publication. The study from the United Kingdom likewise focused on children with amblyopia (caused by anisometropia and/or strabismus) and, according to the registry entry, was completed in 2014. Results for this study are likewise neither available in the registry nor in the form of a publication.

Overall, the potential for publication bias is low, but cannot be completely excluded in view of the 2 unpublished registry entries for amblyopia.

No unpublished data were found for the other relevant developmental therapeutic indications.

Weighing of benefits versus harms

Visual acuity outcome

Although isolated comparisons suggest that active vision training may be of benefit for the visual acuity in the amblyopic eye compared to no vision training or sham training, the differences measured in these comparisons are not expected to be clinically relevant.

The clinical relevance threshold for a between-group difference (improvement) in the outcome of best-corrected visual acuity of the amblyopic eye may be defined as the published value of -0.05 logMAR (+0.5 lines) [55]. In most studies, however, the upper limit of the measured values lies below this threshold. Only in 1 study [65], which compared monocular training versus no training, was the clinical relevance threshold exceeded at 1 out of a total of 4 measurement time points. After 9 weeks of treatment, the upper and lower limits (95% CI) of the measured mean difference were -0.24 logMAR (improvement by +2.4 lines) and -0.06 logMAR (improvement by +0.6 lines), respectively, in this study.

In summary, there was no hint of (greater) benefit of digital dichoptic or monocular vision training for any of the comparisons presented above, neither compared to no training nor to sham training or occlusion treatment.

Outcome of binocular vision

For the patient-relevant outcome of binocular vision, none of the studies on digital training showed a hint of (greater) benefit, neither compared to no training nor to sham training or occlusion treatment. Even if statistically significant effects were found, the lack of clinical relevance thresholds would complicate their interpretation. In addition, for patients with amblyopia from strabismus, improvement in binocular vision is to be expected only after correcting the underlying cause, i.e. eye misalignment [73].

Outcome of adverse events

The number of adverse events was rather low in the present study pool, and no study showed any hint of an increased risk of such events – neither under digital training nor in the control group. However, it must be noted that the rather small number of study participants precludes drawing a reliable conclusion with regard to adverse events.

Further outcomes

No data are available on other outcomes; see Table 2.

Summary

Overall, the available evidence does not allow drawing a reliable conclusion on the benefit-harm ratio of active vision training in children and adolescents with amblyopia. On the one hand, the differences measured in these comparisons cannot be assumed to be clinically relevant. On the other hand, it is unclear to what extent patient-relevant outcomes are influenced by the occasionally large differences in treatment durations (both within vision training and between vision training and occlusion treatment), the lack of adherence to vision training, the heterogeneous age of the participants, and other clinical characteristics (e.g. different forms of amblyopia, different or no criteria concerning stable visual acuity before randomization, or prior treatment status). Except in 1 study, the risk of bias was additionally estimated to be high on both study and outcome levels, further complicating the drawing of reliable conclusions on the benefits and harms of active vision training. In addition, some of the studies had very few participants and used a treatment duration of only a few weeks, failing to reflect the frequently long-term amblyopia treatment.

5 Results: Health economic assessment

5.1 Intervention costs

The costs of active vision training cannot be definitively determined. This is due to the variety of training programmes offered and their typically individualized training contents and durations. In addition, cost estimation is complicated by the fact that vision training is typically offered not as a substitute, but as an add-on to the respective standard therapy, so that the cost of standard therapy must also be taken into account. After all, vision training interventions are not a standard SHI benefit in Germany, and therefore, uniform billing codes are not available.

A (non-systematic) Internet search conducted in the context of the present HTA revealed that particularly opticians and optometrists offer a large number of active training programmes for a wide range of vision problems. The offerings are aimed at a broad target group, ranging from children with deficits in focusing (accommodation and convergence), eye movements, and perception to children with (visual) deficits in reading, spelling, mathematics, and concentration. The therapeutic indication for a training program is usually determined on the basis of a chargeable "optometric" (non-standardized) analysis. Once a therapeutic indication has been established, an individualized programme is offered where necessary. The Internet search did not reveal comprehensive details about the diagnostic criteria or content of the training programmes offered. It is therefore safe to assume that the offered training programmes do not represent a uniformly comparable intervention and that the indication is not necessarily follow evidence-based criteria in all cases. Some provider websites confirm that the costs of the training programmes, including any required ophthalmologic examinations, vary widely as they typically provide only a cost framework comprising the entire range of offered interventions and addressed therapeutic indications. Generally, costs of €300 to €1300 per person can be expected. The costs incurred in individual cases must be borne by the individual and may vary depending on the scope of the training conducted in each case.

Given the broad range of therapeutic indications and the assumed heterogeneity and individualization of the offered vision training interventions, the focus of the health economic evaluation was restricted to the therapeutic indication analysed in the benefit assessment (amblyopia). This was in part due to the fact that no efficacy studies on training programmes for other therapeutic indications were found in the research for the benefit assessment; and a health economic evaluation is meaningful only if an intervention can be safely assumed to be associated with a clinical benefit.

Digital dichoptic (binocular) or monocular training programmes are available for the treatment of amblyopia [73]. They include the online monocular training offered by the

company Caterna Vision GmbH [24], which is the only active vision training in Germany which is reimbursed by several health insurance companies as part of selective contracts. The target group for the monocular training programme offered by Caterna Vision GmbH comprises children aged 4 to 12 years with established functional amblyopia (from anisometropia and/or strabismus) who have a medical prescription. The training consists of computer games played on a screen at home for 30 to 45 minutes daily over a 3-month period, with the stronger (dominant) eye being occluded by a patch. Due to the selective contracts entered into by the health insurance companies and the company Caterna Vision GmbH being confidential for competitive reasons, the costs incurred by the health insurance companies participating in the programme cannot be precisely quantified. According to information on the company's website, self-paying patients must expect costs of €380 for the use and ophthalmological monitoring of the programme over the 3-month treatment period (Table 20 of the full report).

Another digital training tool for adjunctive treatment of amblyopia is the Vivid Vision programme (offered by the company Vivid Vision, Inc.) [74]. Unlike the online training offered by Caterna Vision GmbH, Vivid Vision is a binocular training programme for children and adults which requires the use of VR glasses. These glasses allow presenting images with different stimuli to the amblyopic and dominant eyes (Section 1.2.3). The training takes place under ophthalmological supervision either at home or on an outpatient basis. For this purpose, the supervising Vivid Vision providers (ophthalmologists) purchase a time-limited software license for patient management, which is offered for about €800 per year if patients are exclusively supervised at home (training in the home environment) [75]. The additional costs for the required VR goggles with pre-installed Vivid Vision app equal approximately €230 [75]. It is difficult to assess the extent to which the costs are passed on to the patients. According to company information, training costs vary depending on location, provider experience, severity, and treatment plan. These costs are not covered by SHI in Germany. For this reason and due to the unclear costs per person or per treatment year, the Vivid Vision programme was not included in Table 20.

Since the training programmes for amblyopic patients described above are not offered as a substitute but as an add-on to the respective standard therapy, the question regarding the costs of standard therapy appears to be of secondary importance. From a financial point of view, the costs of standard therapy would be of particular importance if the accompanying vision training were associated with savings in conventional treatment, for example by shortening the duration of therapy. However, there is currently insufficient evidence of this being the case.

In the case of vision training for amblyopia treatment, standard therapies can be used as comparator interventions. The resource consumption and costs of these therapies in Germany were determined in a cost study by König 2003 [76]. Based on the resource consumptions

determined in this study, a current cost estimate was generated using currently valid billing codes and point values. Some of the aids used in amblyopia treatment are not reimbursable (eyeglass frames) or cannot be estimated with confidence via SHI fixed amounts (eyeglass lenses, occlusion patches and foils). Therefore, the prices for medical aids from the year 2002, as determined by König 2003 [76], were used as a basis and converted into prices for the year 2021 using a factor of 1.32 in accordance with the development of the German consumer price index [77], as recorded by the Federal Statistical Office (Table 20 of the full report).

Table 20 of the full report shows the individual items included in the cost estimate of the experimental and comparator interventions with the quantities used for the treatment period of a year. Table 21 of the full report summarizes the reimbursable and non-reimbursable costs per person in the 1st year of treatment. Accordingly, the average total cost per person in the 1st year of treatment is €647 for conventional treatment of amblyopia from strabismus and €606 for the treatment of amblyopia from anisometropia. This includes an out-of-pocket cost of €92. In both cases, over 2/3 of the costs are accounted for by the aids used in the treatment. It should also be noted that the treatment of amblyopia can extend over several years, with the cost study by König 2003 [76] showing that the annual treatment costs decrease continuously with increasing treatment duration. Since digital training methods for amblyopia treatment have so far only been used as add-on therapy, and since, based on the currently available evidence, the replacement of standard therapy by the methods is not advisable [73,78], the costs of standard amblyopia treatment are presumably incurred in full even if vision training (experimental intervention) is conducted. For the monocular online training offered by Caterna Vision GmbH, whose duration of application is currently limited to 3 months per case, the total per-patient cost of amblyopia therapy would increase by €380 as calculated based on training costs for self-payers. It is difficult to estimate the total per-person cost using the binocular Vivid Vision programme because it is unclear to what extent the costs of the training programme are passed on to the patients. Unlike Caterna Vision GmbH, the manufacturer does not specify a limitation of the application period to 3 months. At least in isolated cases, Vivid Vision training may therefore presumably be used over longer periods and thus incur higher costs.

5.2 Systematic review of health economic evaluations

The information procurement did not identify any systematic reviews or cost-effectiveness studies which met the inclusion criteria. The last search was conducted on 1 December 2021.

A review of various vision training interventions published by the Institute for Clinical Systems Improvement (ICSI) in 2003 also reports a lack of appropriate cost-effectiveness studies [79]. A more recent review of binocular training interventions for amblyopia by Pineles 2020 [78] likewise includes no cost-effectiveness studies. However, the authors conclude that, even if

future studies were to prove a benefit, the utilization of the measures might be limited for cost reasons.

Since vision training interventions are currently being used as an add-on to standard therapy in Germany, additional costs are initially incurred. For vision training interventions to be cost effective, health gains in the form of better treatment results or savings from standard therapy supplemented by vision training, e.g. through a shortened treatment period, would therefore be required. As there is currently no clear evidence of either of these prerequisites being met, it is impossible to conclusively assess cost-effectiveness.

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

The experimental intervention investigated by the present HTA report is active vision training guided by an appropriately qualified person. The comparator intervention is no vision training (no treatment), sham training, standard treatment (e.g. occlusion treatment for amblyopia), surgical intervention, or drug treatment. The studies identified for the benefit assessment (Section 4) focused on patients with amblyopia (from anisometropia and/or strabismus). No RCT results have been published on other relevant developmental visual deficits (refractive anomalies and eye misalignment) or on vision training interventions which are not conducted digitally. Because no other active vision training interventions have been studied within RCTs, the results of the ethical, social, legal, and organizational aspects relate primarily to the digital intervention. Analogously to clinical practice (and the studies identified in the benefit assessment), conventional treatment (with occlusion and/or eyeglass lenses) is examined as the comparator intervention from ethical, social, legal, and organizational perspectives.

6.1 Ethical aspects

The scoping search of the scientific and non-scientific literature found few publications which explicitly investigated ethical aspects of active vision training in children and adolescents and their social environment. Rather, literature permitting an ethical assessment was found indirectly in connection with different therapeutic approaches. Therefore, the analysis of the ethical aspects was exclusively based on an established ethical framework for the assessment of health care interventions [33], which was modified for active vision training in children and adolescents (and their social environment) (Table 22 of the full report).

Based on the specified criteria, the ethical aspects were evaluated analytically and argumentatively. This was done based on the results of the other domains, in particular the benefit assessment (Section 4) and social aspects (Section 6.2) as well as the preparatory interviews with affected persons. The normative criteria not only serve as a search matrix for ethically relevant implications of active vision training, but also potentially justify normative recommendations for the ethically appropriate use of the interventions. After examination of the individual criteria, the results are combined into an overarching ethical evaluation.

The ethical analysis and assessments concern primarily the interventions identified in the benefit assessment and the effects observed in the included studies. The intervention to be evaluated represents treatment with active vision training guided by an appropriately qualified person. Active vision training is defined as treatment which requires regular and attentive participation by the individual (such as dichoptic and computer-based interactive training based on perceptual learning methods and eye movement exercises). The intervention may be used in combination with standard therapy (conventional treatment, e.g. eyeglass lenses or occlusion) where appropriate.

Expected health benefit for the target group

In children and adolescents, a monocular or binocular visual development deficit may negatively impact quality of life [80-87]. Thus, appropriate treatment of these visual developmental deficits is of fundamental benefit for the affected individuals as well as their environment.

In amblyopia, for example, the conventional treatment is occlusion of the stronger eye. In this context, occlusion therapy is associated with limitations in the quality of life of adolescents and their families [8,17,88]. For example, taping an eye may result in stigmatization, which may lead to rejection of therapy, especially in children [89]. Based on the associated challenges for the affected patients and their social environment (Section 6.2), there has been a recent focus on new, primarily computer-based treatment approaches. In particular, the use of digital technologies should lead to higher treatment adherence compared to occlusion treatment because these technologies take advantage of the appeal of video games [73,80,90,91]. However, study results [51,88,92,93] suggest that the employed video games do not generate enough interest among study participants to sustain treatment adherence in the long term.

Even if the currently available evidence does not unequivocally prove a clinical benefit of alternative treatment methods (active vision training), the use of vision training would at least eliminate the disadvantages of conventional occlusion treatment in amblyopia, especially with regard to stigmatization (or social exclusion due to occlusion).

Potential harm and burden

The use of digitally supported therapies is perceived as a risk by parents and leads to reservations about digitally supported treatments in children [94]. The facilitated access to computer games for children and adolescents due to the digital offer requires a (parentally) reflected handling of digital devices because the therapy can result in new and/or prolonged screen times (see discussion of media consumption by children and adolescents in Section 6.2). In addition, "serious computer games" (health games) can lead to confusion among children and adolescents in the demarcation between leisure time behaviour and therapy because "serious computer games" demand adherence to therapy, which is not required for "fun computer games". Thus, the use of digitally enhanced forms of therapy may be scrutinized in light of the question whether children and adolescents should spend more time with digital media [73]. This potential criticism was also expressed in the affected person survey (parents of children with amblyopia). Thus, the use of digital therapies is deemed risky.

Effects on autonomy

In principle, improved vision presumably leads to improved social participation of the affected children and adolescents [80] and, as a result, allows a higher degree of (age-appropriate) self-

determined living. As mentioned in the subsection on the potential benefits of vision training, adverse consequences of occlusion therapy may be avoided by vision training, which may in turn result in lower therapy burden, especially in older children and adolescents, with possibly increased individual self-determination. In addition, the utilization of digital forms of therapy may enable the self-determined use of vision training at any time and from anywhere, which may meet a potential desire for self-management (especially in adolescents). These forms of therapy also seem to enable age- and needs-adapted therapy [73]. The interactive nature of many applications associated with digital forms of therapy allows for independent learning or therapy to be experienced, which can improve both self-efficacy and a sense of self-control [95].

Parents and guardians of children and adolescents with visual deficits should be enabled to make an informed decision (including regarding existing conventional treatment methods) by being properly informed about the benefits and risks of vision training. Involving children and adolescents in the choice of therapy based on their stage of development is a relevant aspect of autonomy, particularly with regard to the aforementioned adherence to therapy. In addition, parents and guardians should be adequately supported by the relevant medical professionals when deciding on possible utilization and be informed about alternative forms of therapy (use of technology at home, including cost coverage). In this regard, the survey revealed that the interviewed parents had not received any information regarding the possible use of active vision training at the time of the survey, which means that the relevant information regarding this alternative was not known at that time.

Further, in the context of autonomous decision-making regarding a digital form of therapy, the issue of data autonomy (data protection and data security) must be taken into account because health data may potentially be processed and/or passed on in digital applications [95,96].

Justice-related implications

As shown by the empirical results on social aspects (Section 6.2), social inequality is a concern in technology use for active vision training. This inequality affects, first, individuals lacking both terminal devices and health literacy and, second, individuals in rural areas. In addition, the diversity of online vision training offerings for children and adolescents was noted. Against this background – provided a clinical benefit has been demonstrated – appropriate therapy along with adequate information on the different therapy options should be made accessible. This access is to be made available to children and adolescents with deficits in visual development regardless of their age, origin, socioeconomic status, type of health insurance (statutory or private), or opportunities for technology use.

Expected efficiency

The cost of active vision training cannot be determined exactly. This is due to the variety of training programmes offered and their typically individualized training contents and durations. In addition, estimating costs is complicated by the fact that in Germany, vision training is usually offered not as a substitute but as an add-on to conventional treatment. Thus, the costs of the respective conventional treatment must be taken into account as well (Section 5).

Due to missing data, the health economic evaluation conducted within the present HTA does not allow any conclusive statements on the cost-effectiveness of active vision training (Section 5). In view of the limited and inconclusive evidence on the benefit of active vision training, a valid estimate of the expected efficiency is not available at the present time.

Finally, it must be noted that the complex development process of digital therapies and the associated costs considerably impact efficiency. This is especially true in light of the fact that, by the time the corresponding therapy methods have been developed and tested on the target groups, the technology may already be obsolete [73,78].

6.2 Social aspects

The information processing is based on the comprehensive conceptual framework proposed by Mozygemba 2016 [37]. The analysis of social aspects is based on the stakeholder interviews and a total of 31 included publications (14 from the benefit assessment, 9 from the exploratory database search, and 8 from the exploratory online search). In addition to the ethical aspects outlined above (Section 6.1), this subchapter focuses on the following social aspects: (1) social construct and perception of developmental vision disorders, (2) perception of vision training for developmental vision disorders and its use in society and science, (3) sociocultural aspects of intervention implementation and organization of use.

Social construct and perception of developmental vision disorders

As outlined under the ethical domain (Section 6.1), the overall perception of developmental vision disorders in childhood is associated with negative connotations: For example, adverse effects on children's activities of daily living (e.g. reading or sports), low self-esteem, negative self-image, frustration, shame, and worry have been described [22,23,97].

Perception of vision training for developmental vision disorders and its utilization

The standard treatment for amblyopia is occlusion of the stronger eye (conventional treatment). It is described as simple, safe and (so far) without alternatives, but it is also critically analysed: Occlusion therapy in childhood leads to reduced (psychosocial) quality of life and self-confidence, is associated with mood swings and social problems, is stressful for the child and unpopular with parents or guardians. In addition, this form of treatment may

interfere with school performance and participation in sports. Moreover, poor treatment adherence is common [8,44,94,98-101]. Depending on patient age and treatment adherence, the results of occlusion therapy may also be insufficient and/or non-permanent in some cases (especially in older children who have fallen through the cracks of early detection) [8,100].

Sufficient treatment adherence is essential for the success of treatment. The following aspects were identified as reasons for the common lack of adherence during occlusion treatment: Occlusion works quite well in younger children (under 7 years of age), but visual acuity cannot be restored in up to 1/3 of cases – especially due to lack of adherence to treatment instructions by parents and children [98]. There are multiple efforts in the field to better understand and address the causes of this lack of treatment adherence: A study of part-time occlusion in children with strabismus demonstrated that treatment adherence remained low in children with high somatic distress (e.g. dizziness, fatigue, headaches) [97]. Similarly, Loudon 2009 [88] identified distress (negative stress) on the part of the children as causative for low treatment adherence, with parental lack of knowledge and parental logistical problems having an additional negative impact on treatment adherence. The researched efforts to increase treatment adherence can be divided into 3 areas:

1) Approaches to improve conventional occlusion treatment

Occlusion treatment usually takes place unsupervised in the home setting due to the large amount of time involved [54]. To increase treatment adherence, for example, the occlusion time can be recorded by technical systems that combine occlusion therapy with an information and reward program.

2) Approaches to increase cooperation (with regard to parents and guardians)

Lack of understanding or knowledge about the treatment and its age-specific urgency as well as reservations about the treatment and distress were named as reasons for the frequently low parental cooperation [88,97,99,102,103]. Effective approaches to increase parental cooperation include intensified education by means of written information and keeping a treatment diary [102,104].

3) Approaches based on digital treatment options

Particularly in recent years, approaches have been developed that depart from conventional occlusion therapy in that they specifically incorporate digital media such as computer games which are popular and accepted among children in an effort to reduce the periods of application and increase children's interest in and adherence to treatment [8,54,65,105,106]. In recent years, such approaches have been increasingly investigated. They use a wide variety of digital media, e.g. television, computers, mobile phones, tablets, or iPads, and the approaches are often Internet-based. However, treatment adherence is inconsistent even in digital approaches and, in some cases, has been described as low [40,54]; e.g. in Gao

2021 [54], this is evidenced by short play sessions with frequent breaks, especially in children. Again, it is suspected that for treatment to be successful, detailed instructions would need to be provided to increase knowledge [54].

Looking at the more recent approaches which rely on digital adaptation, the perception of risk has increased in recent years, especially with regard to video games. Since 2019, the WHO officially recognizes "gaming disorder" according to the International Statistical Classification of Diseases, version 11 (ICD-11).

The classification includes both offline and online games, with the main danger being seen in online games [107]. On a national level, a clearer framework has additionally been defined, e.g. by means of the Youth Media Protection Act (*Jugendmedienschutzgesetz*), and the Federal Centre for Health Education [108] regularly issues recommendations on media consumption by children and adolescents. On the part of parents, the increased perception of risk is evidenced by reservations about digitally supported treatments in children [94], which were also expressed in the stakeholder interviews.

Sociocultural aspects of the intervention's implementation of and organization of use

As outlined, lack of treatment adherence constitutes a key problem in the implementation of active vision training interventions for developmental vision disorders. Studies investigating which factors are associated with low adherence to occlusion treatment have shown that relevant factors include socioeconomic status, e.g. poverty, low education level, lack of language skills, and psychosocial aspects (e.g. depression) [101,103]. In particular, people with a low social status, educational level, or migrant background also have low health literacy, which is in turn necessary for maintaining health and coping with illness [109]. Hence, information and counselling on occlusion treatment should focus in particular on families exhibiting the risk factors outlined above.

Since it is funded by SHI, occlusion treatment is not associated with financial burdens which would lead to social inequality regarding the use of technology in Germany. In order to be able to use digitally supported treatment alternatives, however, users need both technical skills and access to the technical prerequisites, e.g. Internet/wireless networks, mobile phones, iPads, or computers [42,106]. In this country, particularly single parents and people with a low level of education express with above-average frequency that they cannot financially afford certain things [109]. Computer games enjoy particular popularity precisely among children and adolescents – and especially male children – in households with long-term income insecurity [110]. Children in families affected by poverty are therefore more computer-savvy on the one hand, but at the same time have poorer access conditions. Against this background, digital treatment approaches which require specific, price-intensive terminal devices, such as iPads [40,55,56] or VR glasses [62], are particularly problematic. In this context, it is important

to note that TVs are available in most households, but even in developing countries, (high-speed) Internet access has not yet been sufficiently expanded into rural areas (even in Germany) [65,109]. While the rapid digital developments are being taken into account in the school sector (by means of a programme called *Digitalpakt Schule* [111]) and in the health sector (by means of the newly created telematics infrastructure for stakeholders in the health sector; www.gematik.de), there is a lack of correspondingly broad-based approaches to facilitating access and promoting digital health literacy among patients. Isolated approaches already exist, such as the Alliance for Health Literacy, which was founded in 2017 and aims to promote (digital) health literacy in particular. This is done, for example, by creating scientifically validated information offerings which laypersons can understand.

In summary, unequal access conditions to (digital) vision training approaches particularly affect people (1) lacking terminal devices, (2) lacking health literacy, and (3) living in rural areas. Furthermore, based on the exploratory review of websites and the identified diversity of online offerings, it must be noted that the communication of available evidence-based and non-evidence-based approaches might be further expanded. Hence, it would be desirable if

- information for professionals, e.g. guidelines [7], as well as
- patient information understandable for laypersons, e.g. the information provided by the German Ophthalmological Association and the German Ophthalmological Society [112]

were regularly updated and published more frequently and centrally. In addition, orthoptists' and ophthalmologists' knowledge about the causes of poor adherence to therapy should be expanded, e.g. through training programs [88].

From a social perspective, the following factors should be taken into account when deciding on conventional versus digitally assisted treatment or on its further scientific investigation:

- target population (in particular the child's age and type of visual impairment).
- practicability of the treatment (e.g. access to the [digital] treatment, necessary skills)
- expected efficacy of treatment (e.g. regarding visual acuity, binocular vision)
- expected adherence to treatment (and the associated likelihood of success of the treatment)
- expected treatment-related burden (e.g. self-esteem, reduction of quality of life, duration of treatment)

6.3 Legal aspects

The information processing on legal aspects is based on the guideline for the identification of legal aspects developed by Brönneke 2016 [38]. In aggregate, the legal aspects in the HTA refer to the legal framework in which the therapy method and its assessment are embedded as well as to the legal aspects associated with the implementation and utilization of the health technology. A distinction is thus made between technology-related and patient-related legal aspects.

Patient autonomy: informed consent

Patient consent to a medical intervention constitutes an expression of the patient's constitutional right to self-determination and the right to the free development of personality [113]. According to Section 630d German Civil Code (BGB), the physician is obliged to obtain the patient's informed consent prior to a medical procedure. The informed consent discussion is tied to the obligation to inform the patient about all circumstances essential for consent. Since the present HTA investigates vision training for children and adolescents and the patients' (children's and adolescents') capacity to give consent must be examined in each individual case, the consent of the parents or guardians is addressed as the first point of reference (Section 630d (1) sentence 2 BGB).

Section 630e BGB includes duties of disclosure which form the basis for consent to therapy. Accordingly, the attending physician is obliged to inform the patient of all circumstances essential for consent. This does not mean that detailed medical knowledge must be imparted, but rather that the scope of the treatment should be explained. In this regard, the law gives as examples the type, scope, implementation, expected consequences, and risks of the measure as well as its necessity, urgency, suitability, and prospects of success with regard to diagnosis or therapy. An interesting aspect in the context of active vision training might be that alternatives to the treatment measure must be pointed out in the information whenever several medically equally indicated and usual methods may be associated with substantially different burdens, risks, or chances of recovery. According to the case law of the Federal Court of Justice, this means that the patient, as the subject of the treatment, must be given the choice between equally medically indicated treatment methods [114]. The Model Medical Code of Practice (*Muster-Berufsordnung für Ärzte*, MBO) [115] likewise specifies that any treatment requires the patient's informed consent (Sections 7 and 8 MBO 2021).

Patient autonomy: consent by children and adolescents

Like adults, children and adolescents have the right to be informed about their treatment and subsequently to make a decision. Due to their age, developmental stage, and also the fact that minors are often legally unable to make decisions on their own, the informed consent process is more complicated than for adults [116]. Even though minors cannot make decisions on their

own, they have a right to participate in decision-making about treatment, therapeutic interventions, and future decisions often associated with therapy [117].

Thus, the central aspect in minor patients is the question of capacity to consent because the prerequisite for effective consent is the patient's capacity to consent [118,119]. Since medical treatment does not require legal capacity, minors can generally give legally valid consent to treatment [113,120]. However, no explicit legal regulation exists to define when a person has the capacity to consent to (or refuse) medical treatment, so the legal assumption is that a patient has capacity to consent as soon as and for as long as the patient is able to understand the nature and scope of the intervention and to direct his or her will accordingly. However, this must always be determined on a case-by-case basis. Accordingly, capacity to consent presupposes a capacity to form a will of the person concerned, whose capacity for insight and judgement must be sufficient to weigh the benefits of the treatment against its risks and then to make an autonomous decision [121]. The consent of a minor to treatment and thus to an intervention concerning his or her physical integrity is legally valid if the person is capable of assessing the significance and scope of the treatment and his or her consent on the basis of mental and moral maturity [122].

Data protection

Health data are subject to special protection due to their qualification as "sensitive data" (Article 9 General Data Protection Regulation [GDPR]) [123]. Health data are defined as personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status (Article 4[15]) GDPR). In principle, health data must not be processed. The GDPR provides for only 2 exceptions to this (Article 9[2] GDPR): (1) the data subject has given consent to the processing voluntarily and in an informed manner, or (2) processing is necessary for the purposes of preventive health care, medical diagnosis, health or social care, or treatment on the basis of a legal regulation or on the basis of a contract with a health professional (Article 9[2] GDPR).

If the vision training is in digital form and therefore represents a "health game" application, the data used must also be categorized as personal data (regardless of whether or not the "health game" is to be categorized as a medical device), so that the data protection provisions of the GDPR apply.

Duty of confidentiality

The medical duty of confidentiality is regulated in Section 9 (1) MBO [115] or in the corresponding provisions of the professional regulations of the state medical associations. This comprehensive duty of confidentiality applies to all information entrusted to physicians or becoming known to them in their capacity, even after the patient’s death. The duty of

confidentiality also arises as a secondary obligation from the treatment contract (see Sections 630a et seq. BGB). The medical confidentiality obligation can sometimes lead to a conflict between the obligation to maintain confidentiality and the obligation to provide information and/or clarification to parents or guardians [124].

Medical device

The available options of digital vision training in the form of Health results in the categorization as a medical device being subject to legal analysis. The legal provisions relevant for this topic can be found in the European Medical Device Regulation, (EU) 2017/745 (MDR), which replaces the Medical Device Directive (93/42/EEC, MDD). The MDR came into force in 2017, with an effective date of 26 May 2021. The question of whether a product falls within the scope of medical device regulation and when each regulatory requirement must be met needs to be examined on a case-by-case basis by the product manufacturer, i.e. the developer of the health game (digital vision training).

In the EU, health and medical apps (video games), unlike lifestyle and wellness apps, require certification under medical device law. According to the MDR, the categorization of the app as either "health and fitness" or "medical" is primarily at the discretion of the provider, as it is based on the manufacturer's subjective purpose for the app (Article 2 MDR). According to a non-binding guideline by the European Commission, the intended use according to the manufacturer's description (not the product description) is relevant for qualification as a medical device. Accordingly, software is a medical device only if it is specifically intended by the manufacturer to be used for one or more of the medical purposes listed in the definition of medical devices, while software for general purposes does not qualify as a medical device, even if it is used in healthcare. This must be determined on a case-by-case basis. A critical discussion of the utilization of health and medical apps with regard to the lack of robust evidence to assess the need, quality, and safety of these applications based on the current, largely unregulated supply is currently ongoing in the literature [125].

Reimbursement of costs in the healthcare system

SHI-insured persons are entitled to health treatment if it is necessary for diagnosing or curing an illness, preventing its aggravation, or alleviating symptoms of illness (Section 27 SGB V). Accordingly, the costs for standard therapy involving occlusion treatment and for eyeglass lenses are covered. However, the vision training discussed in this HTA is not a standard SHI benefit as defined in SGB V, resulting in a lack of uniform billing codes. Specifically, digital monocular or binocular training programmes are offered for the treatment of amblyopia [73]; an example is the online training offered by the company Caterna Vision GmbH, the only vision training which is reimbursed by some health insurance companies in Germany under selective contracts [29].

In the context of digital vision training, the Digital Health Care Act (DVG) should be noted. With the entry into force of the DVG on 19 December 2019, the "app on prescription" for patients was introduced into health care with the objective that contract physicians include digital medical devices (health apps) in medical treatment as part of their health care mandate. As a result, SHI-insured persons are entitled to be provided with digital health apps, i.e. digital medical devices which can be prescribed by physicians and are reimbursed by the health insurer. Insured persons who submit proof of a corresponding therapeutic indication to their health insurer may obtain a desired digital health application even without a doctor's prescription. This requires for the digital health applications to have successfully passed testing by the Federal Institute for Drugs and Medical Devices (BfArM) [126] and to be listed in the directory of reimbursable digital health applications (DiGA directory). At the current time of research, this does not apply to digital vision training.

6.4 Organizational aspects

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

The present HTA used Kadhum 2021 [92], Fronius 2016 [8], Fronius 2020 [73], and Kämpf 2003 [67], studies found in the scoping search, in the content analysis of organizational aspects. The list of relevant publication(s) is found in Section A9.3.4 of the full report.

Influence on the prerequisites of service provision and the organizational processes

In Germany, a dense network of outpatient and inpatient ophthalmologic facilities exists for the care of patients with eye diseases. Ophthalmologists are often supported by orthoptists [27]. This allied health profession is active in the field of ophthalmology (Section 1.3).

While conventional passive treatment methods can usually be integrated into everyday life, in digital training, the technology used determines whether the procedures can be used at home or whether patients must visit a facility for the therapy. If the vision training takes place on an outpatient basis, e.g. because shutter glasses are used, parents may need to take children and adolescents to a central facility on a regular basis for several months. This may be associated with considerable effort, especially if patients live in a rural area. This required effort may potentially reduce motivation and lead to therapy dropouts. Furthermore, outpatient treatment involves an additional time commitment for medical staff (e.g. with regard to patient admission and monitoring). In addition, a suitable space must be available in the practice, clinic or research facility where the outpatient training is offered.

Conducting the active vision training in the patient's home is therefore advantageous from an organizational point of view. As is the case with conventional treatment, the ophthalmologists

(and/or orthoptists) then perform only treatment monitoring. However, a shift to the private home can be successful only if the necessary apparatus is available and if the patients or their parents are instructed accordingly in the use of the devices and supported in case of queries. While a commercially available computer, laptop, or tablet, and an Internet connection (to download the software or the vision training programme) are sufficient for the Caterna vision training, some binocular vision training interventions require additional hardware components (such as VR glasses). This type of (usually cost-intensive) equipment is not available in many households and requires an initial purchase.

If digital training is carried out at home, it is the responsibility of the parents or legal guardians to ensure that the child carries out the training to the prescribed extent and under appropriate conditions. For example, parents must ensure that the dominant eye is properly occluded during monocular training (such as with Caterna) or that glasses do not fog up during binocular training, e.g. with VR glasses or anaglyph glasses under which the child's own visual aid is worn, and that the glasses or headset fit well. The game may need to be interrupted if the glasses fog up or headsets cause discomfort. In addition, children must be carefully monitored to ensure that they do not run off with the VR glasses and injure themselves.

The results of the studies included in the benefit assessment (Section A3.3.8 of the full report) which report data on treatment adherence further show that in practice, problems regarding treatment adherence and treatment discontinuations regularly occur. Especially in younger children, this can be due to patients lacking understanding of the video game and/or being overwhelmed by the game or lacking concentration. With older children, this is often due to boredom since the video games are typically simple (e.g. Tetris). With regard to the home therapy concept, retaining attention therefore plays a critical role in active vision training.

7 Discussion

Amblyopia is conventionally treated by occlusion of the dominant eye, which should be started as early as possible because the plasticity of the nervous system decreases with age. However, occlusion treatment has several disadvantages, especially in older children who may have fallen through the cracks of early detection [17,88,94,98-100]. Occlusion therapy may negatively interfere with personality maturation [89]. In addition, taping the stronger eye prevents the normal interaction between both eyes, which may lead to further visual deficits. Considering the potentially unfavourable aspects of conventional amblyopia treatment with occlusion patches or films, it is unsurprising that new treatment approaches have been explored using (digital) technologies. For example, occlusion patches in the form of digitally controlled occlusion glasses have been tested [101,127]. In addition, various active training methods have been developed on a digital basis [20] (with or without additional occlusion treatment; see Section 4.2). These digital treatment methods are funded based on different models: Some methods have been used only in scientific studies, while others are offered commercially and paid for by patients out of pocket.

The conventional treatment method is usually integrated into everyday life; in the case of active vision training, however, the technology used determines whether the procedures can be used at home or whether patients must visit a facility (such as an eye clinic) to receive therapy. If the typically multi-session vision training is conducted on an outpatient basis, e.g. because it requires special equipment [48], the organizational effort can be considerable and may potentially reduce the motivation of both patients and parents or guardians. Shifting active vision training to the patients' home environment is therefore advantageous. As is the case with conventional treatment, the ophthalmologists (and/or orthoptists) then perform only treatment monitoring. However, a shift to the home setting can be successful only if the equipment allows it and if patients or their parents are appropriately supported in using the equipment. The studies included in the present HTA report which offer data on treatment adherence show that, in practice, problems regarding adherence to the prescribed therapy as well as treatment discontinuations regularly occur. Especially in younger children, reasons include patients lacking understanding of the video game, being overwhelmed by the game, or lacking concentration. With older children, problems are often due to boredom because the video games offered are inferior to innovative computer game genres, especially in terms of complexity and graphic animation. With regard to the home therapy concept, therefore, attention retention plays a key role, requiring efforts not only by patients and their parents, but also by the video game developers. In addition to the frequently lacking treatment adherence, there are some reservations (increased risk perception) concerning digitally supported treatment methods, especially by parents [94]. This higher perceived risk is mainly related to the increased media consumption associated with such methods. Moreover, Gaming Disorder has been officially recognized as a disease by the WHO according to ICD-11

since 2019. It is therefore understandable for parents and guardians in particular to critically question the use of digitally supported forms of therapy in children and adolescents [73].

Decisions regarding digital training should therefore be taken in consideration of the following components:

- Benefit of treatment: Although isolated studies suggest a statistically significant effect in favour of active vision training when compared to no training or to sham training with regard to the outcome "best corrected visual acuity of the amblyopic eye", the measured differences in these comparisons cannot be assumed to be clinically relevant. Most studies with statistically significant results do not meet a clinical relevance threshold of -0.05 logMAR (improvement by +0.5 lines) for the outcome "best-corrected visual acuity of the amblyopic eye". The lack of observed effects in the comparison of digital training versus sham training, in particular, might be due to the comparator intervention: In the 2 studies comparing dichoptic training versus sham training, for instance, the sham training did not involve different contrast elements, but the children still wore image-separating glasses. Likewise, in the studies comparing digital monocular training versus a nondigital near task or another digital sham intervention (without additional stimulation), no differences were observed between the groups being compared. Therefore, the respective comparator intervention (in the form of sham training) might show the same effect as the intervention investigated in the studies. On comparison of vision training versus occlusion, no statistically significant effects in favour of vision training were identified by any of the studies except Birch 2020 [59] (with a treatment period of only 2 weeks) – on the contrary, the effect estimators were in favour of occlusion treatment. For the patient-relevant outcome of binocular vision (defined as stereoscopic acuity and/or depth of suppression of the amblyopic eye), none of the studies showed a hint of greater benefit of digital training – neither compared to no training nor to sham training or occlusion treatment. The lack of published clinical relevance thresholds would additionally complicate any interpretation. The results on binocular vision might be due to inadequacies of the available measurement methods. The clinically used stereoacuity tests (e.g. Titmus test) are suitable for the detection of deficits, but not for the accurate and reliable quantification of thresholds. New digital technologies might improve diagnostics compared to conventional testing. Using stereotests on tablets or 3D monitors with shutter glasses, it should also be possible to derive (reliable) clinically relevant thresholds [128]. However, any improvements may also be related to a learning effect in patients with frequent test repetition rather than to therapy [128]. Furthermore, it was impossible to deduce from the available studies whether younger children draw greater benefit from digital training than do older children or whether patients with amblyopia from anisometropia benefit more from vision training than those with amblyopia from strabismus because this form of

amblyopia often additionally requires surgical correction due to ocular misalignment. It was likewise impossible to determine whether pretreated children and/or adolescents benefit more from digital training than those who have not received any prior treatment.

- For the decision-making process, costs are of importance to the extent that digital forms of treatment are only selectively reimbursed (depending on the SHI) as an add-on to occlusion treatment in Germany. For vision training interventions to be cost-effective, additional costs must be associated either with greater benefit (in the form of better treatment results) or with savings in conventional treatment (e.g. through reduced treatment times to achieve the same benefit). Since neither of these conditions are currently met, the cost-effectiveness of active vision training in amblyopia cannot be conclusively assessed at present.
- In addition, the age of the children plays a key role in the decision-making process. Providing access to digital media too early is risky and often leads to increased media consumption. In addition, “health games” fall into the category of “serious computer games” because video games are used as both a leisure activity and a therapeutic measure. Therefore, due to the required treatment adherence for 'health games', digital vision training interventions may potentially be associated with an increased risk for gaming disorders.

HTA report compared with other publications

A systematic review ("Ophthalmic Technology Assessment") commissioned by the American Academy of Ophthalmology evaluated studies on dichoptic training which had been published by April 2019 [78]. The publication included both RCTs and case series. The results of the comparative studies are similar to those of the present benefit assessment and do not show a greater benefit of dichoptic training compared to sham or conventional treatment. The authors also note that, at this time, replacing conventional therapy by the new binocular therapies cannot be recommended, adding, however, that the effects (which do not differ significantly between interventions) can be achieved in a shorter time than with conventional treatment. In addition to this Ophthalmic Technology Assessment focusing on binocular therapies, other systematic reviews [22,23] evaluating the benefits of digital vision training interventions have been published in recent years. Although the inclusion criteria of these evidence syntheses varied – with some of them including only amblyopia from anisometropia [105] – the conclusions of these papers are comparable to the results of the present HTA.

In May 2022, an additional RCT [129] was published, which, like Bau 2012 [68] and Kämpf 2001 [67], evaluated monocular vision training by Caterna Vision GmbH (although the study referred to the intervention as "Focal Ambient Visual Acuity Stimulation (FAVAS)"). Like Bau 2012 [68] and Kämpf 2001 [67], this intervention was compared to a sham treatment (each with additive occlusion). The study enrolled a total of 37 children and adolescents from the

Russian Federation (Moscow University Medical Centre), some of whom suffered from bilateral amblyopia. The study's authors also reported that 13 of the enrolled patients exhibited pathological changes in the fundus of the eye and 2 others already had an artificial lens (artiphakia). Since children and adolescents with organic eye diseases do not meet the inclusion criteria of the HTA, this study was excluded from the results section of the benefit assessment (Section 4 and Section A3 of the full report). Although the study's authors concluded that the best-corrected logMAR visual acuity measured monocularly after 10 days of treatment showed statistically significant differences in favour of the intervention compared to sham treatment, this study's measured differences – like those of the present HTA – cannot be assumed to be clinically relevant due to the upper and lower limits (95% CIs) of the measured MDs. The interpretation of this RCT's results is further complicated by unclear information regarding the characteristics of the included study population and the unit of analysis (patients and/or eyes) and by visual acuity data referring to different meridians (i.e. for planes with different corneal refractive power).

Perspectives

Technological developments are creating new possibilities for diagnosis and treatment of amblyopia. However, study results suggest that existing binocular games are insufficiently captivating for different age groups if prescribed for therapeutic purposes. Further studies must clarify whether a greater number of games and more interesting games may lead to better results. The rapid development is also problematic in itself: By the time the methods have been fully developed and carefully tested on all target groups, the technology is often already outdated. The question of whether children in particular should spend more time with digital media certainly represents a valid concern. What would be desirable is a wider range of therapy options (potentially including non-digital options) which can be selected individually for patients to fit their circumstances. New, carefully tested diagnostic procedures might provide more reliable insights into the effect of the various therapies. This report did identify a potentially interesting aspect: Although the new therapies did not show any significantly better results, said results seem to be achieved in a shorter time than with patch occlusion. Often, binocular therapy was conducted for only 1 hour each 1-to-3 times per week, whereas occlusion was typically prescribed for 2 hours daily or longer, which might suggest a better dose-response relationship of binocular therapies. Furthermore, these (new) active therapy options might help counteract potential stigmatization resulting from occlusion therapy, especially in older children.

8 Conclusion

A total of 17 randomized trials evaluating active digital vision training in children and adolescents were included in the present HTA. The identified studies focused on patients with amblyopia (from anisometropia and/or strabismus). To date, no results from randomized trials have been published on other relevant deficits in visual development (refractive anomalies or eye misalignment) or on vision training interventions which are not digitally delivered.

Of the 17 included studies, 11 studies (with N = 1138 children and adolescents) evaluated the benefit of dichoptic (binocular) vision training, while 6 studies (with N = 165 children and adolescents) investigated the benefit of monocular vision training.

Dichoptic training was compared with (A) no training, (B) sham training, or (C) conventional treatment (occlusion). Treatment was provided at home in all but 1 study, where children and adolescents attended an outpatient clinic. In total, 2 studies evaluated children with amblyopia induced exclusively by anisometropia (refractive amblyopia). The remaining studies included amblyopia from anisometropia and/or strabismus. The age of the children and adolescents in the 11 studies on dichoptic training ranged from 3 to 17 years, and the proportion of those who had received prior treatment ranged from 26% to 96%. In 10 studies, dichoptic training was performed using a video game (e.g. Tetris), while in 1 study, participants watched films or series. The image separation required during dichoptic training was achieved via anaglyph glasses (8 studies), shutter glasses (1 study), or virtual reality glasses (2 studies). Except in the 2 studies using virtual reality glasses, training was conducted on a computer or tablet.

In total, 6 studies investigated the benefit of monocular vision training compared with (A) no training or (B) sham training. In 4 studies, monocular training, where the stronger eye is occluded, was performed on an outpatient basis. Two studies evaluated only refractive amblyopia, and 4 studies investigated only 2- to 10-year-old children who had received their initial diagnosis. While monocular training involved playing a video game on a computer or tablet in 5 studies, 1 study asked children and adolescents to trace images which were presented digitally. Three studies used special background stimulation (a moving sinusoidal grating for neural stimulation) during monocular training. The remaining 3 studies did not use this background stimulation.

All studies reported data for the outcome "best-corrected visual acuity of the amblyopic eye". (A) Comparing active digital vision training with no training, significant effects were found in favour of active vision training – both dichoptic and monocular. The available study pool fails to show whether the additional occlusion treatment (which some studies used as add-on treatment in both intervention arms) enhances the effect of digital training. (B) When comparing vision training versus sham training, 1 of 6 studies described a statistically

significant effect in favour of the investigated intervention. The missing effects in this comparison category could be due to the fact that the respective sham intervention (which was also based on vision training) showed the same effect as the experimental intervention. (C) Only studies on dichoptic training investigated digital vision training in the form of monotherapy versus occlusion treatment alone. Except for 1 study (with a treatment duration of only 2 weeks), no studies showed any statistically significant effects in favour of vision training – on the contrary, the effect estimators were in favour of occlusion treatment.

Although isolated studies suggest a statistically significant effect in favour of active vision training compared to no training or sham training for the outcome "best-corrected visual acuity of the amblyopic eye", the differences measured in these comparisons cannot be assumed to be clinically relevant. Most studies with statistically significant results do not meet a clinical relevance threshold of -0.05 logMAR (improvement by +0.5 lines) for the outcome "best-corrected visual acuity of the amblyopic eye". Only in 1 study, which compared monocular vision training versus no training, was the clinical relevance threshold exceeded at 1 of 4 measurement time points: The upper and lower limits (95% CIs) of measured mean differences after 9 weeks of treatment were -0.24 logMAR (+2.4 lines) and -0.06 logMAR (+0.6 lines), respectively.

In summary, for the outcome "best-corrected visual acuity of the amblyopic eye," no hint of (greater) benefit of digital dichoptic or monocular vision training was found in any of the comparisons: neither compared to no training nor to sham training or occlusion treatment.

For the patient-relevant outcome of binocular vision, none of the studies showed a hint of greater benefit of digital training – neither compared to no training nor to sham training or occlusion treatment.

In the present study pool, the number of reported adverse events was rather low, and no study showed any hint of an increased risk of such events – neither with digital training nor in the control group. However, it must be noted that the rather small number of study participants precludes drawing a reliable conclusion with regard to adverse events. No data are available on other patient-relevant outcomes.

In Germany, vision training is currently used only as an add-on to occlusion treatment. The average total costs per person for occlusion treatment in the 1st year of treatment are between €606 and €646, which is largely covered by the SHI (2/3 of the costs are for the aids used in the treatment). In addition to these costs, 3 months of treatment with the monocular vision training offered in Germany by the company Caterna Vision GmbH would cost €380. Some health insurance funds cover the costs for the vision training within the framework of selective contracts. Apart from the costs presented for monocular visual training by Caterna Vision GmbH, no further data were available from which a reliable cost estimate for active

vision training might be derived. In summary, for vision training to be cost-effective, the additional costs must be associated with either greater benefit (in the form of better treatment outcomes) or savings in conventional treatment (e.g. through reduced treatment times for the same benefit). Since neither of these conditions is currently met, the cost-effectiveness of active vision training in amblyopia cannot be conclusively assessed. Given that no studies were found on other relevant developmental vision impairments or on other non-digitally delivered vision training, extending the economic evaluations to other therapeutic indications or interventions was not deemed useful.

When making decisions regarding digital training, the early and risk-associated access to digital media and the increased media consumption associated with such therapy must be considered critically from ethical and social perspectives. In terms of adherence to the prescribed therapy, study data additionally show that problems and treatment discontinuations repeatedly occur in practice. These are often due to a lack of understanding of the video game and/or patients being overchallenged (especially younger children) or underchallenged (especially older children and adolescents) because the 'health games' offered are typically video games with a simple design (e.g. Tetris). With regard to the home therapy concept, retaining attention therefore plays a critical role in active vision training.

Overall, the available evidence does not allow drawing a final conclusion on the benefit of active vision training in children and adolescents with amblyopia. Alongside the frequent lack of treatment adherence, it is important to note that the studies' treatment duration was set to only a few weeks, while amblyopia treatment is often required for many years. Furthermore, it was impossible to deduce from the heterogeneous study pool whether children with refractive amblyopia achieve better results than children with amblyopia from strabismus. Such results would be important for the benefit assessment of digital therapies, however, in order to better assess which patients benefit most from such therapy. In addition, further studies are needed to determine whether more interesting (possibly also non-digital) games or vision training interventions lead to better treatment adherence and possibly also show greater benefit with regard to patient-relevant outcomes – especially in older children. Overall, it can be concluded that the outcomes of the new therapies were not superior.

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Please see full HTA report for the full reference list.

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The full HTA report (German version) is published under

https://www.iqwig.de/sich-einbringen/themencheck-medizin/berichte/ht21-03.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 [130] for this purpose. IQWiG is also a member of the network.

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

Table 5: Domains of the EUnetHTA Core Model

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

a) MEDLINE

Search interface: Ovid; Ovid MEDLINE(R) ALL 1946 to July 07, 2021

The following filters were adopted: Systematic review: Wong 2006 [131]] – High specificity strategy

#	Searches
1	Orthoptics/
2	((vergence* or vision* or accommodative* or orthoptic*) adj3 (therap* or examination*)).ti,ab.
3	or/1-2
4	cochrane database of systematic reviews.jn.
5	(search or MEDLINE or systematic review).tw.
6	meta analysis.pt.
7	or/4-6
8	7 not (exp animals/ not humans.sh.)
9	and/3,8
10	9 and (english or german).lg.

b) Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	Orthoptics[mh]
2	"vergence therapy" OR "vision therapy" OR "accommodative therapy" OR "vision examinations" OR "vision examination" OR "accommodative examinations" OR "accommodative examination"
3	#2 OR #1

Search for primary studies

c) MEDLINE

Search interface: Ovid; Ovid MEDLINE(R) 1946 to October 27, 2021

The following filters were adopted: RCT: Lefebvre 2019 [132]] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version

#	Searches
1	Video Games/
2	Learning/
3	Computers, Handheld/
4	or/1-3
5	Vision, Binocular/
6	Visual Acuity/
7	Visual Perception/
8	or/5-7
9	and/4,8
10	((vision* or vergence* or occlusion* or orthoptic* or (pencil adj1 push* adj1 up*)) adj3 therap*).ti,ab.
11	(perceptual adj3 learning*).ti,ab.
12	((training* or game* or video* or ipad* or learning*) and (binocular* or visual activit* or visual acuit* or vernier acuit* or visual function* or visual task* or dichoptic*)).ti,ab.
13	or/9-12
14	exp pediatrics/
15	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
16	(school child* or school*).ti,ab.
17	or/14-16
18	and/13,17
19	Randomized Controlled Trial.pt.
20	Controlled Clinical Trial.pt.
21	(randomized or placebo or randomly or trial or groups).ab.
22	drug therapy.fs.
23	or/19-22
24	exp animals/ not humans/
25	23 not 24 [CHSS-sensitivity-maximizing version]
26	and/18,25
27	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
28	hi.fs. or case report.mp.
29	or/27-28
30	26 not 29
31	30 and (english or german or multilingual or undetermined).lg.

Search interface: Ovid; Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations October 27, 2021

#	Searches
1	((vision* or vergence* or occlusion* or orthoptic* or (pencil adj1 push* adj1 up*)) adj5 therap*).ti,ab.
2	(perceptual adj5 learning*).ti,ab.
3	((training* or game* or video* or ipad* or learning*) and (binocular* or visual activit* or visual acuit* or vernier acuit* or visual function* or visual task* or dichoptic*)).ti,ab.
4	or/1-3
5	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
6	(school child* or school*).ti,ab.
7	or/5-6
8	and/4,7
9	(clinical trial* or random* or placebo).ti,ab.
10	trial.ti.
11	or/9-10
12	and/8,11
13	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta-analysis/ or consensus/ or exp guideline/
14	hi.fs. or case report.mp.
15	or/13-14
16	12 not 15
17	16 and (english or german or multilingual or undetermined).lg.

d) Embase

Search interface: Ovid; Embase 1974 to 2021 October 27

The following filter was adopted: RCT: Wong 2009 [131] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	"Perceptual learning"/
2	Training/
3	Learning/
4	Video Game/
5	Game/
6	or/2-5
7	Visual Acuity/
8	Binocular Vision/
9	or/7-8
10	and/6,9
11	((vision* or vergence* or occlusion* or orthoptic* or (pencil adj1 push* adj1 up*)) adj3 therap*).ti,ab.
12	(perceptual adj3 learning*).ti,ab.
13	((training* or game* or video* or ipad* or learning*) and (binocular* or visual activit* or visual acuit* or vernier acuit* or visual function* or visual task* or dichoptic*)).ti,ab.
14	or/1,10-13
15	exp Pediatrics/
16	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
17	(school child* or school*).ti,ab.
18	or/15-17
19	and/14,18
20	(random* or double-blind*).tw.
21	placebo*.mp.
22	or/20-21
23	and/19,22
24	23 not medline.cr.
25	24 not (exp animal/ not exp human/)
26	25 not (Conference Abstract or Conference Review or Editorial).pt.

e) The Cochrane Library

Search interface: Wiley; Cochrane Central Register of Controlled Trials, Issue 10 of 12, Oct 21

#	Searches
#1	[mh ^"Video Games"]
#2	[mh ^"Learning"]
#3	[mh ^"Computers, Handheld"]
#4	#1 or #2 or #3
#5	[mh ^"Vision, Binocular"]
#6	[mh ^"Visual Acuity"]
#7	[mh ^"Visual Perception"]
#8	#5 or #6 or #7
#9	#4 and #8
#10	((vision* or vergence* or occlusion* or orthoptic* or (pencil NEAR/1 push* NEAR/1 up*)) NEAR/3 therap*):ti,ab
#11	(perceptual NEAR/3 learning*):ti,ab
#12	((training* or game* or video* or ipad* or learning*) and (binocular* or visual activit* or visual acuit* or vernier acuit* or visual function* or visual task* or dichoptic*)):ti,ab
#13	#9 or #10 or #11 or #12
#14	[mh "pediatrics"]
#15	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*)
#16	(school child* or school*):ti,ab
#17	#14 or #15 or #16
#18	#13 and #17
#19	#18 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#20	#19 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)))
#21	#20 in Trials

B.1.2 – Searches in study registries

a) ClinicalTrials.gov

Provider: U.S. National Institutes of Health

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

Search strategy
(EXPAND[Concept] "binocular treatment" OR EXPAND[Concept] "vision therapy" OR EXPAND[Concept] "vergence therapy" OR EXPAND[Concept] "occlusion therapy" OR EXPAND[Concept] "orthoptic therapy" OR pencil push-up OR EXPAND[Concept] "perceptual learning" OR AREA[InterventionSearch] ((training OR game OR video OR ipad OR learning) AND (binocular OR EXPAND[Concept] "visual activity" OR EXPAND[Concept] "visual acuity" OR EXPAND[Concept] "vernier acuity" OR EXPAND[Concept] "visual function" OR EXPAND[Concept] "visual task" OR dichoptic))) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child"

b) International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

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

Search strategy
"binocular treatment" OR "vision therapy" OR "vergence therapy" OR "occlusion therapy" OR "orthoptic therapy" OR pencil push-up OR "perceptual learning" OR ((training OR game OR video OR ipad OR learning) AND (binocular OR "visual activity" OR "visual acuity" OR "vernier acuity" OR "visual function" OR "visual task" OR dichoptic))

B.2 – Search strategies for the health economic evaluation

a) MEDLINE

Search interface: Ovid; Ovid MEDLINE(R) ALL 1946 to November 30, 2021

The following filter was adopted: Health economic evaluation: Glanville 2009 [133] – Emory University (Grady)

#	Searches
1	Video Games/
2	Learning/
3	Computers, Handheld/
4	or/1-3
5	Vision, Binocular/
6	Visual Acuity/
7	Visual Perception/
8	or/5-7
9	and/4,8
10	((vision* or vergence* or occlusion* or orthoptic* or (pencil adj1 push* adj1 up*)) adj3 therap*).ti,ab.
11	(perceptual adj3 learning*).ti,ab.
12	((training* or game* or video* or ipad* or learning*) and (binocular* or visual activit* or visual acuit* or vernier acuit* or visual function* or visual task* or dichoptic*)).ti,ab.
13	or/9-12
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/13,18
20	19 not (comment or editorial).pt.
21	20 and (english or german).lg.

b) Embase

Search interface: Ovid; Embase 1974 to 2021 November 30

The following filters were adopted: Health economic evaluation: Glanville 2009 [133] – Embase G

#	Searches
1	"Perceptual learning"/
2	Training/
3	Learning/
4	Video Game/
5	Game/
6	or/2-5
7	Visual Acuity/
8	Binocular Vision/
9	or/7-8
10	and/6,9
11	((vision* or vergence* or occlusion* or orthoptic* or (pencil adj1 push* adj1 up*)) adj3 therap*).ti,ab.
12	(perceptual adj3 learning*).ti,ab.
13	((training* or game* or video* or ipad* or learning*) and (binocular* or visual activit* or visual acuit* or vernier acuit* or visual function* or visual task* or dichoptic*)).ti,ab.
14	or/1,10-13
15	(Cost adj effectiveness).ab.
16	(Cost adj effectiveness).ti.
17	(Life adj years).ab.
18	(Life adj year).ab.
19	Qaly.ab.
20	(Cost or costs).ab. and Controlled Study/
21	(Cost and costs).ab.
22	or/15-21
23	and/14,22
24	23 not medline.cr.
25	24 not (exp animal/ not exp human/)
26	25 not (Conference Abstract or Conference Review or Editorial).pt.
27	26 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.

c) Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	vision therapy OR "occlusion therapy" OR "pencil push up*" OR "orthoptic therapy" OR "vergence therapy"
2	perceptual learning
3	(binocular OR visual OR vernier OR dichoptic*) AND (training* OR game* OR video* OR ipad* OR learning*)
4	#3 OR #2 OR #1

B.3 – Exploratory searches

a) Exploratory search strategy for ethical aspects in the databases ETHMED, Philosopher's Index and SSCI (02.03.2022)

The search was conducted with an or/and combination of the following subject headings and text words in the title, abstract and keywords: dichoptic, monocular, perceptual, visual, vision, occlusion, train*, therap*, learning, ethics*, ethic*, autonom* , consent*, harm*, benefit*, justice*, access*, child*, adolescen*, boy, boys, girl, girls, paediatr*, pediatri*, preschool*, puberty, school child, schoolchild*, teen, teens, teenager*, youth, youths.

From a total of 1224 initial hits (after duplicate deletion), 48 potentially relevant publications were identified at the title/abstract level and analysed at the full text level.

b) Exploratory search strategy for social aspects in the databases MEDLINE und SSCI (02.03.2022)

The search was conducted with an or/and combination of the following subject headings and text words in the title, abstract and keywords: dichoptic, monocular, perceptual, visual, vision, occlusion, train*, therap*, learning, social*, socio-cultural*, understanding*, construction*, knowledge, accept*, perception*, expectation*, inequalit*, relationship*, access*, child*, adolescen*, boy, boys, girl, girls, paediatr*, pediatri*, preschool*, puberty, school child, schoolchild*, teen, teens, teenager*, youth, youths.

From a total of 1404 initial hits, 52 potentially relevant publications were identified at the title/abstract level and analysed at the full text level.

c) Exploratory search strategy for legal aspects in the databases of the German Federal Court of Justice, the Federal Legal Information System and in the databases "Juris" and "Beckonline". (02.03.2022)

The search was conducted with an or/and combination of the following subject headings and text words: Therapie*, Einwilligung*, Kinder* und Jugendliche*, Erziehungsberechtigte*,

Obsorgebetraute*, Health Games*, Medizinprodukt*, Datenschutz*, Kostenübernahme* (English translation: therapy*, consent*, children* and adolescents*, legal guardians*, guardians*, health games*, medical device*, data protection*, cost coverage*)

From a total of 28 initial hits, 22 potentially relevant publications were identified at the title/abstract level and analysed at the full text level.

d) Exploratory search strategy for organizational aspects in the databases MEDLINE (10.03.2022)

The search was conducted with an or/and combination of the following subject headings and text words in the title, abstract and keywords: dichoptic, monocular, perceptual, visual, vision, train*, therap*, child*, adolescen*.

From a total of 566 initial hits, 22 potentially relevant publications were identified at the title/abstract level and analysed at the full text level.