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# Cognitive Rehabilitation

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## Disclaimer

**Carefully check state regulations and/or the member contract.**
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Legislative Mandates

**EXCEPTION: For Illinois only:** Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

## Coverage

**NOTE 1: State Legislation may apply for Cognitive Rehabilitation and Autism Spectrum Disorder (ASD).**

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 or stroke under the following circumstances:

- Services are prescribed by the attending physician as part of a written care plan; AND

- Prescribed services are provided by a qualified licensed professional; AND
- There is a potential for improvement based on pre-injury function; AND
- Individuals have 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).

**NOTE 2**: Ongoing services may be considered medically necessary **only** when there is demonstrated continued objective improvement in function.

Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) **is considered experimental, investigational and/or unproven** for all other applications, including, but not limited to:

- Post-encephalitic or post-encephalopathy individuals;
- Autism spectrum disorder;
- Seizure disorders;
- Multiple sclerosis;
- The aging population, including individuals with Alzheimer disease; AND
- Individuals with cognitive deficits due to brain tumor or previous treatment for cancer.

## Policy Guidelines

None.

## 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.

**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 outcome 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 or stroke 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.

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.

Sensory integrative therapy, explicitly identified by CPT code 97533, may be considered a component of cognitive rehabilitation. However, sensory integration therapy is considered separately in Medical Policy THE803.020.

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

## Rationale

This medical policy was originally created in 1996 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 3, 2024.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

This medical policy evaluates evidence for cognitive rehabilitation delivered by a qualified professional. Studies of self-administered computer programs are not considered cognitive rehabilitation for this medical policy and are not assessed here. (1-7) Short-term improvements in cognitive test performance measured post-intervention alone will not be considered a health outcome for this policy. Measurements of daily functioning and quality of life (QOL) are the primary health outcomes of interest. Improvements should be demonstrable after longer term follow-up post-intervention, preferably greater than 6 months.

**Traumatic Brain Injury (TBI)**

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 individuals with cognitive deficits due to TBI.

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

*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 1 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.

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*

Austin et al. (2024) reported results of a systematic review and meta-analysis of cognitive rehabilitation interventions in veterans and service members with traumatic brain injuries. (9) The review included RCTs published by February of 2023 that used adult participants who were U.S. veterans or active duty service members who had a history of mild-to-moderate TBI that tested cognitive rehabilitation treatments designed to improve cognition and/or everyday functioning and reported objective neuropsychological testing as a primary outcome measure. 8 trials (N = 303 in cognitive rehabilitation; N=261 in control; 97% of whom had a history of mild TBI) were included. 7 of the 8 trials were published after 2013. The mean age of participants was 37 years (standard deviation [SD]=7) and between 81% and 100% of participants were male. Limited racial and ethnic information was available from the included studies. The mean length of time since TBI was 6 years (SD=52). Cognitive rehabilitation intervention lengths ranged from 4 to 15 weeks (mean=9.5; SD=3.7). Study quality and risk of bias were evaluated using the Cochrane tool. Overall, the studies were rated as having low risk of bias. Given the variation in outcome measures used across studies, effect sizes were transformed into Cohen's d for meta-analysis. Participants in cognitive rehabilitation showed a significant improvement in overall objective neuropsychological functioning compared to controls (d = 0.22; 95% confidence interval [CI], 0.01 to 0.43; p=.04) but not on performance-based measures of functional capacity (d = 0.16; 95% CI, −0.48 to 0.81; p=.62). Participants in cognitive rehabilitation also had comparatively larger improvements in memory (d= 0.42; 95% CI, 0.13 to 0.70; p=.01) and executive functioning (d = 0.26; 95% CI, 0.01 to 0.51; p=.04) but not on attention (d=0.12; 95% CI−0.12 to 0.35; p=.33). 4 of the RCTs included postintervention follow-up visits to measure durability of treatment effects. In these 4 studies, treatment effects on overall neuropsychological test performance at 10- or 12-week follow-up were also statistically significant favoring cognitive rehabilitation (d = 0.45; 95% CI, 0.01 to 0.90; p=.04).

A 2013 Cochrane review assessed cognitive rehabilitation for executive dysfunction (planning, initiation, organization, inhibition, problem-solving, self-monitoring, error correction) in adults with non-progressive acquired brain damage. (10) Sixteen RCTs (total 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.

*Randomized Controlled Trials*

Chiaravalloti et al. (2016) conducted a RCT evaluating the Story Memory Technique (SMT) to improve learning and memory in subjects with moderate-severe with TBI. (11) 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 programme for people with TBI (ReMemBrIn) in 9 sites in England. (12) 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 = 0.37). 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. In a systematic review of RCTs conducted from 2013 to 2023 including U.S. Veterans with mild to moderate TBI, participants receiving cognitive rehabilitation showed a significant improvement in overall neuropsychological functioning, memory, and executive functioning but not in functional capacity or attention compared to controls. The benefits were durable for at least 3 months.

**Dementia**

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional in individuals 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 following PICO was used to select literature to inform this policy.

*Populations*
The relevant population of interest is individuals with cognitive deficits due to dementia. This includes patients with Alzheimer disease (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 1 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*
Kudlicka et al. (2023) reported results of a Cochrane systematic review of cognitive rehabilitation for people with mild to moderate dementia on outcomes related to everyday functioning. (13) The review included 6 trials (N=1702) published between 2010 and 2022. The mean age of participants in the RCTs ranged from 76 to 80 years and the proportion of male

participants ranged from 29% to 79%. Approximately 60% participants had a diagnosis of Alzheimer's Disease (AD). Risk of bias was rated as relatively low for all domains other than blinding, which is not generally feasible with psychosocial interventions. Extracting data for the outcome of everyday functioning was operationalized by extracting the measure of goal attainment used in the individual studies related to activities targeted in the intervention for that study. Results were provided for outcomes at the end of the cognitive rehabilitation and after 3 to 12 months of follow-up post-rehabilitation. The authors concluded that there was high-certainty evidence of large positive effects of cognitive rehabilitation relative to control immediately following rehabilitation on participant self-ratings of goal attainment (standardized mean difference [SMD]=1.5; 95% CI, 1.3 to 1.7; 3 RCTs; N=501), informant ratings of goal attainment (SMD=1.6; 95% CI, 1.01 to 2.21; 3 RCTs; N=476), and self-ratings of satisfaction with goal attainment (SMD=1.3; 95% CI, 1.1 to 1.5; 3 RCTs; N=501). The authors also concluded that there was high-certainty evidence showing a large positive effect of cognitive rehabilitation after 3 to 12 months of follow-up post-rehabilitation on participant self-ratings of goal attainment (SMD=1.5; 95% CI, 1.3 to 1.7; 2 RCTs, N=432), informant ratings of goal attainment (SMD=1.3; 95% CI, 0.78 to 1.72; 3 RCTs; N=446), and self-ratings of satisfaction with goal attainment (SMD=1.2; 95% CI, 0.7 to 1.7; 2 RCTs; N=432). There was less certainty regarding whether cognitive rehabilitation had a meaningful effect on other outcomes immediately or after 3 to 12 months such as participant anxiety and quality of life.

In a Cochrane review, Bahar-Fuchs et al. (2019) evaluated the use of cognitive training for people with mild to moderate dementia. (14) 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. (15) 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. (16) 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. (17) 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. (18)

*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. (19) The majority of participants were diagnosed with Alzheimer dementia. Their mean age was 78.56 years, and their mean Mini-Mental State Examination (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. (20) Six hundred fifty-three patients with mild-to-moderate AD were randomized in a 1:1:1:1 ratio at 40 French clinical sites. Focus was 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, QOL, 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 the 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 one of the 2 scales assessing functional abilities: the Autonomie Gérontologique Groupes Iso-Ressources scale (p=0.02). 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 a RCT of a home-based, 4-session, goal-oriented cognitive rehabilitation program vs. usual care in 55 patients with mild cognitive impairment and early AD. (21) 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 QOL 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. (22) 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, QOL, and behavioral/psychological symptoms) were not observed. (23)

Kurz et al. (2012) conducted an RCT of patients with AD and early dementia. (24) The population comprised 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 on any

outcome measure. There also were no group differences on 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 vs drug treatment alone. (25) 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. (26) 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 QOL 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 1A. Summary of Key RCT Characteristics**

| Study | Countries | Sites | Dates | Participants |
|---|---|---|---|---|
| Clare et al. (2019) (19) | England, Wales | 8 | 2013-2016 | Patients with Early-Stage Alzheimer, vascular or mixed dementia (White, 96.4%; Black, 1.5%; Asian, 1.2%; Mixed, 0.4%; Other, 0.4%) |
| Amieva et al. (2016) (20) | France | 40 | 2008-2009 | Patients diagnosed with Alzheimer disease |
| Thivierge et al. (2014) (22) | Canada | NR | 2008-2011 | Patients with Alzheimer disease (n=20) |
| Kurz et al. (2012) (24) | Germany | NR | NR | Patients with mild Alzheimer Disease (n=201) |
| Chapman et al. (2004) (25) | United States | NR | 1999-2001 | Patients with mild to moderate Alzheimer disease (n=54) |
| Spector et al. (2003) (26) | U.K. | 23 | NR | Patients with dementia |

RCT: randomized controlled trial; NR: not reported; U.K.: United Kingdom.

**Table 1B. Summary of Key RCT Characteristics**

| Study | Interventions | | | |
|---|---|---|---|---|
| | *Therapy 1* | *Therapy 2* | *Therapy 3* | *Therapy 4* |
| Clare et al. (2019) (19) | 10 weekly goal-oriented individual cognitive rehabilitation sessions, followed by 4 maintenance sessions over 6 months (n=281) | Treatment as usual (medication, monitoring, general psychosocial support) (n=208) | NR | NR |
| Amieva et al. (2016) (20) | CTT (n=170) | RT (n=172) | ICRT (n=157) | Usual Medical care (n=154) |
| Thivierge et al. (2014) (22) | ELL and SR cognitive techniques | Controls | NR | NR |
| Kurz et al. (2012) (24) | 12-week cognitive rehabilitation program (n=100) | Standard medical management (site-specific; n=101) | NR | NR |
| Chapman et al. (2004) (25) | Combined cognitive-communication therapy plus an acetylcholinesterase inhibitor (n=28) | Drug Treatment alone (n=26) | NR | NR |
| Spector et al. (2003) (26) | Cognitive stimulation therapy (n=115) | Control (n=86) | NR | NR |

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

**Table 2A. Summary of Key RCT Results**

| Study | Rate of patients alive and without moderately severe to severe dementia at 24 months | Survival rate at 24 months |
|---|---|---|
| **Clare et al. (2019) (19)** | NR | NR |
| Therapy | | |
| Control | | |

| | | |
|---|---|---|
| Mean Difference (95% CI) | | |
| **Amieva et al. (2016) (20)** | | |
| CTT | 81 (47.7%) | 124 (72.9%) |
| RT | 78 (45.4%) | 118 (68.6%) |
| ICRT | 85 (54.1%) | 121 (77.1%) |
| Control | 74 (48%) | 109 (70.8%) |
| **Thivierge et al. (2014) (22)** | NR | NR |
| Therapy | | |
| Control | | |
| **Kurz et al. (2012) (24)** | NR | NR |
| Therapy | | |
| Control | | |
| p-value | | |
| **Chapman et al. (2004) (25)** | NR | NR |
| Therapy | | |
| Control | | |
| **Spector et al. (2003) (26)** | NR | NR |
| Therapy | | |
| Control | | |
| p-value | | |

CI: confidence interval; CTT: cognitive training therapy; NR: not reported; RT: reminiscence therapy; ICRT: individualized cognitive rehabilitation therapy; RCT: randomized controlled trial.

**Table 2B. Summary of Key RCT Results**

| **Study** | **Direct measure of training** | **Functional Ability score at 9 months mean (SD)** | **Overall cognitive functioning at 1 year** | **Change in MMSE scores from baseline to 7 weeks** |
|---|---|---|---|---|
| **Clare et al. (2019) (19)** | Individual goal attainment at 9 months | 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) (20)** | NR | NR | NR | NR |
| CTT | | | | |
| RT | | | | |
| ICRT | | | | |
| Control | | | | |

| | | | | |
|---|---|---|---|---|
| **Thivierge et al. (2014) (22)** | | NR | NR | NR |
| Therapy | 86.78 | | | |
| Control | 81.12 | | | |
| **Kurz et al. (2012) (24)** | NR | | NR | NR |
| Therapy | | 0.729+/-1.82 | | |
| Control | | 0.857+/-1.59 | | |
| p-value | | 0.64 | | |
| **Chapman et al. (2004) (25)** | NR | NR | | NR |
| Therapy | | | 24.62 | |
| Control | | | 26.96 | |
| **Spector et al. (2003) (26)** | NR | NR | NR | |
| Therapy | | | | 0.9 |
| Control | | | | -0.4 |
| p-value | | | | 0.044 |

CI: confidence interval; CTT: cognitive training therapy; MMSE: Mini-Mental Status Examination; NR: not reported; RT: reminiscence therapy; ICRT: individualized cognitive rehabilitation therapy; RCT: randomized controlled trial; SD: standard deviation.

**Table 3. Study Relevance Limitations**

| Study | Population [a] | Intervention [b] | Comparator [c] | Outcomes [d] | Follow-Up [e] |
|---|---|---|---|---|---|
| Clare et al. (2019) (19) | 4. Enrolled populations do not reflect relevant diversity | | | | |
| Amieva et al. (2016) (21) | 4,5. Racial and ethnic demographics for enrolled population are not reported | | | | |
| Thivierge et al. (2014) (22) | | | 4. Not the intervention of interest | | 1,2. Follow-up only 24 weeks |
| Kurz et al. (2012) (24) | | | | | 1,2. Follow-up only 9 months |
| Chapman et al. | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| (2004) (25) | | | | | |
| Spector et al. (2003) (26) | | | | | |

The study limitations stated in this table are those notable in the current literature 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) (19) | | 1. Participants and clinical staff not blinded | | | | |
| Amieva et al. (2016) (20) | | 1. Participants and clinical staff not blinded | | | | |
| Thivierge et al. (2014) (22) | | 1,2. No blinding | | | | |
| Kurz et al. (2012) (24) | | 1. Not blinded to treatment assignment | | | | |
| Chapman et al. (2004) (25) | 1. Randomization process not described | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Spector et al. (2003) (26) | 3. Allocation concealment unclear | 1,2,3. Blinding not clear | | | | |

The study limitations stated in this table are those notable in the current literature 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

A 2023 Cochrane systematic review of cognitive rehabilitation including trials conducted between 2010 and 2022 focusing on outcomes related to everyday function found statistically significantly improved participant self-ratings of goal attainment related to everyday functioning both immediately following rehabilitation and after 3 to 12 months follow-up post rehabilitation. There was less certainty regarding whether cognitive rehabilitation had a meaningful effect on quality of life. 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 individuals 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 medical policy 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 policy.

*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 1 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. (27-30) 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. (27) 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. (28) 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 remain unconfirmed. (31)

- Memory deficit: A 2016 update identified 13 trials with 514 patients. (30) There were statistically significant benefits in subjective measures of memory in the short-term (i.e., the first assessment measurement after the intervention) but not in the longer term (i.e., 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. (32) 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. (33)

*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. (34) 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 (i.e., 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 individuals 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 medical policy 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 policy.

*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 1 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 multiple sclerosis and cognitive impairments. (35-37) 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. (37) There was some evidence of a significant effect of the intervention on objective assessments of memory in both the immediate and long-term follow-up and QOL in intermediate follow-up. However, this effect on objective memory outcomes and QOL 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. (36) Twenty RCTs met inclusion criteria (total 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; SMD, 0.54; 95% CI, 0.20 to 0.88; p=0.002; $I^2$=0%) and working memory (3 very low-quality trials, n=288 patients; SMD=0.33; 95% CI, 0.09 to 0.57; p=0.006; $I^2$=0%) were observed with cognitive training compared to controls. Statistically significant improvements in attention, information processing speed, immediate verbal memory, executive functions, or depression were not observed.

Redero et al. (2023) reported results of a systematic review of neuropsychological rehabilitation in patients with relapsing-remitting MS including studies published between 2012 and 2022. (38) 15 studies (N ranging from 9 to 98) were included; 12 were RCTs, 2 were quasi-experimental and 1 had unclear allocation method. The authors found that most of the RCTs published from 2012 to 2022 evaluated rehabilitation interventions delivered through validated computer software. Therefore, they are not relevant to this policy.

**Table 5. Systematic Review & Meta-Analysis Characteristics**

| Study | Dates | Trials | Participants | Intervention | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|---|
| Rosti-Otajarvi (2014) (36) | 1993-2013 | 20 | Patients with MS | Neuro-psychological rehabilitation | 986 (15-240) | RCTs and Quasi-random-ized trials | Mean 9.5 weeks |
| das Nair et al. (2016) (37) | 1993-2015 | 15 | Patients with MS | Cognitive rehabilitation | 989 (19-240) | RCTs and Quasi-random-ized 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 (2014) (36)** | 0.54 | 0.33 | NR | NR |
| 95% CI | 0.2-0.88 | 0.09-0.57 | NR | NR |
| p-value | 0.002 | 0.006 | NR | NR |
| **das Nair et al. (2016) (37)** | NR | NR | 0.26 | -0.33 |
| 95% CI | NR | NR | 0.03-0.49 | -0.63 to -0.03 |
| p-value | NR | NR | 0.03 | 0.03 |

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 is a multicenter, observer-blinded RCT in patients with relapsing-remitting (65%), primary progressive (10%), or secondary progressive MS (25%). (39, 40) 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 RCT Characteristics**

| Study; Trial | Countries | Sites | Dates | Participants[2] | Interventions[1] | |
|---|---|---|---|---|---|---|
| | | | | | **Active** | **Comparator** |
| Lincoln et al. (2020) CRAMMS RCT (40) | England | 5 | 2015-2017 | People aged 18-69 years with MS who reported cognitive problems in daily life | 10 weekly sessions of cognitive rehabilitation, delivered by an Assistant Psychologist to groups of 4-6 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; RCT: randomized controlled trial.

**Table 8. Summary of Key RCT Results**

| Study | Multiple Sclerosis Symptoms Measure | Employment Measures | Quality of Life Measures |
|---|---|---|---|
| **Lincoln et al. (2020) (40)** | 387 | 382 | 382 |
| | Mean MSIS (SD) Psychological score at 12 months | Any employment at 12 months | Mean (SD) EQ-5D visual analog at 12 months |
| 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) (40) | | | 3. Delivery not similar intensity as intervention | | |

The study limitations stated in this table are those notable in the current literature 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) (40) | | 1. Participants and assistant psychologists aware of allocation | | | | |

The study limitations stated in this table are those notable in the current literature 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 |
|---|---|---|---|---|---|
| Nauta et al. (2023) (41) | 110 | 66% relapsing-remitting; 17% secondary progressive; 12% primary progressive | 9 weekly group-based sessions of 2.5 hours | Enhanced treatment as usual: 1 individual appointment with MS specialist nurse focused on psycho-education | CRT alleviated cognitive complaints immediately after rehabilitation but benefits in cognition did not persist to 6 months. At 6-month follow-up, CRT showed benefits on personalized cognitive goals (goals concerning |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | daily life problems identified at baseline for each participant) and processing speed. |
| Brissart et al. (2020) (42) | 110 | MS; 22% Relapsing-remitting MS | 13 2-hour extended cognitive rehabilitation sessions delivered over 6 months | 13 2-hour non-cognitive exercise sessions delivered over 6 months | 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-month follow-up. |
| Chiaravalloti et al. (2005) (43) | 117 | Primarily Relapsing-remitting MS | 8 biweekly 45-min cognitive rehabilitation sessions | Control sessions with the same therapist at the same frequency, engaging in non-training tasks (e.g., 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) (44) | 88 | MS | 10 biweekly, 45- to 60-min sessions of modified SMT | Control sessions with the same therapist at the same frequency, engaging in | Mixed effects at 5 weeks, but majority of benefits were not sustained at 6 months. At 5 weeks, there were significant improvements in |

| | | | | | |
|---|---|---|---|---|---|
| | | | | non-training tasks (e.g., reading and recalling a story) | 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-months follow-up, the only persistent between-group difference was general contentment. |
| Rosti-Otajarvi et al. (2013) (45)<br><br>Mantynen et al. (2014) (46) | 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 week 13 or at 6 months, there was improvement in perceived cognitive deficits at both time points and in a subset of patients who completed 1-year follow-up (83% completers in the therapy group vs. 67% in the control group).[a] |
| Hanssen et al. (2016) (47) | 120 | MS | 4 weeks 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 months. |

| | | | | | |
|---|---|---|---|---|---|
| Shahpouri et al. (2019) (48) | 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 months after study initiation. |
| Chiaravalloti et al. (2019) (49) | 20 | Learning-impaired participants with primarily relapsing-remitting MS (65%) | STEM: 2, 30-45 min sessions per week for 4 weeks; 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. |

CRT: cognitive rehabilitation therapy; Min: minutes; MS: multiple sclerosis; SMT: Story Memory Technique; STEM: Strategy-based Training to Enhance Memory; wks: weeks.

[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 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.

**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 individuals with cognitive deficits due to epilepsy, autism spectrum disorder (ASD), post-encephalopathy, or cancer.

The question addressed in this medical policy is: Does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits due to epilepsy, ASD, post-encephalopathy, or cancer?

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

*Populations*
The relevant population of interest is individuals with cognitive deficits due to epilepsy, ASD, post-encephalopathy, 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, post-encephalopathy, or cancer has varying lengths of follow-up, ranging from 2 to 6 months. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 6 months of follow-up is considered necessary to demonstrate efficacy.

<u>Study Selection Criteria</u>
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. (50) 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 the American Congress of Rehabilitation Medicine (ACRM) evaluated cognitive rehabilitation in epilepsy. (51) Based on 2 comparative studies (1 randomized; N=156), the 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. (52) 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 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 difference in inhibitory capacity was observed. Self-reported cognitive complaints, absentmindedness, and QOL improved more with cognitive rehabilitation. Overall, the different rehabilitation methods were similarly effective.

Helmstaedter et al. (2008), in a nonrandomized study, assessed short-term effects of cognitive rehabilitation on memory deficits in 2 retrospective, matched cohorts of temporal lobe epilepsy surgical patients. (53) Mean age was 36 years; mean age at onset of epilepsy was 4 years; and mean 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. Limitations of the study 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 a systematic review of psychosocial interventions administered by non-specialists for children and adolescents with intellectual disability (IQ<70) or lower functioning autism spectrum disorder (ASD). (54) 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. (55) 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. (56) Cognitive Enhancement Therapy, 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, 92-157). 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.

*Post-encephalitis*

The 2013 updated ACRM systematic review also evaluated cognitive rehabilitation for post-encephalitis cognitive deficits. (51) 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 in 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). (57) 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 post-intervention. 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 RCT Characteristics**

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | **Active** | **Comparator** |
| Akel et al. (2019) (57) | Turkey | 1 | NR | Children aged 6-12 years 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 |

NR: not reported; MMSE: Mini-Mental Status Examination; RCT: randomized controlled trial.

**Table 13. Summary of Key RCT Results**

| Study | Cognitive Measures | Fatigue Measures | Functional Independence Measures |
|---|---|---|---|
| **Akel et al. (2019) (57)** | 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 |
| Cognitive rehabilitation | 121.54 ± 3.18/135.36 ± 10.24 | 5.45 ± 1.01/1.72 ± 0.98/3.69/< 0.001 | 52.45 ± 8.90/62.68 ± 9.74/1.15/< 0.001 |

| | | | |
|---|---|---|---|
| Control group | NR | 3.16 ± 2.45/2.16 ± 1.79/0.41/0.01 | 52.33 ± 9.29/53.11 ± 8.73/0.08/0.068 |
| Relative measure | NA | NR | NR |

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

**Table 14. Study Relevance Limitations**

| Study | Population [a] | Intervention[b] | Comparator [c] | Outcomes [d] | Follow-Up [e] |
|---|---|---|---|---|---|
| Akel et al. (2019) (57) | | | 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 literature 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) (57) | | 1. Partici-pants aware of allocation | | | 1. Power Calcula-tions not reported | 4. Comparative treatment effects not calculated |

The study limitations stated in this table are those notable in the current literature 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. (51) 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. (58) Time since craniotomy was not reported. Adjuvant chemotherapy or radiotherapy was not administered until after the trial. Of 109 consecutive patients screened for trial 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 weekly for 4 weeks and comprised 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 (i.e., 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*

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). (59) 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 post-intervention 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 post-intervention. 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. (60) Three case-control studies and 7 RCTs with 433 patients (range, 22-98 patients), published between January 2010 and September 2015, were included. Most trials assessed the effects of the intervention immediately post-intervention 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 post-intervention 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. (51) 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. (61) In children and adolescents, 2 prospective, comparative studies (1 an RCT by Butler et al. [2008]) (62) 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. (62) 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.

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). (63) 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%), it cannot be ruled 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 RCT Characteristics**

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | **Active** | **Comparator** |
| Richard et al. (2019) (63) | Canada | 1 | NR | Adults aged ≥ 18 years with a diagnosis of a primary brain tumor who were ≥ 3 months post-radiation or surgery with persistent cognitive dysfunction (≤1 SD below executive function | 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-hour individual sessions of a psycho-educational BHP, also with homework of more general "brain challenges"; n=8 Waitlist control; n=6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | testing norms) | | |

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

**Table 17. Summary of Key RCT Results**

| Study | Cognitive Measures[a] | Functional Outcomes | Quality of Life Outcomes |
|---|---|---|---|
| **Richard et al. (2019) (63)** | 19 | 19 | 19 |
| Measures | Mean change (SD) in the Executive Functioning Composite at 4 months follow-up | Functional goal attainment at 4 months | 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 | 0.046 | 0.064 | NR |

[a] The 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; GMT: Goal Management Training; BHP: Brain Health Program; WAIT: Wait-list control; NR: Not Reported; RCT: randomized controlled trial; SD: standard deviation.

**Table 18. Study Relevance Limitations**

| Study | Population [a] | Intervention [b] | Comparator [c] | Outcomes [d] | Follow-Up [e] |
|---|---|---|---|---|---|
| Richard et al. (2019) (63) | | | | 1. Key health outcomes not Addressed<br>4. Not establish and validated measurements<br>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 literature 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) (63) | 3. Allocation concealment unclear | 1. Participants aware of allocation | | 1. High loss to follow-up or missing data (GMT=9%, BHP=25%, WAIT=33%)<br>6. Not intent to treat analysis (per protocol for non-inferiority trials) | 1. Power calculations not reported | |

GMT: Goal Management Training; BHP=Brain Health Program; WAIT: Wait-list control.
The study limitations stated in this table are those notable in the current literature 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, autism spectrum disorder, post-encephalopathy, 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.

**Summary of Evidence**

For individuals who have cognitive deficits due to traumatic brain injury (TBI) who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes randomized controlled trials (RCTs), nonrandomized comparison studies, case series, and systematic reviews. Relevant outcomes are functional outcomes and quality of life. The cognitive rehabilitation trials have methodologic limitations and have reported mixed results, indicating there is no uniform or consistent evidence base supporting the efficacy of this technique. Systematic reviews have generally concluded that efficacy of cognitive rehabilitation is uncertain. Since there is some limited potential for reduction in adverse outcomes, and treatment options for this patient population are few, the evidence has been deemed sufficient to determine that cognitive rehabilitation improves the net health outcomes in patients with cognitive deficits due to TBI.

For individuals who have cognitive deficits due to dementia who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, case series, and systematic reviews. Relevant outcomes are functional outcomes and quality of life. A Cochrane systematic review focusing on outcomes related to everyday functioning both immediately following rehabilitation and after 3 to 12 months follow-up post-rehabilitation. There was less certainty regarding whether cognitive rehabilitation had a meaningful effect on quality of life. One large RCT evaluating a goal-oriented cognitive rehabilitation program reported a significantly less functional decline in 1 of 2 functional scales and lower rates of institutionalization in the cognitive rehabilitation group compared with usual care at 24 months. These results need replication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have cognitive deficits due to stroke who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Although the significance is unclear, recent systematic reviews have reported some limited short-term effects in stroke patients receiving cognitive rehabilitation. Therefore, the evidence has been deemed sufficient to determine that cognitive rehabilitation improves the net health outcomes in patients with cognitive deficits due to stroke.

For individuals who have cognitive deficits due to multiple sclerosis (MS) who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Systematic reviews of RCTs have shown no significant effects of cognitive rehabilitation on cognitive outcomes. Although numerous RCTs have investigated cognitive rehabilitation for MS, 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 available RCTs have been mixed, with positive studies mostly reporting short-term benefits. Evidence for clinically significant, durable improvements in cognition is currently lacking. The

evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who have cognitive deficits due to epilepsy, autism spectrum disorder (ASD), post-encephalopathy, or cancer who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, and case series. Relevant outcomes are functional outcomes and quality of life. The quantity of studies for these conditions is much less than that for the other cognitive rehabilitation indications. Systematic reviews generally have not supported the efficacy of cognitive rehabilitation for these conditions. Relevant RCTs have had methodologic limitations, most often very short lengths of follow-up, which do not permit strong conclusions about efficacy. The evidence is insufficient to determine that the technology results in an improvement on health outcomes.

**Practice Guidelines and Position Statements**

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. (51)

American Heart Association/American Stroke Association

In 2016, the American Heart Association (AHA) and the American Stroke Association published guidelines on adult stroke rehabilitation and recovery. (71) These guidelines provide a synopsis of best clinical practices in the rehabilitative care of adults recovering from stroke, including the following statement on cognitive rehabilitation: “Use of cognitive rehabilitation to improve attention, memory, visual neglect, and executive functioning is reasonable.” (Class IIa, Level of Evidence B)

National Institute for Health and Care Excellence (NICE)

In 2013 (updated in 2023), NICE guidance on stroke rehabilitation recommended cognitive rehabilitation for visual neglect and memory and attention deficits that impact function. (64) Interventions should focus on relevant functional tasks (e.g., “errorless learning”) and “elaborative techniques” (e.g., “mnemonics,” “encoding” strategies) for memory impairments. The guidance states that providers should 'Make special arrangements for people after stroke who have communication or cognitive needs (for example, by holding joint speech and language therapy and physiotherapy sessions for those with communication difficulties).'

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." (65)

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

The Institute of Medicine published a report in 2011 on cognitive rehabilitation for traumatic brain injury that included a comprehensive review of the literature and recommendations. (66) 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

The Veterans Administration/Department of Veterans Affairs published guidelines on the treatment of concussion and mild TBI in 2009, (67) which were updated in 2016 (68), and most recently in 2021. (69) These guidelines addressed cognitive rehabilitation in the setting of persistent symptoms. The 2021 guidelines state:

- "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 2024 Veterans Administration/Department of Defense practice guideline on the management of stroke rehabilitation found "insufficient evidence to recommend for or against the use of pharmacologic agents or computer-assisted cognition rehabilitation to improve cognitive outcomes." (70)

**Ongoing and Unpublished Clinical Trials**

Some currently ongoing or unpublished trials that might influence this policy are listed in Table 20.

**Table 20. Summary of Key Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |

| | | | |
|---|---|---|---|
| NCT01138020 | Cognitive Rehabilitation of Blast-induced Traumatic Brain Injury (CRbTBI) | 77 | Oct 2026 |
| NCT03900806 | Internet-based WOrk-related Cognitive Rehabilitation for Cancer Survivors: a Randomized Controlled Trial (i-WORC) | 261 | Aug 2023 (unknown status) |
| NCT03168360 | Effect of Intensive Cognitive Rehabilitation in Subacute Stroke Patient | 150 | Dec 2023 |
| NCT03225482 | Cognitive Rehabilitation for Older Veterans With Mild Cognitive Impairment | 216 | Mar 2024 |
| 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 (COMPLEX) | 700 | Dec 2024 |
| NCT03948490 | Rehabilitation and Longitudinal Follow-up of Cognition in Adult Lower Grade Gliomas | 180 | Mar 2025 |
| NCT06021470 | The StrokeCog Study: A Randomised Pilot Study of a Novel Cognitive Rehabilitation Intervention in Stroke | 64 | Oct 2025 |
| NCT05954741 | Comparing the Effectiveness of Multidimensional Rehabilitation Programs for Cognitive Impairment in Comorbid Outpatients: A Randomized Controlled Trial | 75 | Jan 2026 |
| NCT05934786 | Rehabilitation of Cognition and Psychosocial Well-being – A better Live with Epilepsy | 70 | Dec 2028 |
| ***Unpublished*** | | | |
| NCT03237676 | The Effect of Cognitive Rehabilitation Therapy in Improving Cognitive Function of Attention Following Mild Traumatic Brain Injury | 90 | Dec 2019 |
| NCT03679468 | Improving Cognition in People with Progressive Multiple Sclerosis: A Multi-Arm, Randomized, Blinded, Sham-Controlled Trial of Cognitive Rehabilitation and Aerobic Exercise. | 309 | Feb 2023 |

NCT: national clinical trial.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

| | |
|---|---|
| **CPT Codes** | 97129, 97130 |
| **HCPCS Codes** | None |

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

| Policy History/Revision | |
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| **Date** | **Description of Change** |
| 10/15/2024 | Document updated with literature review. Coverage unchanged. References 6, 7, 9,1 3, 31, 38, 41, and 69 added; others updated. |
| 01/01/2024 | Reviewed. No changes. |
| 10/15/2022 | Document updated with literature review. Coverage unchanged. Added reference 7 and 63, other references were updated. |
| 01/01/2022 | Document updated with literature review. Coverage unchanged. Added references 11, 12, 17, 35-37, 43-44, 51, 53, 57, 59 and 63. |
| 01/01/2021 | Reviewed. No changes. |
| 02/15/2019 | Document updated with literature review. Coverage unchanged. Added references 16, 17, 26, 32, 45 and 53; several others removed. |
| 07/15/2017 | Reviewed. No changes. |
| 02/15/2017 | Document updated with literature review. The following change(s) were made to Coverage: 1) "Stroke" moved from experimental/investigational/unproven list to conditionally medically necessary; 2) "Cognitive impairment due to" added to medical necessity statement; 3) Cognitive deficits due to brain tumor, prior treatment for cancer, or multiple sclerosis added as experimental/investigational/unproven examples. |
| 01/01/2015 | Document updated with literature review. Coverage is unchanged; however, the following additional examples were added to the list of indications that are considered experimental, investigational and/or unproven: 1) Autism spectrum disorders 2) Seizure disorders. |
| 04/15/2012 | Document updated with literature review. The following was added: Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) may be considered medically necessary in the rehabilitation of patients with traumatic brain injury under the following circumstances: 1) Services are prescribed by the attending physician as part of a written care plan; 2) Prescribed services are provided by a qualified licensed professional; 3) There is potential for improvement based on pre-injury function: 4) Patients have sufficient cognitive function to understand and participate in the program, as well as adequate language expression and |

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| | comprehension, (i.e., participants should not have severe aphasia). NOTE: Ongoing services may be considered necessary only when there is demonstrated continued objective improvement in function. References and rationale updated. |
| 01/01/2010 | CPT/HCPCS code(s) updated. |
| 09/15/2009 | Revised/updated entire document, no coverage change. Illinois legislation will change on January 1, 2010. |
| 09/01/2007 | Revised/updated entire document |
| 09/01/2005 | Revised/updated entire document |
| 03/01/2002 | Revised/updated entire document |
| 03/01/2000 | Revised/updated entire document |
| 09/01/1998 | Revised/updated entire document |
| 09/01/1996 | New medical document |