

8.03.10 Cognitive Rehabilitation**Original Policy Date:** October 15, 1997**Effective Date:** June 1, 2023**Section:** 2.0 Medicine**Page:** Page 1 of 38**Policy Statement**

- I. Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) may be considered **medically necessary** in the rehabilitation of individuals with cognitive impairment due to traumatic brain injury.
- II. Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) is considered **investigational** for all other applications, including, but not limited to:
 - A. Aging population, including patients with Alzheimer disease
 - B. Autism spectrum disorder
 - C. Multiple sclerosis
 - D. Individuals with cognitive deficits due to brain tumor or previous treatment for cancer
 - E. Postencephalitic or post encephalopathy individuals
 - F. Seizure disorders
 - G. Stroke

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

For services to be considered medically necessary, they must be provided by a qualified licensed professional and must be prescribed by the attending physician as part of the written care plan. Additionally, there must be a potential for improvement (based on preinjury function), and patients must be able to participate actively in the program. (Active participation requires sufficient cognitive function to understand and participate in the program, as well as adequate language expression and comprehension, i.e., participants should not have severe aphasia.) Ongoing services are considered necessary only when there is demonstrated continued objective improvement in function.

Duration and intensity of cognitive rehabilitation therapy programs vary. One approach for comprehensive cognitive rehabilitation is a 16-week outpatient program comprising 5 hours of therapy daily for 4 days each week. In another approach, cognitive group treatment occurs for three 2-hour sessions weekly and three 1-hour individual sessions (total, 9 hours weekly). Cognitive rehabilitation programs for specific deficits (e.g., memory training) are less intensive and generally have 1 or 2 sessions (30 or 60 minutes) a week for 4 to 10 weeks.

Coding

The following CPT code is specific to cognitive rehabilitation:

- **97127:** Therapeutic interventions that focus on cognitive function (e.g., attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (e.g., managing time or schedules, initiating, organizing and sequencing tasks), direct (one-on-one) patient contact

Sensory integration therapy, explicitly identified by CPT code 97533, is addressed separately in Blue Shield of California Medical Policy: Sensory Integration Therapy and Auditory Integration Therapy.

Description

Cognitive rehabilitation is a therapeutic approach designed to improve cognitive functioning after central nervous system insult. It includes an assembly of therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions. Cognitive rehabilitation comprises tasks to reinforce or reestablish previously learned patterns of behavior or to establish new compensatory mechanisms for impaired neurologic systems. Cognitive rehabilitation may be performed by a physician, psychologist, or a physical, occupational, or speech therapist.

Related Policies

- Sensory Integration Therapy and Auditory Integration Therapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Cognitive rehabilitation is not subject to regulation by the U.S. Food and Drug Administration.

Rationale

Background

Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual's ability to think, use judgment, and make decisions. The focus is on improving deficits in memory, attention, perception, learning, planning, and judgment. The term *cognitive rehabilitation* is applied to various intervention strategies or techniques that attempt to help patients reduce, manage, or cope with cognitive deficits caused by brain injury. The desired outcomes are improved quality of life and function in home and community life. The term *rehabilitation* broadly encompasses reentry into familial, social, educational, and working environments, the reduction of dependence on assistive devices or services, and general enrichment of quality of life. Patients recuperating from traumatic brain injury have traditionally been treated with some combination of physical therapy, occupational therapy, and psychological services as indicated. Cognitive rehabilitation is considered a separate service from other rehabilitative therapies, with its own specific procedures.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

This review evaluates evidence for cognitive rehabilitation delivered by a qualified professional. Studies of self-administered computer programs are not considered cognitive rehabilitation for this evidence review and are not assessed here.^{1,2,3,4,5} Short-term improvements in cognitive test performance measured post-intervention alone will not be considered a health outcome for this review. Measurements of daily functioning and quality of life are the primary health outcomes of interest. Improvements should be demonstrable after longer-term follow-up post-intervention, preferably greater than 6 months.

This evidence review was initially informed by a TEC Assessment (1997).⁶ The Assessment addressed a broad range of patient indications resulting from neurologic insults, including traumatic brain injury (TBI), stroke, postencephalopathy, and aging (including Alzheimer disease [AD]). Eighteen controlled trials were reviewed, primarily focusing on stroke and TBI. No controlled trials were available that specifically addressed other patient indications. No clear answer on the efficacy of cognitive rehabilitation emerged from the Assessment. The evidence was conflicting either because of study designs, low power to detect differences, or variations in treatment. The Assessment concluded that data in the published peer-reviewed literature were inadequate to validate the effectiveness of cognitive rehabilitation as an isolated component or as a component of a multimodal rehabilitation program.

In 2013, the American Congress of Rehabilitation Medicine published a systematic review of cognitive rehabilitation on medical conditions affecting cognitive function.⁷ Literature was searched through the end of 2008. Of 11 clinical conditions reviewed (anoxia/hypoxia, encephalitis, epilepsy, HIV-AIDS encephalopathy, Huntington disease, systemic lupus erythematosus, Lyme disease and other tick-borne encephalopathy, neoplasms, Parkinson disease, metabolic encephalopathy), evidence supported only a practice guideline for children and adolescents with brain tumors who underwent surgical resection and/or radiotherapy (see Practice Guidelines and Position Statements section). The evidence for patients with seizure-related cognitive impairments is discussed in a later section herein.

Traumatic Brain Injury

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation, in patients with cognitive deficits due to TBI.

The question addressed in this evidence review is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to TBI?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to TBI. The severity of TBI is commonly objectively assessed using the Glasgow Coma Scale (GCS) based on impairment of conscious level.⁸ The GCS measures 3 components - levels of eye, verbal and motor responsiveness. GCS scores can range from 3 (lowest level of responsiveness) to 15 (highest level of responsiveness). Based on associations between GCS score and outcomes, TBI severity has been classified as Mild=GCS of 13 to 15, Moderate=GCS of 9 to 12, and Severe=GCS of 3 to 8.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after central nervous system (CNS) insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without a specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to TBI has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, a minimum of 6 months of follow-up is considered necessary to demonstrate efficacy.

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded

Review of Evidence

Systematic Reviews

A 2013 Cochrane review assessed cognitive rehabilitation for executive dysfunction (planning, initiation, organization, inhibition, problem-solving, self-monitoring, error correction) in adults with nonprogressive acquired brain damage.⁹ Sixteen RCTs (N=660 patients; 395 TBI, 234 stroke, 31 other acquired brain injury) were included in pooled analyses. No statistically significant effects on measures of global executive function or individual component functions were found.

A 2008 TEC Assessment evaluated cognitive rehabilitation specifically for adults with TBI.⁶ The objective of this Assessment was to determine whether the evidence showed that cognitive rehabilitation improved health outcomes. Eleven RCTs for specific cognitive deficits showed inconsistent support for cognitive rehabilitation. Of these 11 studies, 8 reported daily functioning or quality of life outcomes. Three studies showed statistically significant differences between

intervention groups and control groups on 1 outcome. However, 2 studies were extremely small. Findings were inconsistent across other outcomes measured. In 1 study, significant findings after the intervention were no longer present at 6-month follow-up. All 11 trials also reported outcomes of various cognitive tests. These trials had numerous methodologic limitations, such as small sample sizes, lack of long-term follow-up, minimal interventions, and multiple outcomes. In summary, the RCTs considered in this Assessment did not show strong evidence for efficacy in the treatment of TBI.

Randomized Controlled Trials

Chiaravalloti et al (2016) conducted an RCT evaluating the Story Memory Technique to improve learning and memory in subjects with moderate-severe TBI.¹⁰ Sixty-nine subjects were randomized to treatment or control. Assessments were performed at the end of treatment (5 weeks) and 6 months posttreatment. Statistically significant outcomes favored the treatment group for several measures assessing memory at 5 weeks, while results at 6 months were less definitive.

das Nair et al (2019) conducted the large (N=328), multicenter, assessor-blinded, RCT, which evaluated a group memory rehabilitation program for people with TBI (ReMemBrIn) in 9 sites in England.¹¹ The group memory rehabilitation intervention involved 10 weekly sessions, each lasting about 1.5 hours, which were delivered by a trained Assistant Psychologist to groups of between 4 to 6 participants. The intervention focused on retraining memory functions and strategies to improve encoding and retrieval. The control group received usual care, which typically included employment rehabilitation services, self-help groups, or specialist charity support. Between 2013 and 2015, 328 individuals were randomized to therapy (N=171) or usual care (N=157). The participants were characterized by a mean age of 45.1 years, median GCS closest to admission of 11.5 (25th, 75th centile=6, 14), a length of initial hospital stay for TBI of 84.2 days, and time since TBI of 100.9 months. On the primary outcome of frequency of memory failures in daily life assessed using the Everyday Memory Questionnaire-patient version at 6 months' follow-up, the between-group difference was not clinically important (adjusted difference in mean scores -2.1 ; 95% confidence interval [CI] -6.7 to 2.5; p=.37). For secondary outcomes, there was a significant improvement in goal attainment both at 6 and 12 months, but no differences on others such as mood or quality of life. Important methodological limitations included lack of an active control arm, incomplete assessment of intervention fidelity, and exclusion of over 20% of the sample from the primary analysis.

Section Summary: Traumatic Brain Injury

Although some RCTs have shown improvements in some outcomes with cognitive rehabilitation in individuals with moderate-severe TBI, systematic reviews have provided mixed findings with no consistent evidence of efficacy in patients with TBI.

Dementia

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional in patients with cognitive deficits due to dementia is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation.

The question addressed in this evidence review is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to dementia?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to dementia. This includes patients with AD.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to dementia has varying lengths of follow-up, ranging from 3 months to 2 years. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded

Review of Evidence**Systematic Reviews**

In a Cochrane review, Bahar-Fuchs et al (2019) evaluated the use of cognitive training for people with mild to moderate dementia.¹² This review included 33 RCTs published between 1988 and 2018. Most RCTs were small and single-site, with sample sizes of 20 patients or below in each trial arm.

Participants in most trials had a mean age between 70 and 80 years, and the presumed etiology of the cognitive dysfunction was Alzheimer dementia. The review authors rated their methodological quality as high or unclear risk of bias due to limitations including lack of allocation concealment and lack of blinding of participants and personnel. Based on low or very low quality evidence, the review found no clear effect of cognitive training on any outcome, including global cognition and function, 3 to 12 months following treatment. Duration of follow-up beyond 12 months post-treatment was not reported.

Huntley et al (2015) performed a meta-analysis of cognitive interventions in dementia.¹³ Thirty-three studies were included. Interventions were divided into categories such as cognitive training, cognitive stimulation, and cognitive rehabilitation. Studies classified as cognitive stimulation had a significant effect as measured on the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale. Reviewers concluded that benefits measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale were generally not clinically significant. In a Cochrane review, Bahar-Fuchs et al (2013) evaluated the use of cognitive training (task-focused) or rehabilitation (strategy-focused) in AD and vascular dementia.¹⁴ Evidence from 11 RCTs did not demonstrate improved cognitive function, mood, or activities of daily living in patients with mild-to-moderate AD or vascular dementia with cognitive training. Reviewers cited a 2010 high-quality RCT of cognitive rehabilitation in 69 patients with early-stage AD, which showed short-term

improvements in patient-rated outcomes.¹⁵ A 2011 Cochrane review assessing interventions for persons with mild cognitive impairment concluded that there was little evidence on the effectiveness or specificity of such interventions because improvements observed were similar to effects seen with active control interventions.¹⁶

Randomized Controlled Trials

Individual randomized trials not included in the systematic reviews have shown variable outcomes of cognitive rehabilitation; see Tables 1 and 2.

Clare et al (2019) reported on results from the multicenter, assessor-blinded Individual Goal-oriented Cognitive Rehabilitation to Improve Everyday Functioning for People with Early-stage Dementia (GREAT) RCT that compared individual goal-oriented cognitive rehabilitation to treatment as usual in individuals with early-stage dementia.¹⁷ The majority of participants were diagnosed with Alzheimer dementia. Their mean age was 78.56 years, and their mean MMSE score was 23.82 points. The primary outcome was participant-rated 3-month goal attainment. Goals were identified using the semi-structured Bangor Goal-Setting Interview. Attainment was assessed based on a 0 to 10 scale. Study authors noted that an improvement of 2 points in the goal attainment rating was considered to be clinically significant. Improvement in goal attainment was significantly greater in the therapy group than in the control group both at 3 months and at 9 months. However, there were no significant between-group differences on any of the secondary outcomes at 3 or 9 months, including self-reported self-efficacy (Generalised Self-Efficacy Scale), mood (Hospital Anxiety and Depression Scale), dementia-specific health-related quality of life, memory (story recall from the Rivermead Behavioural Memory Test), attention (elevator counting and elevator counting with distraction subtests from the Test of Everyday Attention), or executive function (verbal letter fluency from the Delis-Kaplan Executive Function System). No measure of functional ability was assessed.

Ameiva et al (2016) reported on results from the group and individual cognitive therapies in Alzheimer's disease (ETNA3) multicenter RCT that compared 4 therapies strategies: standardized programs of cognitive training (group sessions), reminiscence therapy (group sessions), individualized cognitive rehabilitation program (individual sessions), and usual care.¹⁸ Six hundred fifty-three patients with mild-to-moderate AD were randomized in a 1:1:1:1 ratio at 40 French clinical sites. We focus on the cognitive rehabilitation program and usual care arms. The primary outcome was the rate of survival without moderately severe to severe dementia at 2 years. Secondary outcomes were cognitive impairment, functional disability, behavioral disturbance, apathy, quality of life, depression, caregiver burden, and resource utilization. Participants and clinical staff were not blinded to treatment assignment, but outcome assessments were done by blinded physicians and psychologists. The cognitive rehabilitation therapy consisted of a "made-to-measure" program conducted in individual sessions and adapted to patients' cognitive abilities, with goals selected to be personally relevant to the patient. Intention-to-treat analyses were performed using "missing equal failure" to replace missing values. Approximately 90% of participants had a 3-month follow-up visit, and 72% had a 24-month visit. There was no difference between the cognitive rehabilitation group and the usual care group with respect to the primary outcome. However, patients who received cognitive rehabilitation therapy had a less functional decline at 24 months compared with the usual care group, as measured by 1 of the 2 scales assessing functional abilities: the Autonomie Gérontologique Groupes Iso-Ressources scale ($p=.02$). The rate of institutionalization was lower in the cognitive rehabilitation therapy group (27%) than in the usual care group (19%). These results are promising but, given the lack of consistency in benefits on the 2 functional scales, replication is needed to confirm these positive findings.

Regan et al (2017) reported on an RCT of a home-based, 4-session, goal-oriented cognitive rehabilitation program versus usual care in 55 patients with mild cognitive impairment and early AD.¹⁹ Patients were community-dwelling with a diagnosis of mild cognitive impairment or AD within 6 months of enrollment and an MMSE score greater than 20. The intervention group received 4 weekly 1-hour therapy sessions delivered by experienced therapists with a focus on addressing

personally meaningful goals. All participants identified at least 1 goal for improvement. The usual care group had no contact with the research team between their initial and final assessments. The primary outcome measures were goal performance and satisfaction scores on the Canadian Occupational Performance Measure. Twelve participants in the intervention group and 3 participants in the control group discontinued study participation and were excluded from the final, per-protocol analysis. For the first identified goal, the intervention group had significantly greater improvements in performance and satisfaction on the Canadian Occupational Performance Measure than the control group. There were no differences in secondary measures of quality of life or anxiety and depression. The per-protocol results were biased due to the high rate of missing data.

Thivierge et al (2014) in Canada reported on a small (N=20), assessor-blinded, block-randomized, crossover trial of an individualized memory rehabilitation program in patients with mild-to-moderate AD.²⁰ The Memory Rehabilitation Program comprised 4 weeks of training by a patient's caregiver to improve performance of an instrumental activity of daily living selected by the patient and caregiver. Errorless learning (assistance provided to minimize errors) and spaced retrieval (expanded delays, from 30 seconds to 8 minutes, between each correct performance of the task) were used to facilitate learning at each patient's own pace. The primary outcome was a measure of assistance required to perform the task correctly at 1, 4, and 8 weeks after training. Compared with untrained (in period 1) or previously trained (in period 2) controls, statistically, significant improvements in performance were observed at posttreatment week 1 in both periods and at posttreatment week 4 in period 2. A statistically significant improvement in performance occurred in period 1 controls compared to baseline. Performance of the target instrumental activity of daily living declined within 2 to 3 months post-training. Improvements in other outcomes (general memory and cognitive ability, overall function, quality of life, and behavioral/psychological symptoms) were not observed.²¹

Kurz et al (2012) conducted an RCT of patients with AD and early dementia.²² The population was comprised of 201 patients with clinical evidence of dementia and an MMSE score of at least 21 (of 30 points) who were randomized to a 12-week cognitive rehabilitation program or standard medical management (site-specific). There were no between-group differences in any outcome measure. There also were no group differences in subgroup analyses by age, sex, education level, or baseline cognitive ability. A difference in outcomes were seen in depression scores, which improved significantly for females in the intervention group, but not for males.

Another randomized study of 54 patients by Chapman et al (2004) evaluated the combined effect of a cognitive-communication therapy plus an acetylcholinesterase inhibitor versus drug treatment alone.²³ A positive effect for the inhibitor cognitive rehabilitation group was found for discourse abilities, functional abilities, emotional symptoms, and overall global performance. Beneficial effects were reported up to 10 months after active intervention.

Spector et al (2003) published an RCT on 115 patients assigned to a cognitive stimulation program or a control group.²⁴ The intervention program ran for 7 weeks, and patients were only evaluated at completion. The treatment group had significantly higher scores on the principal outcome MMSE, with a group difference of 1.14 points. Differences were also significant for secondary outcomes, a quality of life score for AD, and an AD assessment scale. The trialists limited assessment of outcomes to the 7-week period of treatment and concluded that the intervention would need to be continued on a regular basis beyond 7 weeks.

Table 1. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions			
					Therapy 1	Therapy 2	Therapy 3	Therapy 4
Clare et al (2019) ¹⁷	England, Wales	8	2013-2016	Patients with early-stage	10 weekly goal-oriented individual cognitive	Treatment as usual (medication,	NR	NR

Study	Countries	Sites	Dates	Participants	Interventions			
				Alzheimer, vascular or mixed dementia (White, 96.4%; Black, 1.5%; Asian, 1.2%; Mixed, 0.4%; Other, 0.4%)	rehabilitation sessions, followed by 4 maintenance sessions over 6 mos (n=281)	monitoring, general psychosocial support) (n=208)		
Amieva et al (2016) ¹⁸	France	40	2008-2009	Patients diagnosed with Alzheimer disease	CTT (n=170)	RT (n=172)	ICRT (n=157)	Usual medical care (n=154)
Thivierge et al (2014) ²⁰	Canada	NR	2008-2011	Patients with Alzheimer disease (n=20)	ELL and SR cognitive techniques	Controls	NR	NR
Kurz et al (2012) ²²	Germany	NR	NR	Patients with mild Alzheimer disease (n=201)	12-week cognitive rehabilitation program (n=100)	Standard medical management (site-specific; n=101)	NR	NR
Chapman et al (2004) ²³	U.S.	NR	1999-2001	Patients with mild to moderate Alzheimer disease (n=54)	Combined cognitive-communication therapy plus an acetylcholinesterase inhibitor (n=28)	Drug treatment alone (n=26)	NR	NR
Spector et al (2003) ²⁴	U.K.	23	NR	Patients with dementia	Cognitive stimulation therapy (n=115)	Control (n=86)	NR	NR

CTT: cognitive training therapy; ELL: errorless learning; ICRT: individualized cognitive rehabilitation therapy; NR: not reported; RT: reminiscence therapy; SR: spaced retrieval.

Table 2. Summary of Key Randomized Controlled Trial Results

Study	Rate of patients alive and without moderately severe to severe dementia at 24 mos	Survival rate at 24 mos	Direct measure of training	Functional Ability score at 9 mos mean (SD)	Overall cognitive functioning at 1 y	Change in MMSE scores from baseline to 7 wks
Clare et al (2019) ¹⁷	NR	NR	Individual goal attainment at 9 mos	NR	NR	NR
Therapy			N=205, +2.52			
Control			N=211, +0.67			
Mean Difference (95% CI)			1.70 (1.32 to 2.09)			
Amieva et al (2016) ¹⁸			NR	NR	NR	NR
CTT	81 (47.7%)	124 (72.9%)				
RT	78 (45.4%)	118 (68.6%)				

Study	Rate of patients alive and without moderately severe to severe dementia at 24 mos	Survival rate at 24 mos	Direct measure of training	Functional Ability score at 9 mos mean (SD)	Overall cognitive functioning at 1 y	Change in MMSE scores from baseline to 7 wks
ICRT	85 (54.1%)	121 (77.1%)				
Control	74 (48%)	109 (70.8%)				
Thivierge et al (2014) ²⁰ , Therapy	NR	NR	86.78	NR	NR	NR
Control			81.12			
Kurz et al (2012) ²² , Therapy	NR	NR	NR	0.729+/-1.82	NR	NR
Control				0.857+/-1.59		
p-value				.64		
Chapman et al (2004) ²³ , Therapy	NR	NR	NR	NR	24.62	NR
Control					26.96	
Spector et al (2003) ²⁴ , Therapy	NR	NR	NR	NR	NR	0.9
Control						-0.4
p-value						.044

CI: confidence interval; CTT: cognitive training therapy; ICRT: individualized cognitive rehabilitation therapy; MMSE: Mini-Mental Status Examination; RCT: randomized controlled trial; RT: reminiscence therapy; SD: standard deviation.

Table 3. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Clare et al (2019) ¹⁷ ,	4. Enrolled populations do not reflect relevant diversity				
Amieva et al (2016) ¹⁸ ,	4,5. Racial and ethnic demographics for enrolled population are not reported				
Thivierge et al (2014) ²⁰ ,		4. Not the intervention of interest			1,2. Follow-up only 24 wks
Kurz et al (2012) ²² ,					1,2. Follow-up only 9 mos
Chapman et al (2004) ²³ ,					
Spector et al (2003) ²⁴ ,					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not

prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Follow-Up ^d	Power ^e	Statistical ^f
Clare et al (2019) ¹⁷		1. Participants and clinical staff not blinded				
Amieva et al (2016) ¹⁸	2. Allocation not concealed	1. Participants and clinical staff not blinded				
Thivierge et al (2014) ²⁰	2. Allocation not concealed	1,2. No blinding				
Kurz et al (2012) ²²	2. Allocation only concealed from outcome raters	1. Not blinded to treatment assignment				
Chapman et al (2004) ²³	1. Randomization process not described					
Spector et al (2003) ²⁴	3. Allocation concealment unclear	1,2,3. Blinding not clear				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Dementia

Systematic reviews of RCTs have generally shown no benefit of cognitive rehabilitation or effects of clinical importance. Most randomized trials either have not shown effects, shown only short-term effects, or did not evaluate long-term outcomes. One large RCT with a goal-oriented cognitive rehabilitation program has reported significantly less functional decline on 1 of 2 functional scales and institutionalization in the cognitive rehabilitation group compared with usual care at 24 months. Studies in AD lack relevant racial and ethnic diversity.

Stroke

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional in patients with cognitive deficits due to stroke is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation.

The question addressed in this evidence review is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to stroke?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to stroke.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to stroke has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded

Review of Evidence**Systematic Reviews**

Four Cochrane reviews have assessed the effectiveness of cognitive rehabilitation for recovery from stroke.^{25,26,27,28} The reviews evaluated spatial neglect, attention deficits, and memory deficits. The most recent updates of these reviews for these 3 domains drew the following conclusions:

- Spatial neglect: A 2013 update identified 23 RCTs with 628 patients.²⁵ There was very limited evidence for short-term improvements on tests of neglect with cognitive rehabilitation. However, for reducing disability due to spatial neglect and increasing independence, the effectiveness of cognitive rehabilitation remained unproven.
- Attention deficit: A 2013 update identified 6 RCTs with 223 patients.²⁶ There was limited evidence of short-term improvement in divided attention (ability to multitask), but no indication of short-term improvements in other aspects of attention. Evidence for persistent effects of cognitive rehabilitation on attention or functional outcomes was lacking. A 2019 update identified no new trials and concluded that the effectiveness of cognitive rehabilitation for attention deficits following stroke remains unconfirmed.²⁹
- Memory deficit: A 2016 update identified 13 trials with 514 patients.²⁸ There were statistically significant benefits in subjective measures of memory in the short-term (ie, the first assessment measurement after the intervention) but not in the longer term (ie, the second assessment measurement after the intervention). The quality of the evidence ranged from very low to moderate; there was poor quality of reporting in many studies, lack of consistency in the choice of outcome measures, and small sample sizes.

Gillespie et al (2015) published an overview of Cochrane reviews and a more recent RCT assessing rehabilitation for post-stroke cognitive impairment.³⁰ Data from 44 trials (N=1,550) were

summarized. In addition to post-stroke spatial neglect and attention and memory deficits (addressed in the 4 Cochrane publications previously described), post-stroke perceptual disorders, motor apraxia, and executive dysfunction were reviewed. Conclusions were:

- Very little high-quality evidence exists for the effectiveness of cognitive rehabilitation for post-stroke cognitive deficits.
- Current evidence has shown that cognitive rehabilitation for spatial neglect, attention deficits, and motor apraxia improve standardized assessments of impairment immediately after treatment. However, the durability and clinical significance of these improvements are unclear.
- Evidence for the effectiveness of cognitive rehabilitation for post-stroke memory deficits, perceptual disorders, or executive dysfunction was not identified.

A 2001 review of the rehabilitative management of post-stroke visuospatial inattention also concluded that the long-term impact of visual scanning and perceptual retraining techniques on overall recovery and functional outcomes were unclear.³¹

Randomized Controlled Trials

Zucchella et al (2014) conducted an assessor-blinded RCT of comprehensive cognitive rehabilitation, combining computer training and metacognitive strategies within 4 weeks after stroke.³² Of 288 consecutive stroke survivors admitted to a neurorehabilitation unit in Italy, 92 (32%) met inclusion criteria and were randomized to cognitive rehabilitation (n=45) or control (n=47). At the end of treatment (ie, at week 4), statistically significant differences were found between groups on some measures of memory and visual attention. The clinical significance of these short-term outcomes is unclear.

Section Summary: Stroke

Recent systematic reviews have generally reported limited effects of cognitive rehabilitation in stroke patients.

Multiple Sclerosis

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional in patients with cognitive deficits due to multiple sclerosis (MS) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation.

The question addressed in this evidence review is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to MS?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to MS.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to MS has varying lengths of follow-up, ranging from 6 months to 1 year. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 1 year of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded

Review of Evidence

Systematic Reviews

Three Cochrane reviews have evaluated cognitive rehabilitation for patients with MS and cognitive impairments.^{33,34,35} In an update, das Nair et al (2016) included 15 studies with 989 patients. There were no differences in subjective reports of memory functioning or mood.³⁵ There was some evidence of a significant effect by intervention on objective assessments of memory in both the immediate and long-term follow-up and quality of life in intermediate follow-up. However, this effect on objective memory outcomes and quality of life was no longer statistically significant when studies at high-risk of bias were excluded.

Rosti-Otajarvi and Hamalainen (2014) conducted a Cochrane review of neuropsychological rehabilitation in MS.³⁴ Twenty RCTs met inclusion criteria (N=986 patients), including 7 of the 8 trials in the das Nair et al (2016) Cochrane review. Overall quality and comparability of included trials were low due to methodologic limitations and variations in interventions and outcome measures across trials, respectively. In meta-analysis, statistically significant improvements in memory span (based on 2 low-quality trials, n=150 patients; standardized mean difference, 0.54; 95% CI, 0.20 to 0.88; p=.002; $I^2=0\%$) and working memory (3 very low-quality trials, n=288 patients; standardized mean difference, 0.33; 95% CI, 0.09 to 0.57; p=.006; $I^2=0\%$) were observed with cognitive training compared with controls. Statistically significant improvements in attention, information processing speed, immediate verbal memory, executive functions, and depression were not observed.

Table 5. Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	Intervention	N (Range)	Design	Duration
Rosti-Otajarvi et al (2014) ³⁴	1993-2013	20	Patients with MS	Neuropsychological rehabilitation	986 (15-240)	RCTs and quasi-randomized trials	Mean 9.5 wks
Das Nair et al (2016) ³⁵	1993-2015	15	Patients with MS	Cognitive rehabilitation	989 (19-240)	RCTs and quasi-randomized trials	NR

MS: multiple sclerosis; NR: not reported; RCT: randomized controlled trials;

Table 6. Systematic Review & Meta-Analysis Results

Study	Memory Span Improvement (SMD)	Working Memory Improvement (SMD)	Objective Assessment of Memory (SMD)	Activities of Daily Living (SMD)
Rosti-Otajarvi et al (2014) ³⁴	0.54	0.33	NR	NR
95% CI	0.2 to 0.88	0.09 to 0.57	NR	NR
p-value	.002	.006	NR	NR
Das Nair et al (2014) ³⁵	NR	NR	0.26	-0.33
95% CI	NR	NR	0.03 to 0.49	-0.63 to -0.03
p-value	NR	NR	.03	.03

CI: confidence interval; NR: not reported; SMD: standardized mean difference;.

Randomized Controlled Trials

The largest and longest-term RCT conducted in people with MS receiving cognitive rehabilitation was published by Lincoln et al (2020) (Table 7). It was a multicenter, observer-blinded RCT in patients with relapsing-remitting (65%), primary progressive (10%) or secondary progressive MS (25%).^{36,37} Participants were recruited between 2015 and 2017 and randomized to 10 weekly sessions of a group cognitive rehabilitation program (n=245) or usual care (n=204). Outcomes were assessed at 6 and 12 months after randomization. Although there were small improvements in mood and everyday memory problems, there were no significant long-term benefits in cognitive abilities, fatigue, employment, or quality of life (Table 8). Its main methodological limitation was that there was no sham cognitive rehabilitation group and participants were not masked to treatment assignment (Tables 9 and 10).

Table 7. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants ²	Interventions ¹	
					Active	Comparator
Lincoln et al (2020) ³⁷ ; CRAMMS RCT	England	5	2015-2017	People aged 18 to 69 yrs with MS who reported cognitive problems in daily life	10 weekly sessions of cognitive rehabilitation, delivered by an Assistant Psychologist to groups of 4 to 6 participants; standardized content defined by a treatment manual; n=245	Usual care, n=204

CRAMMS: Cognitive Rehabilitation for Attention and Memory in people with Multiple Sclerosis; MS: multiple sclerosis.

Table 8. Summary of Key Randomized Controlled Trial Results

Study	Multiple Sclerosis Symptoms Measure	Employment Measures	Quality of Life Measures
Lincoln et al (2020) ³⁷	387	382	382
	Mean MSIS (SD) Psychological score at 12 mos	Any employment at 12 mos	Mean (SD) EQ-5D visual analog at 12 mos
Cognitive rehabilitation	22.2 (6.1)	60 (29%)	61.6 (19.3)
Usual care	23.4 (6.0)	50 (29%)	59.7 (20.0)
Relative measure	Adjusted mean difference, -0.6; 95% CI, -1.5 to 0.3	Odds ratio, 0.99; 95% CI, 0.60 to 1.63	Adjusted mean difference, 2.6; 95% CI, -0.9 to 6.0

CI: confidence interval; EQ-5D: European Quality-of-Life Five-Level; MSIS: Multiple Sclerosis Impact Scale; SD: standard deviation;

Table 9. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Lincoln et al (2020) ³⁷			3. Delivery not similar intensity as intervention		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Lincoln et al (2020) ³⁷		1. Participants and assistant psychologists aware of allocation				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Several additional smaller, single-center and shorter-term RCTs have been conducted (Table 11). These RCTs are heterogeneous in terms of MS type, intervention format, frequency and duration, and outcome assessment methods. Overall, results of the RCTs have been mixed, with the majority of benefits for cognitive rehabilitation only observed in the short-term and either not measured or not sustained in the longer-term.

Table 11. Summary of Small and Shorter-Term Trials in Individuals with Multiple Sclerosis Undergoing Cognitive Rehabilitation

Author Year	N	MS type	Intervention	Comparator	Summary of Results
Brissart et al (2020) ³⁸	110	MS; 22% relapsing-remitting MS	13 2-hour extended cognitive rehabilitation sessions delivered over 6 mo s	13 2-hour non-cognitive exercise sessions delivered over 6 mo s	Some improvement was observed in the cognitive rehabilitation group in measures of memory function, but there were no differences between groups in executive function or quality of life measures at 6 to 9 mo follow-up.

Author	Year	N	MS type	Intervention	Comparator	Summary of Results
Chiaravalloti et al (2005)³⁹		117	Primarily relapsing-remitting MS	8 biweekly 45-min cognitive rehabilitation sessions	Control sessions with the same therapist at the same frequency, engaging in nontraining tasks (eg, reading and recalling a story)	Mixed at 5 and 11 wks. No statistical differences between groups in new learning or emotional functioning. Self-reported improvements in memory were greater in the cognitive rehabilitation group at both time points. Results for other neuropsychological assessments were not reported.
Chiaravalloti et al (2013)⁴⁰		88	MS	10 biweekly, 45- to 60-min sessions of modified SMT	Control sessions with the same therapist at the same frequency, engaging in nontraining tasks (eg, reading and recalling a story)	Mixed effects at 5 wks, but majority of benefits were not sustained at 6 months. At 5 wks, there were significant improvements in learning efficiency, objective everyday memory, general contentment (subjective everyday cognition and emotional functioning), apathy, and executive dysfunction, but not awareness level, depression, or anxiety. At 6-mos follow-up, the only persistent between-group difference was general contentment.
Rosti-Otajarvi et al (2013)⁴¹, Mantynen et al (2014)⁴²		102	Relapsing-remitting MS and attentional deficits	strategy-oriented neuropsychological rehabilitation (13 weekly 60-min sessions)	No intervention	Although no improvement in cognitive performance at wk 13 or at 6 mos, there was improvement in perceived cognitive deficits at both time points and in a subset of patients who completed 1-y follow-up (83% completers in the therapy group vs. 67% in the control group). ^a
Hanssen et al (2016)⁴³		120	MS	4 wks of multidisciplinary cognitive rehabilitation	Standard rehab	Improvement on a health-related quality of life measure relating to psychological health, but no differences in executive function at 4 or 7 mos.
Shahpouri et al (2019)⁴⁴		56	Primarily relapsing remitting (70%)	10, 2-h individualized sessions held every 7-10 days - approaches developed considering the severity of cognitive impairment and with the aim of optimization of the residual functions	Same number and duration of sessions, but content was not supporting cognitive rehabilitation	Memory, attention, quality of life, and depression were all significantly improved within 3 mos after study initiation.
Chiaravalloti et al (2019)⁴⁵		20	Learning-impaired participants with primarily relapsing remitting MS (65%)	STEM: 2, 30 to 45 min sessions per wk for 4 wks; guided practice of a set of structured and standardized tasks to train individuals on self-generation, spaced-learning, and retrieval practice.	Participants met individually with the therapist at the same frequency and locations as the treatment group, engaging in non-training oriented tasks.	Although STEM improved measures of subjective cognitive function outcomes immediately following the intervention, it did not lead to improved performance on objective neuropsychological functioning.

MS: multiple sclerosis; SMT: Story Memory Technique; STEM: Strategy-based Training to Enhance Memory.

^a Due to the possibility that dropout was related to the outcome of interest (e.g., patients with perceived cognitive decline might have been more likely to drop out), findings should be interpreted cautiously.

Section Summary: Multiple Sclerosis

Although numerous RCTs have investigated cognitive rehabilitation in MS, large, high-quality trials are lacking. The ability to draw conclusions based on the overall body of evidence is limited by the heterogeneity of patient samples, interventions, and outcome measures. Further, results of the RCTs evaluated are mixed, with positive studies mostly reporting short-term benefits. Evidence for clinically significant, durable improvements in cognition is currently lacking.

Post-Acute Cognitive Sequelae of SARS-CoV-2 Infection

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation in patients with cognitive deficits due to post-acute sequelae of SARS-CoV-2 infection (PASC).

The question addressed in this evidence review is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to PASC?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to PASC infection. The Centers for Disease Control and Prevention define the post-acute period as symptoms persisting at four or more weeks following infection with SARS-CoV-2.⁴⁶ The World Health Organization developed the following consensus case definition of 'post COVID-19 condition': individuals with "a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time."⁴⁷

While subjective reports of cognitive impairment (ie, 'brain fog') have been reported by individuals not requiring hospitalization,⁴⁸ current understanding of objective cognitive sequelae of COVID-19 is predominantly limited to individuals who required hospitalization.^{49,50} Ceban et al (2022) conducted a meta-analysis of 43 studies with 12 or more weeks follow-up that reported a 22% overall prevalence of cognitive impairment (95% CI, 17% to 28%; $I^2=98\%$; $N=13232$).⁵¹ Subjectively ascertained cognitive impairment (e.g., patient self-report) was reported in 18% of patients (95% CI, 12% to 24%; $I^2=97.9\%$; 31 studies), which was significantly lower than in studies with objective ascertainment of cognitive status utilizing validated tools (36%; 95% CI, 27% to 46%; $I^2=94.9\%$; 12 studies; $p=.002$). No significant difference in cognitive symptom prevalence was found in subgroup analyses of hospitalized versus non-hospitalized patients (30% versus 20%; $p=.096$) or patients with <6 months versus ≥ 6 months of follow-up (22% versus 21%; $p=.794$).

Objective cognitive deficits have been reported for verbal fluency, attention, working memory, processing speed, executive functioning, learning, and memory - with no clear pattern of cognitive impairment across studies. While cognitive impairment following intensive treatment of critical illness

is not a new phenomenon,⁵² the disease course of cognitive impairment experienced by individuals with post-acute sequelae of SARS-CoV-2 infection is an ongoing research priority.^{53,54}

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The natural history of PASC has not been fully categorized, particularly in non-hospitalized individuals. A prospective study measuring cognitive performance among patients who experienced mild disease noted that declines in cognitive scores reported at 6 months spontaneously resolved at 18 month follow-up.⁵⁵ Persistent cognitive deficits have been reported in 16% of COVID-19 survivors at 1 year who were treated in the intensive care setting.⁵⁶ Therefore, at least 1 to 2 years of follow-up may be considered necessary to demonstrate efficacy and to fully observe outcomes.

The American Academy of Physical Medicine and Rehabilitation Multi-Disciplinary PASC Collaborative issued a consensus guidance statement recommending that patients should be screened for signs of cognitive symptoms using validated tools and instruments, such as the Montreal Cognitive Assessment (MoCA) or MMSE.⁴⁹ Additional neuropsychological measures used to assess cognitive and behavioral alterations in PASC are described by De Luca and coworkers⁵⁴ and are listed on the CDC website.⁴⁶

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded

Review of Evidence

Initial reports of patient rehabilitation after COVID-19 recovery have largely been observational, without clearly identifiable cognitive rehabilitation components within multidisciplinary rehabilitation programs.^{57,58} Other reports have primarily focused on respiratory⁵⁹ and physical⁶⁰ rehabilitation. No studies specifically assessing the efficacy of cognitive rehabilitation programs for PASC were identified.

Section Summary: Post-Acute Cognitive Sequelae of SARS-CoV-2 Infection

No direct evidence on the efficacy of cognitive rehabilitation programs in patients with PASC was identified. Controlled prospective studies in well-defined patient populations with sufficient follow-up duration are necessary to evaluate net health outcomes. Ongoing research continues to elucidate the natural course of cognitive symptoms associated with PASC.

Other Cognitive Deficit Conditions**Clinical Context and Therapy Purpose**

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation in patients with cognitive deficits due to epilepsy, autism spectrum disorder (ASD), postencephalopathy, or cancer.

The question addressed in this evidence review is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to epilepsy, ASD, postencephalopathy, or cancer?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cognitive deficits due to epilepsy, ASD, postencephalopathy, or cancer.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after CNS insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life. The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to epilepsy, ASD, postencephalopathy, or cancer has varying lengths of follow-up, ranging from 2 to 6 months. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 6 months of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded

Review of Evidence**Epilepsy/Seizure Disorders**

Farina et al (2015) in Italy conducted a systematic review of the literature on cognitive rehabilitation for epilepsy.⁶¹ Literature was searched through December 2013, and 18 articles of different types (reviews, methodologic papers, case reports, experimental studies) were identified. Studies were heterogeneous for patient characteristics (type of epilepsy, type of previous treatment [surgery, antiepileptic drugs]), intervention modalities (e.g., holistic, focused) and duration, and outcome

measures. Reviewers considered the overall quality of evidence to be moderate to low, and results inconsistent (e.g., not all studies showed benefit; some showed greater benefit in left-sided seizures, and others showed greater benefit in right-sided seizures).

The 2013 updated systematic review by American Congress of Rehabilitation Medicine (ACRM) evaluated cognitive rehabilitation in epilepsy.⁷ Based on 2 comparative studies (1 randomized; N=156), ACRM recommended cognitive rehabilitation for attention and memory deficits as a "possibly effective" practice option for seizure-related attention and memory deficits. The RCT by Engelberts et al (2002) prospectively enrolled 50 patients with focal seizures who were receiving carbamazepine monotherapy.⁶² Patients were randomized to a retraining method aimed at retraining impaired cognitive functions (n=19), to a compensation method aimed at teaching compensatory strategies (n=17), or to a wait-list control group (n=8). Both interventions focused on divided attention (ability to multitask). At 6-month follow-up, performance on cognitive tests improved more in both intervention groups than in the control group. No differences in inhibitory capacity were observed. Self-reported cognitive complaints, absentmindedness, and quality of life improved more with cognitive rehabilitation. Overall, the different rehabilitation methods were similarly effective.

Helmstaedter et al (2008), in a nonrandomized study, assessed the short-term effects of cognitive rehabilitation on memory deficits in 2 retrospective, matched cohorts of temporal lobe epilepsy surgical patients.⁶³ Mean age was 36 years. Mean age at onset of epilepsy was 4 years, and mean intelligence quotient (IQ) was 105. Patients who received cognitive rehabilitation (n=55) participated in a 1-month program comprising educational sessions about brain function and cognitive exercises. A cohort of 57 patients received no cognitive rehabilitation. Statistically significant improvements in verbal learning and recognition were observed in right-resected patients who received cognitive rehabilitation. Cognitive rehabilitation had nonsignificant effects in left-resected patients. Study limitations included its retrospective design and baseline imbalances in patients' memory and attention deficits (more severe deficits in the control cohort). The limited evidence base precludes conclusions about cognitive rehabilitation for this indication.

Autism Spectrum Disorder

Reichow et al (2013) reported on a systematic review of psychosocial interventions administered by nonspecialists for children and adolescents with intellectual disability (IQ<70) or lower functioning ASD.⁶⁴ Five comparative trials in patients with ASD (N=255 patients) who received cognitive rehabilitation, training, and support were included. Improvements in school performance and developmental outcomes were inconsistent across trials.

Wang and Reid (2013) conducted a pilot study of a novel virtual reality-cognitive rehabilitation intervention in 4 children (mean age, 7.4 years) with ASD.⁶⁵ Children with autism, who are difficult to engage, may respond better to virtual reality approaches than to traditional cognitive rehabilitation. Mean nonverbal IQ ranged from 93 to 139. Each child viewed training programs on laptop computers equipped with tracking webcams. The child's image and movements were projected into virtual environments where he/she was required to manipulate virtual objects. Outcomes were measures of contextual processing, defined as "the ability to determine an object's meaning or relevance in a particular context," and of abstraction and cognitive flexibility, with executive functions considered components of contextual processing. After 4 to 6 weeks, all children demonstrated statistically significant improvements in contextual processing and cognitive flexibility. Abstraction scores at baseline were at or close to maximum.

Eack et al (2013) conducted a feasibility study of a comprehensive cognitive rehabilitation intervention, called Cognitive Enhancement Therapy, in 14 "high-functioning" adults (mean age, 25 years) with ASD.⁶⁶ Cognitive Enhancement Therapy, which was originally developed for patients with schizophrenia, provides social interaction and cognitive training focused on attention, memory, and problem-solving. Mean fullscale IQ of the patient sample was 118 (range, 92 to 157). Eleven (79%) of 14 patients completed 18 months of treatment. Statistically significant changes from baseline were

observed in mean composite measures of neurocognition, cognitive style, social cognition, and social adjustment. All components of neurocognition (e.g., processing speed, working memory) improved statistically, except attention/vigilance.

Postencephalitis

The 2013 updated ACRM systematic review also evaluated cognitive rehabilitation for postencephalitis cognitive deficits.⁷ Eight identified studies were considered poor quality evidence and insufficient for forming conclusions.

Cancer

Cognitive rehabilitation has been investigated in 3 cancer-related settings: in children receiving oncological treatment with regular inpatient stays, patients with brain tumors, and cancer survivors whose cognitive deficits are attributed to cancer treatment.

Pediatric Cancer Treatment

For children with cancer receiving cognitive rehabilitation, the evidence includes 1 small (N=46), single-center RCT by Akel et al (2019) (Table 12).⁶⁷ The cognitive rehabilitation was delivered in the inpatient treatment clinic of the Department of Pediatric Oncology at University Hospital in Ankara, Turkey. Cognitive skills targeted by the cognitive rehabilitation therapy included place and time orientation, internal and external spatial perception, praxis, attention, visio-motor construction, and thinking operations. Children were characterized by a mean age of 10 years and 55% were male. Cancer diagnoses included non-Hodgkin lymphoma (40%), Hodgkin lymphoma (30%) and bone tumors (30%). Outcomes were evaluated only immediately postintervention. Although compared to the routine therapy groups (Table 13), numerically larger effect sizes for change in fatigue and functional independence were reported for the cognitive rehabilitation group, it is unknown whether the differences were clinically or statistically significant as the comparative treatment effects were not calculated and clinically significant difference were not prespecified. Significant improvements in cognitive measures were reported pre/post in the intervention group, but no data were reported for the routine therapy group on this outcome. In addition to these inadequate outcome assessment methods, interpretation of these findings are limited by other methodological shortcomings (Tables 14 and 15) including lack of blinding of participants and lack of long-term follow-up. Therefore, this evidence is not sufficient to draw conclusions on effect on health outcomes

Table 12. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants ²	Interventions ¹	
					<i>Active</i>	<i>Comparator</i>
Akel et al (2019) ⁶⁷	Turkey	1	NR	Children aged 6 to 12 yrs receiving oncological treatment with regular inpatient stays for non-brain tumors or brain metastasis and an MMSE for children score >24	15 sessions of structured cognitive rehabilitation that used play to target various cognitive skills; n=25	15 sessions of routine therapy, including relaxation training and task-oriented activity of daily life training; n=21

MMSE: Mini-Mental Status Examination; NR: not reported..

Table 13. Summary of Key Randomized Controlled Trial Results

Study	Cognitive Measures	Fatigue Measures	Functional Independence Measures
Akel et al (2019) ⁶⁷	40	40	40
Measures	Mean total DOTCA-Ch (SD) score pre/post-intervention	Mean (SD) VAS-fatigue pre/post-intervention for post-activity/Effect size/P-value	Mean (SD) WeeFIM total score pre/post-intervention/Effect size/P-value

Study	Cognitive Measures	Fatigue Measures	Functional Independence Measures
Cognitive rehabilitation	121.54 ± 13.18/135.36 ± 10.24	5.45 ± 1.01/1.72 ± 0.98/3.69/<.001	52.45 ± 8.90/62.68 ± 9.74/1.15/<.001
Control group	NR	3.16 ± 2.45/2.16 ± 1.79/0.41/.01	52.33 ± 9.29/53.11 ± 8.73/0.08/.068
Relative measure	NA	NR	NR

DOTCA-Ch: Dynamic Occupational Therapy Cognitive Assessment for Children; NA: not applicable; NR: not reported; SD: standard deviation; WeeFIM: Functional Independence Measure for Children; VAS: Visual Analog Scale.

Table 14. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Akel et al (2019) ⁶⁷			3. Delivery not similar intensity as intervention	5. Clinical significant difference not prespecified	1. Not sufficient duration for benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 15. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Akel et al (2019) ⁶⁷		1. Participants aware of allocation			1. Power calculations not reported	4. Comparative treatment effects not calculated

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Brain Tumors

The 2013 ACRM systematic review evaluated cognitive rehabilitation for adults with brain tumors.⁷ In 5 case reports and case series (N=36 patients), some patients showed benefit with various cognitive rehabilitation interventions. This evidence was considered insufficient to support any recommendations.

Zucchella et al (2013) conducted an RCT of cognitive rehabilitation in adults after neurosurgery at a single rehabilitation facility in Italy.⁶⁸ Time since craniotomy was not reported. Adjuvant chemotherapy or radiotherapy was not administered until after the trial. Of 109 consecutive patients screened for participation, 62 (57%) met minimum cognitive deficit and other criteria and were randomized to usual rehabilitative care with (n=30) or without (n=32) cognitive rehabilitation. Treatment sessions were held 4 times a week for 4 weeks and were comprised of 45 minutes of therapist-guided computer exercises in 6 cognitive domains (time and spatial orientation, visual attention, logical reasoning, memory, executive function) and 15 minutes of cognitive strategizing. At the end of treatment (ie, at week 4), statistically significant improvements in visual attention and verbal memory were observed in the treatment group compared with controls. Improvements in logical reasoning and executive function were not statistically significant. Limited study follow-up makes the clinical significance of these findings unclear.

Cancer Survivors

Systematic Reviews

Fernandes et al (2019) published a systematic review of cognitive rehabilitation programs in adults with non-CNS cancers. It included 1,124 participants (n range, 11 to 242) from 19 studies published between 2007 and 2018, of which the majority were RCTs (N=12).⁶⁹ Waitlist was the most common comparator in the RCTs. As with the previous reviews, most studies in this review assessed the effects of the intervention immediately postintervention or at short-term follow-up (≤ 6 months), and most trials were conducted in breast cancer survivors. This review did not perform any meta-analyses. Findings across the studies were mixed. Although the review reported that among the RCTs and nonrandomized controlled studies "87% found short-term improvements on at least one objective cognitive measure," this finding primarily pertained to measurements taken immediately postintervention. In contrast, in the longest-term (26-month follow-up) and largest trials (n=242) included, there were no significant effects on various objective cognitive measures. Only 63% of studies found improvements in short-term quality of life measures and none found any improvements in functional outcomes. An important limitation of all studies is that participants were not blinded to group assignment.

Zeng et al (2016) published a meta-analysis of a neuropsychologic intervention for cognitive function in cancer survivors.⁷⁰ Three case-control studies and 7 RCTs with 433 patients (range, 22 to 98 patients), published between January 2010 and September 2015, were included. Most trials assessed the effects of the intervention immediately postintervention or at short-term follow-up (≤ 6 months). More than half of the trials were conducted in breast cancer survivors. Three trials assessed the effects of cognitive rehabilitation programs and the weighted mean difference for the intervention effect at postintervention follow-up was -0.19 (95% CI, -2.98 to 2.61).

The 2013 systematic review by ACRM evaluated cognitive rehabilitation for cognitive impairments in adult and pediatric cancer survivors.⁷¹ A German RCT, by Poppelreuter et al (2008), showed no benefit with cognitive rehabilitation in 157 adult inpatients who had cognitive impairments after hematopoietic cell transplantation.⁷¹ In children and adolescents, 2 prospective, comparative studies (1 an RCT by Butler et al [2008]⁷²) evaluated cognitive rehabilitation in treatment survivors (resection, cranial radiotherapy, and/or chemotherapy) involving the CNS (N=192 patients). Reviewers concluded that process-based cognitive rehabilitation techniques (e.g., strategy acquisition, corrective feedback) were "probably effective" in treating attention and memory deficits in these patients. However, the Butler et al (2008) RCT had several methodologic limitations.⁷² It randomized 161 pediatric survivors of treatment for brain tumors, leukemia, bone marrow transplant involving total body irradiation, and non-Hodgkin lymphoma 2:1 to a cognitive remediation program (n=108) or wait-list controls (n=53). Documented attentional deficit was required for trial eligibility. The cognitive remediation program comprised 2-hour weekly sessions of practice, strategy acquisition, and cognitive-behavioral interventions for up to 20 sessions. Both groups were assumed to receive special education services if needed; this factor was not analyzed in the results. The primary outcome was change from baseline in 5 investigator-developed, multi-test indices (academic achievement, brief

focused attention, working memory, memory recall, vigilance) at approximately 6 months after baseline assessments. These indices incorporated results from 11 validated scales completed by blinded study assessors and unblinded parents, teachers, and patients. Mean patient age was 11 years. Sixty percent of patients in the cognitive remediation group completed the entire program; 80% completed 75% (15 sessions). Six-month follow-up was differential between groups (83% in the cognitive remediation group vs. 98% in the control group). The analysis was intention-to-treat. The statistically greater improvement was observed in the cognitive remediation group than in the control group only in academic achievement, although the treatment effect was small (standardized mean difference, 0.24) and of uncertain clinical relevance. Given the lack of improvement on the neurocognitive scales, it did not appear that improved academic achievement was due to improved neurocognitive function.

Randomized Controlled Trials

For cancer survivors receiving cognitive rehabilitation, the evidence published subsequent to the above-described systematic reviews includes 1 small (N=25), single-center RCT by Richard et al (2019) (Table 16).⁷³ This RCT randomized 46 participants to either Goal Management Training, a Brain Health Program active control that promotes general brain health, or a wait-list control group. The study reported outcomes immediately following the 8-week treatment period and 4 months following treatment completion. Participants had a mean age of 48 years, and 60% were male. Disease characteristics included various tumor types (28% meningioma, 32% low-grade glioma, 24% high-grade glioma) with a mean duration of 23 years since diagnosis. The most common cancer treatment was surgical resection (72%). The most recent type of treatment was whole-brain radiotherapy, which occurred a mean of 3 years prior. The primary outcome measure was change on an investigator-developed executive functioning test composite score. Although compared to the active and wait-list control groups, improvements in executive functioning and real-life functional goal attainment were significantly greater for the Goal Management Training group immediately following treatment, the improvement was only maintained at the 4 month follow-up period for the executive functioning outcome (Table 17). No quality of life measure was reported. Although the improved executive functioning outcome is encouraging, numerous important study and relevance shortcomings seriously limit the interpretation of these findings (Tables 18 and 19). For example, the clinical significance of the executive functioning outcome is unclear as it is not an established measure and its validity is unknown. Additionally, as the executive functioning outcome was not evaluated using an intent-to-treat analysis and excluded a larger proportion of wait-list control group participants than in the Goal Management Training groups (33% vs. 9%), we cannot rule out that the results were biased based on the high and differential exclusions. In addition, interpretation of these findings are limited by other methodological shortcomings including lack of blinding of participants and lack of long-term follow-up. Therefore, this evidence is not sufficient to draw conclusions on effect on health outcomes

Table 16. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants ²	Interventions ¹	
					<i>Active</i>	<i>Comparator(s)</i>
Richard et al (2019) ⁷³	Canada	1	NR	Adults aged ≥ 18 yrs with a diagnosis of a primary brain tumor who were ≥ 3 mos postradiation or surgery with persistent cognitive dysfunction (≤ 1 SD below executive function testing norms)	8 weekly 2-h individual sessions of a structured and standardized GMT program, a behavioral intervention delivered by a clinical neuropsychologist, with homework between sessions; n=11	8 weekly 2-h individual sessions of a psycho-educational BHP, also with homework of more general "brain challenges"; n=8 Waitlist control; n=6

BHP: brain health program; GMT: goal management training; NR: Not reported; SD: standard deviation.

Table 17. Summary of Key Randomized Controlled Trial Results

Study	Cognitive Measures ^a	Functional Outcomes	Quality of Life Outcomes
Richard et al (2019)⁷³	19	19	19
Measures	Mean change (SD) in the Executive Functioning Composite at 4 mos follow-up	Functional goal attainment at 4 mos	NR
GMT	+0.69 (0.51)	NR	
BHP	+0.13 (0.50)	NR	NR
WAIT	-0.07 (0.44)	NR	NR
P-value for time-by-group interaction	.046	.064	NR

^aThe Executive Functioning Composite score was calculated by averaging component measure z-scores at each time point across a number of tests including the Trail Making Test B, Test of Everyday Attention (TEA), Sustained Attention to Response Task (SART), Behavioral Assessment of the Dysexecutive Syndrome (BADs), and the Hotel Test.

BHP: Brain Health Program; GMT: Goal Management Training; WAIT: Wait-list control; NR: Not Reported; SD: standard deviation.

Table 18. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Richard et al (2019)⁷³				1. Key health outcomes not addressed 4. Not establish and validated measurements 5. Clinical significant difference not prespecified	1. Not sufficient duration for benefit

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 19. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Richard et al (2019)⁷³	3. Allocation concealment unclear	1. Participants aware of allocation		1. High loss to follow-up or missing data (GMT=9%, BHP=25%, WAIT=33%) 6. Not intent to treat analysis (per protocol for noninferiority trials).	1. Power calculations not reported	

BHP=Brain Health Program; GMT: Goal Management Training; WAIT: Wait-list control.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician; 4. Unclear blinding of outcome assessment

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Other Cognitive Deficit Conditions

Systematic reviews of cognitive rehabilitation for a number of conditions, including epilepsy, ASD, spectrum disorder, postencephalopathy, and cancer, have generally concluded that there is no strong evidence supporting the efficacy of cognitive rehabilitation. Randomized trials of cognitive rehabilitation have numerous methodologic flaws that preclude strong conclusions about its efficacy.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input

In response to requests, input was received from 3 physician specialty societies and 5 academic medical centers while this policy was under review in 2015. Input was mixed on cognitive rehabilitation for patients with stroke, multiple sclerosis, brain tumors, or cognitive impairments after previous treatments for cancer. While input was not specifically requested for TBI, due to strong support provided in 2009 and no signals of any subsequent evidence or clinical practice changes, the American Association of Physical Medicine & Rehabilitation voluntarily and additionally reasserted its position of support for cognitive rehabilitation after TBI.

2009/2010 Input

In response to requests, input was received from 2 physician specialty societies and 5 academic medical centers while this policy was under review in 2010. The strongest support was for the use of cognitive rehabilitation as part of the treatment of those with TBI. The level of support varied for other diagnoses (e.g., use in post-stroke patients).

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Physical Medicine and Rehabilitation

In 2021, the American Academy of Physical Medicine and Rehabilitation (AAPM&R) Multi-Disciplinary Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Collaborative issued a consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with PASC.⁴⁹ PASC cognitive symptom assessment and treatment recommendations are summarized in Table 20.

Table 20. Post-Acute Sequelae of SARS-CoV-2 Infection Cognitive Symptom Assessment and Treatment Recommendations^a

Assessment Recommendations	
Recommendation #	Statement
1	"Patients should be screened for signs of cognitive symptoms using validated tools and instruments."
2	"Patients should be evaluated for conditions that may exacerbate cognitive symptoms and warrant further testing and potential subspecialty referral. [...] Particular areas include: • Sleep impairment • Mood, including anxiety, depression, and posttraumatic stress disorder • Fatigue • Endocrine abnormalities • Autoimmune disorders Note: Patients often report dissatisfaction with their care because of their persistent symptoms being attributed to psychological factors. It is important to note that mood disorders may be secondary to persistent medical conditions or one of many factors leading to cognitive symptoms."
3	"Patients should have a thorough neurological examination to identify focal neurological deficits."
3a	"For those patients identified with new or worsening focal neurological deficits (including new or worsening cognitive symptoms) an emergent evaluation is warranted; neuroimaging should be considered."
4	"The following basic lab workup should be considered to screen for reversible factors contributing to cognitive symptoms. The initial lab workup in new patients or those without lab workup in the 3 months prior to visit including complete blood count, vitamin B12, thiamine, folate, homocysteine, 1,25-dihydroxy vitamin D, magnesium, liver function tests, comprehensive metabolic panel thyroid function tests (thyroid stimulating hormone, free T3, free T4). In high-risk patients, one may consider syphilis rapid plasma regain and human immunodeficiency virus testing [...]"
5	"Clinicians should conduct a full patient history with review of preexisting conditions and comprehensive medication and supplement review for those that may contribute to cognitive symptoms. Of note, patients with PASC often present on antihistamine, anticholinergic, and antidepressant/anxiolytic medications that can contribute to cognitive symptoms."
5a	"Clinicians should validate patient history through the collection of collateral history, including preexisting function and conditions, from care team/primary care, patient family or care partner, or close contact as available."
6	"Clinicians should assess impact of cognitive symptoms using standardized patient-reported assessments, to include activities of daily living, instrumental activities of daily living, school, work and avocational (ie, hobbies), and quality of life."
Treatment Recommendations	
Recommendation #	Statement
1	"For patients who screen positive for cognitive symptoms, refer to a specialist (ie, speech-language pathologist, occupational therapist, neuropsychologist) with expertise in formal cognitive assessment and remediation."
2	"Treat, in collaboration with appropriate specialists, underlying medical conditions, such as pain, insomnia/sleep disorders (including poor sleep hygiene), and mood disorders that may be contributing to cognitive symptoms."
3	"Complete, in collaboration with patient primary care provider, medication polypharmacy reduction, weaning or deprescribing medications if medically feasible with emphasis on medications that may impact cognition."
4	"Reinforce sleep hygiene techniques including nonpharmacologic approaches as first line of sleep remediation."
5	"Similar to patients experiencing "physical" fatigue, patients should be advised to begin an individualized and structured, titrated return to activity program."

Assessment Recommendations

5a	"For patients who achieve a return to their normal, daily activities, regular exercise (at least 2–3 times/week of aerobic exercise) may be effective in improving cognition and also contribute to improved sleep patterns."
5b	"Frequent assessment of the impact of return to normal, daily activities (including school, work, driving, operating heavy machinery, etc.) is recommended to ensure that symptoms do not flare and exercise is tolerated."

^a Adapted from Fine et al (2021).⁴⁹

American Congress of Rehabilitation Medicine

In 2013, based on a systematic review, the American Congress of Rehabilitation Medicine recommended process-based cognitive rehabilitation strategies (e.g., attention process training, strategy acquisition and internalization, self-monitoring, corrective feedback) to treat attention and memory deficits in children and adolescents with brain cancers who undergo surgical resection and/or radiotherapy. The strength of evidence for recommendations were determined according to American Academy of Neurology study classification, and no financial conflicts of interest were declared by the authors.⁷

National Institute for Health and Care Excellence

In 2013, NICE guidance on stroke rehabilitation recommended cognitive rehabilitation for visual neglect and memory and attention deficits that impact function.⁷⁴ Interventions should focus on relevant functional tasks (e.g., "errorless learning") and "elaborative techniques" (e.g., "mnemonics," "encoding" strategies) for memory impairments.

In 2018, NICE guidance on dementia management suggested: "Consider cognitive rehabilitation or occupational therapy to support functional ability in people living with mild to moderate dementia."⁷⁵ In 2021, NICE issued a rapid guideline on managing the long-term effects of COVID-19.⁷⁶ The guideline recommends using a "multidisciplinary approach to guide rehabilitation, including physical, psychological and psychiatric aspects of management." Cognitive rehabilitation was not specifically addressed. Assessing the clinical effectiveness of "different service models of multimodality /multidisciplinary post-COVID-19 syndrome rehabilitation in improving patient-reported outcomes (such as quality of life)" was listed as a key recommendation for research.

The NICE guidance development is a transparent process that provides detailed information on the strength of recommendations and information on potential conflicts of interest for guideline committee members.

Institute of Medicine

In 2011, the Institute of Medicine published a report on cognitive rehabilitation for traumatic brain injury that included a comprehensive review of the literature and recommendations.⁷⁷ The report concluded that "current evidence provides limited support for the efficacy of CRT [cognitive rehabilitation therapy] interventions. The evidence varies in both the quality and volume of studies and therefore is not yet sufficient to develop definitive guidelines for health professionals on how to apply CRT in practice." The report recommended that standardization of clinical variables, intervention components, and outcome measures was necessary to improve the evidence base for this treatment. The Institute of Medicine also recommended future studies with larger sample sizes and more comprehensive sets of clinical variables and outcome measures.

Veterans Administration

In 2009, the Veterans Administration/Department of Veterans Affairs published guidelines on the treatment of concussion and mild traumatic brain injury,⁷⁸ which were updated in 2016⁷⁹ and most recently in 2021.⁸⁰ These guidelines addressed cognitive rehabilitation in the setting of persistent symptoms. The 2021 guidelines stated:

- "We suggest that patients with symptoms attributed to mild traumatic brain injury [mTBI] who present with memory, attention, or executive function problems despite appropriate

management of other contributing factors (e.g., sleep, pain, behavioral health, headache, disequilibrium) should be referred for a short trial of clinician-directed cognitive rehabilitation services." [Strength of recommendation: "weak for."]

- "We suggest against the use of self-administered computer training programs for the cognitive rehabilitation of patients with symptoms attributed to mTBI." [Strength of recommendation: "weak against."]

A 2019 Veterans Administration/Department of Defense practice guideline on the management of stroke rehabilitation found "insufficient evidence to recommend for or against the use of any specific cognitive rehabilitation methodology or pharmacotherapy to improve cognitive outcomes" and noted "there has been very little advancement in the evidence regarding the use of specific cognitive rehabilitation strategies or techniques to improve clinical outcomes following stroke."⁸¹

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 21.

Table 21. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT01138020	Cognitive Rehabilitation of Blast-induced Traumatic Brain Injury (CRbTBI)	77	Oct 2025
NCT04852718	Evaluate a Rehabilitation Program for the Sequelae of COVID 19 Infection: Description of a Clinical Practice	120	Apr 2021 (recruiting)
NCT03168360	Effect of Intensive Cognitive Rehabilitation in Subacute Stroke Patient	150	Dec 2023
NCT04615390	Recovery Profiles in Patients With COVID-19 Outcomes Undergoing Rehabilitation	200	Nov 2023
NCT03900806	Internet-based Work-related Cognitive Rehabilitation for Cancer Survivors: a Randomized Controlled Trial (i-WORC)	261	Aug 2023
NCT05172206	Symptom-based Rehabilitation Compared to Usual Care in Post-COVID - a Randomized Controlled Trial (RELOAD)	132	Mar 2023
NCT03679468	Improving Cognition in People With Progressive Multiple Sclerosis: A Multi-Arm, Randomized, Blinded, Sham-Controlled Trial of Cognitive Rehabilitation and Aerobic Exercise.	309	Dec 2022 (ongoing)
NCT03225482	Cognitive Rehabilitation for Older Veterans With Mild Cognitive Impairment	216	Mar 2024
NCT03948490	Rehabilitation and Longitudinal Follow-up of Cognition in Adult Lower Grade Gliomas	180	Mar 2025
NCT04632719	MentalPlus® for Assessment and Rehabilitation of Cognitive Functions After Remission of Symptoms of COVID-19 (MP-COVID)	200	Dec 2023
NCT04229056	Computer-Assisted Self-Training to Improve Executive Function Versus Unspecific Training in Patients After Stroke, Cardiac Arrest or in Parkinson's Disease: A Randomized Controlled Trial (COMPEX)	700	Dec 2024
NCT05676047	Symptom-Targeted Rehabilitation for Cognitive Complaints in Long COVID (STAR-C3)	100	Dec 2024
NCT05494424	Cognitive Rehabilitation in Post-COVID-19 Condition: A Study Protocol for a Randomized Controlled Trial	240	Jan 2029

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Unpublished</i>			
NCT03237676	The Effect of Cognitive Rehabilitation Therapy in Improving Cognitive Function of Attention Following Mild Traumatic Brain Injury	90	Dec 2019

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- Reason for cognitive rehabilitation

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	97129	Therapeutic interventions that focus on cognitive function (e.g., attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (e.g., managing time or schedules, initiating, organizing, and sequencing tasks), direct (one-on-one) patient contact; initial 15 minutes
	97130	Therapeutic interventions that focus on cognitive function (eg, attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (e.g., managing time or schedules, initiating, organizing, and sequencing tasks), direct (one-on-one) patient contact; each additional 15 minutes (List separately in addition to code for primary procedure)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/15/1997	BCBSA Medical Policy adoption	Medical Policy Committee
06/28/2007	Policy Review Statement unchanged, but clarification added "for all other indications that the procedure is investigational."	Medical Policy Committee
04/02/2010	Policy revision without position change	Medical Policy Committee
10/25/2010	Policy revision with position change	Medical Policy Committee
03/14/2011	Administrative update	Administrative Review
07/31/2015	Coding update	Administrative Review
10/30/2015	Policy revision with position change	Medical Policy Committee
05/01/2016	Policy revision without position change	Medical Policy Committee
05/01/2017	Policy revision without position change	Medical Policy Committee
01/01/2018	Coding update	Administrative Review
03/01/2018	Coding update	Administrative Review
05/01/2018	Policy revision without position change	Medical Policy Committee
05/01/2019	Policy revision without position change	Medical Policy Committee
06/01/2023	Policy reactivated. Previously archived from 05/01/2020 to 05/31/2023.	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	AFTER <u>Blue font: Verbiage Changes/Additions</u>
Reactivated Policy Policy Statement: N/A	Cognitive Rehabilitation 8.03.10 Policy Statement: I. Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) may be considered medically necessary in the rehabilitation of individuals with cognitive impairment due to traumatic brain injury. II. Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) is considered investigational for all other applications, including, but not limited to: A. Aging population, including patients with Alzheimer disease B. Autism spectrum disorder C. Multiple sclerosis D. Individuals with cognitive deficits due to brain tumor or previous treatment for cancer E. Postencephalitic or post encephalopathy individuals F. Seizure disorders G. Stroke