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Cognitive Rehabilitation for the Treatment of Traumatic Brain Injury

Full In-Depth Health Care Technology Assessment

Contract No. H94002-05-D-0003

Task Order No. 33

October 2, 2009

Prepared for:
Department of Defense
TRICARE Management Activity
Aurora, Colorado

Policy Statement

This report was prepared by ECRI Institute's Health Technology Assessment Information Service (HTAIS) under contract to TRICARE Management Activity (Contract No. H94002-05-D-0003). ECRI Institute is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization. ECRI Institute has been designated an Evidence-based Practice Center (EPC) by the U.S. Agency for Healthcare Research and Quality. ECRI Institute's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI Institute's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships. The purpose of this technology assessment is to provide information for policy makers on the current state of knowledge on this topic. It is not intended as instruction for medical practice, or for making decisions regarding individual patients.

October 2, 2009

Ms. René Morrell
Contracting Officer's Representative
Department of Defense
TSO/TRICARE Management Activity (CMP)
16401 E. Centretech Parkway
Aurora, CO 80011-9043

Re: Contract No. H94002-05-D-0003
Delivery Order No. 33
Task Order No. 33
Full In-Depth Health Technology Assessment Report
Cognitive Rehabilitation for the Treatment of Traumatic Brain Injury

Dear Ms. Morrell:

ECRI Institute is pleased to provide the report *Cognitive Rehabilitation for the Treatment of Traumatic Brain Injury*, pursuant to the contract and delivery order cited in the subject line of this letter.

We trust you will find that this report conforms to TRICARE's specifications and meets with your satisfaction.

If we can be of further assistance or if you have any questions regarding this report, please contact me at (610) 825-6000, ext. 5337.

Sincerely,

Karen M. Schoelles, M.D.

Karen Schoelles, M.D., S.M., F.A.C.P.
Director, ECRI Institute Evidence-based Practice Center
Medical Director, Health Technology Assessment Group

Enclosure

/ldd

cc: V. Coates (ECRI Institute)
D. Downing (ECRI Institute)
PROJECT FILE (ECRI Institute)

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Summary of Findings

A traumatic brain injury (TBI) is defined as "a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain." Not all blows or jolts to the head result in a TBI. The severity of such an injury may range from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury. TBI may lead to permanent or temporary impairments of cognitive, physical, and psychosocial functions.

According to the Centers for Disease Control and Prevention (CDC), each year an estimated 1.4 million Americans sustain a TBI (adjusted annual incidence rate of 85.5 per 100,000 population). Since some patients with mild TBI may not go to a hospital, this is probably an underestimate of the true number of TBIs. Among those who experience TBI, 50,000 die, 230,000 are hospitalized, and 80,000 to 90,000 experience the onset of long-term disability.(1) The National Institutes of Health Consensus Development Panel on Rehabilitation of Persons with TBI estimated that 2.5-6.5 million Americans live with TBI-related disabilities. Groups at highest risk for TBI include males, young children (between ages 0 to 4) adolescents (between ages 15 to 19), active duty military personnel, African Americans, and persons older than 75 years. The risk of TBI among males is twice the risk than among females.

Several domains of neurocognitive functioning may be affected as a result of TBI. Deficits of executive functioning, attention, memory, communication, and visual processing are the most frequently reported neurocognitive sequelae in adults. The nature and severity of the deficits that occur following TBI depend largely on the location and extent of damage. However, because of the interrelated nature of the brain's organization, deficits in cognitive functioning rarely exist in isolation. In addition to cognitive deficits, many individuals with TBI experience behavioral and emotional problems, such as anger outbursts, depression, and anxiety.

Cognitive rehabilitation therapy (CRT) focuses on remediating cognitive deficits resulting from TBI. The Brain Injury Interdisciplinary Special Interest Group (BI-ISIG) of the American Congress of Rehabilitation defines CRT as a "systematic, functionally-oriented service of therapeutic cognitive activities, based on an assessment and understanding of the person's brain-behavior deficits." Further, according to the BI-ISIG, "services are directed to achieve functional changes by 1) reinforcing, strengthening, or reestablishing previously learned patterns of behavior, or 2) establishing new patterns of cognitive activity or compensatory mechanisms for impaired neurological systems." CRT primarily focuses on the alleviation of acquired neurocognitive impairment and disability. However, CRT may be provided as part of a comprehensive, holistic program that focuses on addressing the cognitive, psychosocial, behavioral, and vocational needs of individuals with TBI.

This report addresses eight key questions that pertain to the efficacy and safety of using CRT to treat patients with TBI:

1) In patients with TBI, does CRT for deficits of attention improve attention or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?

2) In patients with TBI, does CRT for language and communication deficits improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?
3) In patients with TBI, does CRT for memory deficits improve memory function or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?
4) In patients with TBI, does CRT for visuospatial deficits improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?
5) In patients with TBI, does CRT for deficits of executive function (e.g., problem solving and awareness) improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?
6) In patients with TBI, does multi-modal CRT (treatment structured to address multiple cognitive deficits) improve cognitive functioning or other patient-oriented outcomes compared to no treatment, sham treatment, or other non-pharmacological treatment?
7) In patients with TBI, does comprehensive, holistic CRT (treatment structured to address multiple cognitive deficits) improve patient-oriented outcomes compared to no treatment, sham treatment control, or other non-pharmacological treatment?
8) For persons with TBI, what are the reported harms/adverse events associated with CRT?
9) For persons with TBI, what is the consensus of experts regarding the efficacy and safety of CRT?

We based the answers to the first eight questions on a systematic review of data from clinical studies, whereas the last question is based on the expert opinion of professional societies. In answering these questions, we provide two ratings of the evidence, one for the evidence underlying our qualitative conclusions (which answer the question "Does it work?"), and one for the evidence underlying our quantitative conclusions (which answer the question "How well does it work?"). We express the ratings for evidence underlying qualitative conclusions as the strength of the evidence, and the ratings for the evidence underlying quantitative conclusions as the stability of the evidence. The following table presents the ratings we use and the definitions of each relevant term.

Table 1. Definitions of Strength and Stability of Evidence Ratings

Strength of Evidence Rating	Interpretation
Qualitative Conclusion (Direction of Effect)	
High	Evidence supporting the qualitative conclusion is convincing, making it highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. However, a small chance exists that new evidence will overturn or strengthen our conclusion. Regular monitoring of the relevant literature is recommended at this time.
Low	Although some evidence supports the qualitative conclusion, this evidence is tentative and perishable. A reasonable chance exists that new evidence will overturn or strengthen our conclusions. Frequent monitoring of the relevant literature is recommended at this time.
Insufficient	The available evidence that exists is not of sufficient strength to warrant drawing an evidence-based conclusion. Frequent monitoring of the relevant literature is recommended at this time.
Quantitative Conclusion (Magnitude of Effect)	
High Stability	The estimate of effect size in the conclusion is stable, making it highly unlikely that the magnitude of this estimate will substantially change as a result of the publication of new evidence.
Moderate Stability	The estimate of effect size in the conclusion is somewhat stable. However, a small chance exists that the magnitude of this estimate will substantially change as a result of the publication of new evidence. Regular monitoring of the relevant literature is recommended at this time.
Low Stability	The estimate of effect size in the conclusion is likely to be unstable. A reasonable chance exists that the magnitude of this estimate will substantially change as a result of the publication of new evidence. Frequent monitoring of the relevant literature is recommended at this time.
Unstable	Estimates of the effect size are too unstable to allow a quantitative conclusion to be drawn at this time. Frequent monitoring of the relevant literature is recommended.

A summary of our findings for each of the nine questions we addressed is presented below. For Key Question 1 through 6, we considered both intermediate outcomes, such as change in scores on standardized neuropsychological tests measuring areas of cognitive function, and patient-oriented outcomes, such as improved functional independence and quality of life. For Key Question 7, which considered the effect of comprehensive, holistic CRT, we only considered patient-oriented outcomes.

The overall evidence base for this report consisted of 18 studies, published in 20 separate publications, enrolling a total of 1,088 patients. To aid in assessing the quality of each of the studies included in this assessment, we used the quality assessment instrument developed by ECRI Institute for controlled trials. This instrument examines different factors of study design that have the potential to reduce the validity of the conclusions that can be drawn from a study. The overall quality of the studies included in the evidence base for this report was moderate.

Key Question 1: *In patients with TBI, does CRT for deficits of attention improve attention or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?*

For adults with moderate to severe TBI, the evidence is insufficient to determine if CRT for attention deficits is more effective than a sham treatment control condition for improving intermediate measures of attention and memory or patient-oriented outcomes.

None of the studies that made up the evidence base for this question included adults with mild TBI.

Three studies enrolling a total of 92 patients with moderate to severe TBI addressed this question. Each study compared CRT directed toward remediating deficits of attention to a sham treatment control condition, and each study used multiple neuropsychological tests to measure the effects of CRT on patients' attention skills. In addition to tests of attention, all three studies also included tests designed to measure various aspects of memory (e.g., short- and long-term memory recall). One of the included studies also considered the effect of CRT on a patient-oriented outcome. This study used the Functional Independence Measure (FIM) to examine patients' functional recovery. The median quality assessment score for the studies that addressed Key Question 1 was moderate. The primary reason for the moderate quality of these studies was lack of blinding of patients and outcome assessors.

Random-effects meta-analyses combining the results of the neuropsychological tests were performed. In all, we performed two separate meta-analyses: one for tests of attention and one for tests of memory. The estimated random-effects summary statistic for each of the two analyses was not statistically significant. Further, the 95% confidence interval surrounding the summary statistic in each analysis did not exclude the possibility of a clinically significant effect. Therefore, the evidence from intermediate outcomes measuring the effect of CRT directed toward remediating attention deficits was inconclusive, and no evidence-based conclusion could be drawn. Further, since only one study of moderate quality reported data on a patient-oriented outcome, we drew no conclusion as to whether CRT for attention deficits is more effective than a sham treatment control for improving patient-oriented outcomes.

Key Question 2: *In patients with TBI, does CRT for language and communication deficits improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?*

- **Patients with moderate to severe TBI who receive social skill training demonstrate improvement on measures of social communication compared to patients who receive no treatment. Strength of evidence: Low**
- **For adults with moderate to severe TBI, the evidence is insufficient to determine if social skill training improves community integration or other patient-oriented outcomes.**

None of the studies that made up the evidence base for this question included adults with mild TBI.

Two studies enrolling a total of 103 patients with moderate to severe TBI addressed this question. Both studies evaluated the efficacy of group social skills training for improving and remediating social communication deficits in adults with TBI. In one study, patients were

randomized to social skills training, a placebo control group, or a waitlist control group. In the other study, patients were randomized to social skills training or a delayed treatment group.

In both studies, improvement in social communication skills was considered a primary outcome. In addition to this outcome, one study measured improvement in social perception, depression, and anxiety. In the other study, goal setting was considered a primary outcome. Each study also measured a number of secondary outcomes, including community integration. The average quality rating of both studies across all outcomes was moderate. Both of the studies used appropriate methods of randomization, and for outcomes rated by trained observers (e.g., social behavior and communication skills) the observers were blinded in both studies. However, only one study reported concealment of allocation, and less than 85% of the enrolled patients completed the other study.

We pooled data from the social communication and community integration measures used in each study in two separate random-effects meta-analyses. The results of our first meta-analysis indicated that patients who received social skills training performed significantly better on measures of social communication than patients who received no treatment (95% confidence intervals surrounding the effect size estimate was 0.356 to 0.828). However, because the results of our analysis were based on the findings of two small studies of moderate quality, we rated the strength of evidence supporting our conclusion as low. The results of our second analysis on measures of community integration were inconclusive—the 95% confidence intervals surrounding the summary statistic overlapped zero and did not exclude the possibility of a clinically significant effect. Thus, the evidence was considered insufficient, and no evidence-based conclusion was drawn.

Key Question 3: *In patients with TBI, does CRT for memory deficits improve memory function or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?*

- **For adults with TBI, the evidence was insufficient to determine if CRT for memory deficits is more effective than a sham or no treatment control for improving intermediate outcomes of memory or patient-oriented outcomes.**

Four studies enrolling a total of 134 patients addressed this question. Patients in the CRT group in the four studies participated in various cognitive strategies and exercises intended to improve deficits in memory. In all four studies patients were randomized to receive CRT or a sham treatment, and two of the four studies also included a no treatment (waitlist) group. The severity of brain injury ranged from mild to severe across the studies. The studies considered a wide range of outcomes including performance on neuropsychological assessments of memory, patient ratings of memory problems, and other measures, such as community integration and employment status.

The overall quality rating of the studies was moderate. The primary reasons for the moderate quality rating were lack of blinding or not reporting whether the patients or outcome assessors were blinded, not reporting the method used to randomize patients, not reporting whether there was concealment of allocation, and the subjective nature of the instruments used to measure the outcomes. Because none of the studies that addressed this question measured the same or similar outcomes, data from the studies could not be pooled in any analyses. Further, in two studies, data were not reported in a manner that allowed us to calculate individual study effect sizes. Thus, the evidence was considered insufficient, and no evidence-based conclusions were drawn.

However, the study results reported by the authors of the studies addressing this question suggest that memory training in general benefits patients with TBI compared to no treatment. But, in studies that compared memory training to a sham/placebo treatment group, no significant between-group differences were observed. These findings may indicate that the sham control condition used in the studies had some kind of effect on the target problem (memory deficits).

Key Question 4**:** *In patients with TBI, does CRT for visuospatial deficits improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?*

- **None of the studies that met the inclusion criteria for this report addressed this question.**

Key Question 5*: In patients with TBI, does CRT for deficits of executive function (e.g., problem solving and awareness) improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?*

- **For adults with TBI, the evidence is insufficient to determine if CRT for deficits in executive functioning is more effective than standard care or a sham treatment for improving intermediate or patient-oriented outcomes.**

Four studies enrolling 157 patients addressed this question. One study randomized patients with TBI to receive either a new program developed by the authors to address impaired self-awareness called Awareness Intervention Program (AIP) or to standard care. Another study randomized patients to receive problem solving training or standard care, and in another study patients were randomized to Goal Management Training (GMT) or Motor Skills Training (MST). In the final study, patients were randomized to receive either functional skills training in meal preparation or remedial training involving practice on a block assembly task. Three of the four studies assessed executive functioning using various neuropsychological tests, ranging from a single test to a series of tests. Two studies measured patient-oriented outcomes, such as functional independence, problem solving, and psychosocial functioning. However, none of the studies used the same or similar instruments to measure the outcomes.

The median quality assessment rating for the studies was moderate. Overall, the primary reasons for the moderate quality rating were lack of blinding or not reporting whether the outcome assessors or patients were blinded to treatment, not reporting whether appropriate methods of randomization were used, and not reporting whether or not randomization was concealed. Further, in two studies the patients in the study groups were not comparable in terms of age. Patients in the control group in both of these studies were significantly older than patients in the experimental group.

Because none of the studies that addressed Key Question 5 measured the same or similar outcomes, data from the studies could not be pooled in any analyses. Further, the moderate quality and small size of the individual studies precluded us from drawing any qualitative conclusions. In general, however, few significant differences were observed between patients in the experimental group and patients in the sham control group, suggesting that the sham control condition used in the studies had some kind of effect on the target problem (deficits of executive function).

Key Question 6: *In patients with TBI, does multi-modal CRT (treatment structured to address multiple cognitive deficits) improve cognitive functioning or other patient-oriented outcomes compared to no treatment, sham treatment control, or other non-pharmacological treatment?*

- **For adults with moderate to severe TBI, the evidence is insufficient to determine whether CRT used to treat multiple cognitive deficits is more effective than alternative treatment focused on general or functional activities in improving intermediate measures of cognitive functioning or patient-oriented outcomes.**

None of the studies that made up the evidence base for this question included adults with mild TBI.

For this question, we considered studies in which CRT was intended to treat multiple cognitive deficits. Two studies, enrolling a total of 400 patients, met our inclusion criteria. In one study, adults with severe TBI were randomized to receive either a cognitive remediation program that focused on the following areas of cognitive functioning: attention, visuospatial integration, memory, and problem solving, or to an alternate treatment program that focused on general activities and psychosocial issues. The other study was a multicenter study in which active duty military members or veterans admitted to an inpatient brain injury program at four participating Veterans Administration Medical Centers (Minneapolis, Palo Alto, Richmond, and Tampa) were randomized to receive one of two forms of CRT—cognitive-didactic (CD) treatment or functional-experimental (FE) treatment. The CD treatment focused on four cognitive domains: attention, memory, executive function, and pragmatic communication.

The outcomes assessed in each study varied. One study primarily assessed neuropsychological functioning as measured by a battery of neuropsychological tests, while the other study considered patient-oriented outcomes, such as return to work and independent living. The median quality assessment rating was moderate. The primary reasons for the moderate quality rating were lack of comparability of patients in one study and lack of blinding of outcome assessors in both studies.

No pooled analyses were performed on the data reported from the studies addressing Key Question 6, because the studies did not include similar outcomes. Overall, the individual study results did not indicate statistically or clinically significant differences between patients who received multi-modal CRT (treatment addressing multiple cognitive deficits) and patients who received an alternate form of treatment (general or functional activities). Thus, we considered the evidence for this question insufficient, and no evidence-based conclusions were drawn.

Key Question 7: *In patients with TBI, does comprehensive, holistic CRT (treatment structured to address multiple cognitive deficits) improve patient-oriented outcomes compared to no treatment, sham treatment control, or other non-pharmacological treatment?*

- **Patients with TBI who receive comprehensive, holistic CRT report improvement on measures of quality of life compared to patients who receive a less intensive form of therapy. Strength of evidence: Low**
- **For adults with TBI, the evidence is insufficient to determine if comprehensive, holistic CRT is more effective than less intensive care in improving patients' employment status or other patient-oriented outcomes.**

Three studies enrolling a total of 208 patients addressed this question. In two of the studies, patients were randomized to receive either inpatient, comprehensive CRT or a less intense form of treatment. In the third study, patients were randomized to receive outpatient comprehensive CRT or delayed treatment. The studies considered a number of outcomes, ranging from return to work to community functioning to neurocognitive functioning. For this question, we only considered patient-oriented outcomes as these are the primary outcomes of interest in most comprehensive CRT programs. The median quality assessment rating of the studies was moderate. The primary reasons for the moderate quality rating were lack of blinding of patients in all three studies, lack of blinding of outcome assessors in one study, and the subjective nature of most of the outcomes.

From the data reported on in two of the three studies, we performed two separate random effects meta-analyses—one pooling data on return to work status and the other on measures of quality of life. The results of our meta-analyses indicated that adults with TBI who receive comprehensive CRT report significant improvement on measures of quality of life compared to adults who receive a less intense form of therapy. However, the estimated effect of treatment was small (0.28) and possibly not clinically significant (the 95% confidence intervals overlapped the bounds of clinical significance). Thus, the strength of the evidence supporting this conclusion was considered low. For return to work, the results were inconclusive. The estimated summary odds ratio for the analysis of the number of patients who returned to work at one year was not statistically significant and the 95% confidence intervals surrounding the summary statistic did not exclude the possibility of a clinically significant effect.

Key Question 8: *For persons with TBI, what are the reported harms/adverse events associated with CRT?*

- **None of the studies included in this review reported on any harms associated with CRT or any of the comparative treatments.**

Key Question 9: *For persons with TBI, what is the consensus of experts regarding the efficacy and safety of CRT?*

ECRI Institute's search of the National Guideline Clearinghouse™ (NGC) and the Healthcare Standards database identified treatment guidelines for TBI that included recommendations for the use of CRT to treat cognitive deficits from the following organizations:

- New Zealand Guidelines Group (NZGG, 2006)
- European Federation of Neurological Society (EFNS, 2005)

The NZGG published a comprehensive set of guidelines for the management of patients with TBI that included recommendations for diagnosing, acute care management, and rehabilitation. The guidelines include the following recommendations for providing CRT:

- In the acute phase, CRT should include structured and targeted programs for patients with executive difficulties that are provided in a distraction-free environment.
- In later phases of rehabilitation, CRT should include attempts to improve attention and information-processing skills, and teaching of compensatory techniques (e.g., memory aids)

The NZGG also recommends that errorless learning methods, instead of trial and error learning, be used with patients who have memory problems. As the name implies, errorless learning involves learning without errors or mistakes. In this method of learning, information is presented in such a way as to avoid or significantly reduce mistakes. Research conducted by Baddeley and Wilson (1994) suggests that patients with severe memory deficits learn better if prevented from making mistakes during the learning process. The reason for this, however, remains unclear.

The EFNS developed a set of guidelines to be used in the management of adult patients with cognitive deficits. In general, the guidelines recommended the use of neglect and apraxia rehabilitation after stroke, attention training after TBI in the post-acute stage, and memory rehabilitation with compensatory training in patients with mild amnesia.

Our searches also identified position and consensus statements from the following organizations:

- Brain Injury Association of America (BIAA, 2006)
- The Society for Cognitive Rehabilitation (SCR, 2004)
- The Academy of Neurologic Communication Disorders and Sciences (ANCDS, 2004)
- National Academy of Neuropsychology (NAN, 2002)
- British Society of Rehabilitation Medicine (BSRM, 1998)
- The National Institute of Health (NIH, 1998)
- The Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ISIG, 1992)

In general, the organizations listed above support the use of CRT to remediate cognitive deficits resulting from acquired brain injury (e.g., TBI, stroke). The positions of these organizations are based on a mix of expert opinion, consensus panels, and empirical evidence.

Overall Conclusions

The evidence base for this report consisted of 18 studies published in 20 different publications that met our inclusion criteria. The overall quality of the studies that made up the evidence base for this report was moderate. The primary reasons for the moderate quality of the studies were lack of blinding or not reporting that the patients or outcome assessors were blinded, lack of reporting about the methods used to randomize patients, lack of reporting about whether randomization was concealed, the subjective nature of most of the outcomes assessed, lack of comparability between the study groups, and attrition.

Overall, the evidence base for CRT permitted us to draw the following conclusions: 1) Adults with moderate to severe TBI who receive social skills training perform significantly better on measures of social communication than patients who receive no treatment and 2) Adults with TBI who receive comprehensive, holistic CRT report significant improvement on measures of quality of life compared to patients who receive a less intense form of therapy. Both conclusions, however, are based on the meta-analytic results of two small studies of moderate quality. Thus, the strength of the evidence supporting these conclusions is low. We were unable to draw any definitive conclusions about the effectiveness of CRT used to treat deficits related to the following cognitive areas: attention, memory, visospatial, and executive function. We were also precluded from drawing conclusions about the effectiveness of CRT used to treat multiple areas

of cognitive functioning. The following factors limited our ability to draw conclusions for these areas: inconclusiveness of meta-analytic results (no clear indication of whether CRT is more effective than the control condition), differences in the outcomes assessed in the studies, or insufficient number of studies addressing an outcome.

The small size of the evidence base is the most likely reason why the results of our meta-analysis are inconclusive (i.e., the evidence base has insufficient power to detect a clinically significant difference if one exists). However, another possible reason is that the sham control condition used in many of the studies had some kind of effect on the target problem. In general, individual results of studies that included a sham control condition indicated that both the treatment and control groups demonstrated similar pre- to post-treatment performance on most outcomes. This suggests that the active ingredient in the treatment condition may have been no more effective than the common factors (i.e., professional attention, stimulation) associated with the sham condition. Thus, in addition to more studies with larger sample sizes, future studies of CRT should be based on well-founded hypotheses about the active ingredient(s) of the treatment before testing the treatment against a sham condition.

Preface

Organization of This Report

There are six major sections in this report: 1) *Overview*, 2) *Economic and Regulatory Issues*, 3) *Key Questions and Outcomes Assessed*, 4) *Methods*, 5) *Synthesis of Results*, and 6) *Conclusions*. In the *Overview* section, we provide background information about the health condition or illness under evaluation, including details about its epidemiology, diagnosis, and treatment. This includes background information on other procedures used for diagnosing the condition or illness, and details about the specific intervention(s) evaluated in this report. The final parts of the *Overview* section address previous systematic reviews and meta-analyses of studies of this technology. This background material supports the *Key Questions and Outcomes Assessed*. The questions were developed in consultation with TRICARE; and the section on Key Questions explains the rationale for each question and the type of evidence that can answer it.

In the *Economic and Regulatory Issues* section, we provide information on the manufacturers of devices or technologies used in the studies analyzed for this assessment. Where available, we also provide cost information for the device. We include information on whether the technology is regulated by the U.S. Food and Drug Administration (FDA) and, if so, the status of the technology in the FDA market clearance/approval process. We provide information on health insurance coverage for the technology under evaluation. This includes a discussion of the coverage policies of Medicare, Medicaid, and other third party payers.

The *Methods* section details how we identified and analyzed information for this report. It covers our literature searches, criteria for including studies in our analysis, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesizing of clinical study results. The *Methods* section provides a synopsis of these activities. Specific details of literature searches, study quality and evidence strength measurement, and statistical approaches (understanding of which is not necessary for understanding the findings of this technology assessment) are documented in appendices.

The *Synthesis of Results* section of this report is organized by Key Question. For each question, we report the quality and quantity of the studies that provided relevant evidence. Then we summarize the results of the reported clinical studies that met our criteria for analysis. Detailed results from each included study are found in evidence tables in Appendix D. Each subsection closes with our evidence-based conclusions on the Key Question.

This report ends with a *Conclusions* section that briefly summarizes the answers to the questions addressed in it, and summarizes other important information that was presented in other sections.

Scope

This report evaluates the efficacy of cognitive rehabilitation therapy (CRT) for the treatment of adult patients with mild, moderate, or severe traumatic brain injury (TBI), and serves to update a previous report published by ECRI Institute in July, 2007 on the same topic. This report expands on the previous report in that it includes patients with mild TBI and considers comprehensive, holistic treatment programs. Specifically, this report considers CRT interventions that are directed toward treating specific cognitive deficits (e.g., deficits of attention, memory, or

communication) as well as comprehensive, holistic programs that are designed to address the cognitive, emotional, psychosocial, and behavioral deficits of TBI. The use of CRT to treat cognitive or related deficits as a result of other disorders, such as stroke or dementia, is outside the scope of this report. Also outside the scope of this report are any other methods used to treat TBI.

Overview

In this section, we provide background information on traumatic brain injury and cognitive rehabilitation. Although this background information is necessary for understanding the evidence discussed later in this assessment, it is based largely upon opinion, and ECRI Institute has not critically assessed its accuracy. This section of the assessment is therefore not evidence-based, and no statement in this *Overview* section should be interpreted as an endorsement or a criticism by ECRI Institute. The section headed *"Methods"* begins the evidence-based section of the report.

Traumatic Brain Injury (TBI)

A traumatic brain injury (TBI) is defined as "a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain."(2) Not all blows or jolts to the head result in a TBI. The severity of such an injury may range from "mild," i.e., a brief change in mental status or consciousness to "severe," i.e., an extended period of unconsciousness or amnesia after the injury.(2) TBI may lead to permanent or temporary impairments of cognitive, physical, and psychosocial functions.

Epidemiology

According to the Centers for Disease Control and Prevention (CDC), each year an estimated 1.4 million Americans sustain a TBI (adjusted annual incidence rate of 85.5 per 100,000 population).(2) Since some patients with mild TBI may not go to a hospital, this is probably an underestimate of the true number of TBIs. Among those who experience TBI, 50,000 die, 230,000 are hospitalized, and 80,000 to 90,000 experience the onset of long-term disability.(1) The National Institutes of Health Consensus Development Panel on Rehabilitation of Persons with TBI estimated that 2.5 to 6.5 million Americans live with TBI-related disabilities.(3) Groups at highest risk for TBI include males, young children (between ages 0 to 4) adolescents (between ages 15 to 19), active duty military personnel, African Americans, and persons older than 75 years.(2) The risk of TBI among males is twice the risk than among females.

According to information from the National Center for Health Statistics (NCHS), the leading causes of TBI are:

- Motor vehicle crashes (the leading cause of TBI resulting in hospitalization)
- Violence, especially suicidal behavior and assaults that involve firearms (the leading cause of TBI-related death)
- Falls (the leading cause of TBI among the elderly)
- Blasts (the leading cause of TBI for active duty military personnel in war zones)

The injuries that result from TBI have both short- and long-term effects on individuals, their families, and society, and the financial cost of these injuries can be enormous. The estimated cost of providing inpatient rehabilitation care and services for a person with severe TBI over an average lifetime ranges from $600,000 to $1,875,000.(4) These estimates, however, do not include the additional costs stemming from lost wages of survivors or of family members who remain home to provide care. The estimated total cost of TBI-related work loss and disability in the United States is around $20.6 billion.(5)

Etiology

There are two major classes of traumatic head injury—open and closed. Open head injuries tend to produce more discrete or focal lesions, while closed head injuries are more likely to cause generalized or diffuse cerebral damage.(6) Features of both types of injuries, however, may be seen in the same individual depending on the nature of the injury.

An open head injury results when the scalp and skull are penetrated by an object (e.g., bullet, shell fragment, rock). The primary damage in such injuries tends to be localized around the path of the penetrating object. Primary damage may also result from penetrating bone fragments in the case of skull fractures. With proper medical care, including surgical cleansing of the wound and debridement, other areas of the brain usually remain intact and unharmed, unless the force of the impact was severe enough to produce remote lesions.(6)

The mechanical forces present in closed head injury produce a complex mixture of focal and diffuse damage to the brain. Focal damage results from inward compression of the skull at the point of impact and rebound effects.(6) The forces in such blows may literally bounce the brain off the inside of the skull at the point of impact and at the opposite side. As brain surfaces are pushed against the inside of the skull, the brain sustains contusion or bruising. Because of the shape of the inner surface of the skull, focal injuries are most commonly seen in the frontal and temporal lobes. The consequences of these injuries typically manifest as changes in the regulation of behavior, affect, emotions, executive functions, memory and attention. Cerebral contusions are readily identifiable on computed tomography (CT) scans, but might take a day or two to become visible.(7)

Diffuse axonal injury (DAI) is associated with high levels of acceleration and deceleration (e.g., whiplash injuries in motor vehicle accidents). The resulting twisting movement of the head causes high-velocity rotation of the brain within the skull, putting strain on delicate nerve fibers and blood vessels.(8)This can cause stretching, tearing, and shearing of these microscopic structures, which almost always result in widespread diffuse brain dysfunction. The most consistent effect of diffuse brain injury is altered consciousness, which occurs from a disruption of the nerve fibers in the brainstem reticular formation. DAI is only visible on CT scan in the worst 5% to 10% of cases, and is most commonly seen as multiple subcortical lesions in and around the corpus callosum and deep white matter (axons).(7) Injury to axons is thought to result in reduced speed in processing and responding to information and in attention deficits.

Trauma to the head, whether from open or closed injury, is associated with both primary and secondary or delayed complications. Primary complications are the direct result of the impact, and lead to a variable degree of irreversible damage to the neurological tissue. Following the initial blow to the head, a negative chain of events occurs, which causes ongoing complications in the brain (secondary complications). Secondary complications may result from intracranial causes (mass lesions, brain swelling, intracranial pressure, seizures, vasospasm or infection) and/or extracranial causes (hypotension, hypoxia, hypoglycemia, anemia, and electrolyte abnormalities). These injuries eventually lead to cerebral ischemia, inflammation, oxidative stress, and neuronal death.(8)

Screening, Diagnosis, and Staging

The severity of TBI is typically evaluated by the findings on CT and magnetic resonance imaging (MRI) scans, the depth of coma, and the length of post-traumatic amnesia (PTA).(9,10) Degrees of severity are differentiated as follows:

- Moderate and severe TBI lesions include contusions, hemorrhages, and hematomas, which are rare in mild head injury.
- Scores on the Glasgow Coma Scale (GCS), which reflect level of arousal as determined by the patient's motor, verbal, and eye responses are stratified as follows: mild brain injury corresponds to a GCS score of 13 to 15, moderate corresponds to a score of 9 to 12, and severe injury corresponds to a score of 3 to 8.(11)
- PTA is defined as the length of time from the point of injury until the individual has a continuous memory for ongoing events.(12) The PTA in mild head injury usually lasts for seconds or minutes, whereas in moderate to severe brain injuries PTA can last for days and weeks. In severe head injuries, PTA typically lasts 7 or more days. The presence of PTA is judged by using the Galveston Orientation Amnesia Test (GOAT).(13) The GOAT evaluates the major spheres of orientation (i.e., time, place, and person) and provides an estimation of the interval both prior to and following injury for which the patient is unable to recall events. Evaluating PTA can be difficult with confused or aphasic patients.

Length of loss of consciousness (LOC) is also sometimes used as a measure of brain injury severity.(10) LOC is the length of time the patient is non-responsive, with longer periods of time typically associated with more severe brain injury. LOC should be used with some caution, however, as patients are sometimes unaware of whether or not they had a period of LOC. The injury may have been unwitnessed and the patient may have regained consciousness by the time they are evaluated.(10)

Table 2. Classification Criteria for TBI

Criteria	Mild TBI	Moderate TBI	Severe TBI
Imaging findings (CT and MRI)	Normal	Normal or abnormal	Normal or abnormal
Glasgow Coma Scale score	13 to 15	9 to 12	3 to 8
Posttraumatic Amnesia	0 to 1 day	>1 and <7 days	>7days
Loss of Consciousness	0 to 30 minutes	>30 minutes <24 hours	>24 hours

Note: Information for this table was taken from data provided in the Veterans Administration/Department of Defense clinical practice guidelines titles *Management of Concussion/mild Traumatic Brain Injury*.(14)

Course and Stages of Recovery

The course of recovery from TBI varies among patients and is related to such factors as age, site and extent of damage, and the length of time that a patient experiences PTA.(6) In general, according to Bond, recovery from moderate to severe TBI occurs in three stages.(15) In the first stage (acute stage), generally lasting from days to weeks, the patient is comatose and physical support is required. The main features of the second stage (subacute stage) are the end of PTA and the time during which patients make the greatest gains in recovery of function. The second stage generally extends from three to six months post injury. According to Sohlberg and Mateer, several mechanisms are likely to be responsible for the rapid spontaneous recovery that occurs during this stage.(6) They suggest the following: resolution and absorption of hematomas, decrease in swelling, normalization of blood flow, and return of electrolyte and neurochemical balance. Others suggest that spontaneous recovery may also depend on factors such as plasticity (change in the structure of the nervous system) and neuronal regrowth.(16)

In the third stage (chronic stage) of recovery, the rate of improvement begins to slow, and final levels of disability are revealed. The major causes of disability during the later stage of recovery are cognitive and behavioral deficits. The extent of mental changes that result after TBI is primarily related to the severity of diffuse damage that occurred. As mentioned earlier, diffuse damage is due to either primary axonal injury or secondary ischemia.(17) Although most recovery occurs in the first six months after the injury, improvement in physical skills, cognition, and social and vocational skills can continue from one to six years post injury.(18)

Recovery from mild TBI occurs within three to six months after injury for about 70% of individuals, with 85% of individuals reporting no symptoms at 12 months post injury.(19) However, between eight to 15% of individuals with mild TBI report experiencing difficulties a year or more after their initial injury.(19) The term “postconcussive syndrome” is often applied to individuals with mild TBI whose symptoms persist for more than a year. Some debate exists about applying this term to individuals who experience mild TBI.(14) The debate centers on the lack of an accepted case definition of postconcussive syndrome (PCS) and the fact that none of the symptoms (e.g., headache, dizziness, mild impairments in cognitive functioning, and emotional distress) associated with PCS are unique. These symptoms can occur with other conditions (e.g., depression, chronic pain).

Neurocognitive Sequelae of TBI

Several domains of neurocognitive functioning may be affected as a result of TBI. Deficits of executive functioning, attention, memory, communication, and visual processing are the most frequently reported neurocognitive sequelae in adults and children.(9,20,21) The nature and severity of the deficits that occur following TBI depend largely on the location and extent of damage. However, because of the interrelated nature of the brain’s organization, deficits in cognitive functioning rarely exist in isolation.

Executive Functioning

Executive functioning controls the initiation, planning, execution, and regulation of behavior. Deficits in executive functioning typically occur as a result of damage to the frontal lobes of the brain.(6) Patients with frontal lobe damage usually have some degree of difficulty with certain aspects of problem solving and goal-directed behavior. Previous investigations of patients with

lesions to the frontal lobes of the brain indicated that most patients were unable to systematically analyze the conditions of a problem and select the important connections and relationships necessary for developing a plan for solving a problem.(6)

Patients with moderate to severe frontal lobe damage may also exhibit impaired self-awareness (ISA, also called anosognosia).(22) Self-awareness is a process involving the interaction of information from external reality and internal experience. Prigatano and Schachter define self-awareness as the capacity to perceive the self in relatively objective terms while maintaining a sense of subjectivity.(23) Self-awareness, therefore, requires the integration of objective knowledge and subjective feelings. Patients with ISA often have difficulty recognizing deficits or problem circumstances caused by their brain injury.(24)

Attention Deficits

Deficits in attention are often a prominent clinical feature associated with TBI. Attention is thought to involve multiple brain areas and systems. Thus, damage to any area of the brain can result in mild to severe problems of attention.(17) Further, attention is thought to be complex, multi-dimensional phenomena. According to Sohlberg and Meteer (1989), there are five levels of attention: focused attention, sustained attention, selective attention, alternating attention, and divided attention.(6)

Focused attention is the ability to respond discretely to specific visual, auditory, or tactile stimuli. This level of attention is often disrupted in the early stages of emergence from a coma, but is usually quickly recovered in almost all patients. Sustained attention refers to the ability to maintain a consistent behavioral response during continuous and repetitive activity. Patients with this type of attention deficit can only focus on a task or maintain responses for brief periods of time, usually lasting only seconds or minutes. Selective attention is the ability to maintain a behavioral or cognitive set of actions in the face of distracting or competing stimuli. Patients with deficits at this level are easily distracted by either external (e.g., sights, sounds, or activities) or internal (e.g., worries, thoughts) stimuli. Alternating attention is the capacity for mental flexibility that allows individuals to shift their focus of attention and move between tasks having different cognitive requirements. Finally, divided attention involves the ability to respond simultaneously to multiple tasks or multiple demands (e.g., holding a conversation while driving a car). Disruption in any one level of attention can affect other levels of attention as well as other neurocognitive functions such as memory and executive functioning.

Memory Impairment

Memory impairment following TBI can range from mild, intermittent forgetfulness to profound inability to recall anything from the past (retrograde amnesia) or to integrate new information (anterograde amnesia).(25) In most cases, retrograde amnesia shrinks forward in time as the patient recovers.(20) Thus, memory loss measured in years may resolve into amnesia measured in minutes once the patient has emerged from the transitional period of PTA. However, in some cases, memory impairment can continue to present difficulties subsequent to the termination of PTA.

Impairments in memory can affect how information is stored and processed by the brain. Information processing involves several stages, any of which can be disrupted following TBI. The stages include attention, encoding, storage, consolidation, and retrieval. Disruption to any

one or more of these stages will lead to impairments in both short- and long-term memory systems.

The major neuroanatomic structures of the brain involved in memory and new learning include the lateral temporal cortex, hippocampus, thalamus, and areas of the lateral frontal lobe.(6) Structures of the lateral temporal cortex appear to be important in immediate and short-term recall, while the hippocampus and thalamus are critical for registering and integrating new information. The frontal lobe has more recently been recognized for its important role in allocating attention and organizing memories. Like attention, memory is a multidimensional system with multiple components. Thus, damage to any one neuroanatomic structure can affect other aspects of memory processing as well as the integrity of other cognitive functions.

Cognitive-communication Impairments

TBI may result in cognitive-communication impairments involving both the transmission of spoken, written, or non-verbal messages and the reception of auditory, printed or non-verbal messages.(6) Patients with communication impairments may show the following deficits:

- Disorganized or impoverished discourse (receptively and expressively)
- Awkward or inappropriate social interaction (i.e., difficulty with pragmatic dimensions of language, including difficulty interpreting social cues)
- Difficulty with abstract forms of language (i.e., figures of speech, irony, sarcasm)
- Difficulty with flexibility in linguistic processing
- Difficulty with speed of processing

Certain components of speech and language are thought to be correlated and mediated by specific neurological structures within the brain, and damage to a particular area produces predictable deficits. Deficits in communication are generally the result of damage to either the left frontal lobe or the left parietotemporal region.(26)

Visuospatial Deficits

According to Sohlberg and Mateer (1989), patient reports of visual processing problems following TBI suggest a range of changes including double vision, light sensitivity, and difficulty judging distance.(6) Formal testing frequently reveals visual spatial confusion, slow visual/motor integration, and/or unilateral neglect. Like other cognitive functions, visual processing involves multiple anatomical areas of the brain and the interaction of various neural systems. Visuospatial deficits are generally assessed using the following model, which incorporates the function of five major parts of the brain.

- ***Peripheral and brainstem mechanisms:*** This system supports visual acuity and ocular motor function. Damage to this system, typically caused by increased intracranial pressure, can result in abnormal pupillary response to changes in light, less efficient lens refraction, and impaired function of primary sensory receptor cells (rods and cones).
- ***Upper brainstem and midbrain mechanisms:*** This system supplies information about the location and movement of visual stimuli. Damage to this system can result disturbances in visual orienting, visual tracking, and localization of objects in the visual fields.

- ***Occipital lobe mechanisms:*** This system supports visual discrimination, color vision, and the appreciation of visual detail. Extensive damage to the occipital lobe can result in impairments in pattern perception and form discrimination for objects or visual stimuli in the contralateral field.
- ***Temporal lobe mechanisms:*** This system supports object recognition. Damage to this system typically results in visual agnosia in which a patient can describe the features of an object and discriminate it from other objects, but cannot name the object or describe how it is used.
- ***Parietal lobe mechanisms:*** This system supports both appreciation of spatial information and the integration of visuomotor responses and assist in visual attention to the full range of visual space. Damage to this system can result in unilateral neglect (failure to respond to visual information of one side of visual space), failure to perceive the spatial aspects of visual experience, or difficulty in visuomotor coordination.

Behavioral and Emotional Sequelae of TBI

In addition to the cognitive deficits described above, many individuals who experience TBI may also suffer from behavioral and emotional symptoms, such as anger outburst, disinhibition, depression, anxiety, and posttraumatic stress disorder (PTSD).(27) These symptoms may be directly related to the brain injury. For instance, frontal lobe injuries often result in disinhibition and inappropriate or childish behavior, and temporal lobe injuries often cause irritability and aggression.(27) However, emotional problems may also result from the individual's awareness of his/her experience of the injury or the cognitive or physical limitations that result from the injury. In either case, such symptoms can have a substantial impact on the course of recovery for individuals with TBI.(27)

Neuropsychological Assessment

Identifying and diagnosing cognitive deficits following TBI requires a comprehensive assessment that typically involves establishing a patient's preinjury background, reviewing relevant medical history, conducting behavioral observations, and administering neuropsychological tests.(6,28,29) Establishing a patient's preinjury background is necessary in order to properly interpret other examination data. For instance, distinguishing a low post-injury neuropsychological test score from an already low pre-injury score is important in determining if an actual loss in performance level has occurred.(29) A thorough assessment of a patient's background usually includes gathering information about his/her formal education experience, work history, social activities, and relationships. Interviews with family members and friends are also thought to be helpful to determine preinjury levels of independence, stability, judgment, and general personality style.

A review of the medical history typically includes information about the nature of the injury, medical procedures undertaken and complications, and results of medical assessments, neuroradiological findings (e.g., CT scans), or electrophysiologic responses (e.g., evoked potentials). Knowledge of previous injuries, coexisting medical problems, and past or current drug and/or alcohol use is also important. Further, behavioral observations made during the assessment can provide critical information about how the patient functions. Observations about a patient's ability to self-regulate, manage a test situation, and communicate both in

understanding and expressing information can provide insight about aspects of brain functioning that may be difficult to measure through specific testing procedures.(6,28)

Finally, neuropsychological tests are administered to determine specific areas of cognitive weaknesses and strengths. Several standardized test batteries are available. For a review of some of the commonly used test batteries, see Lezak (1983).(29) The basic test battery includes tests that measure a broad range of cognitive capabilities, including general intellectual functioning, attention and concentration, speed of information processing and motor responding, memory and new learning capability, communication and language functions, perceptual and perceptual-motor functions, and executive functions. The timing of the initial neuropsychological assessment should be sensitive to the patient's phase of recovery. The results of tests given during the subacute period (first three to six months after injury) of rapid recovery may become inaccurate soon after testing.(30) Further, tests may need to be modified to accommodate severely brain injured individuals or special patient populations, such as the elderly.(29)

Data collected from these tests are used to identify specific areas of cognitive deficits as well as intact cognitive abilities.(30) However, while important, neuropsychological tests may not be sufficient for establishing levels of functioning in everyday life. According to Wilson, test scores "are unable to pinpoint in sufficient detail the nature of the everyday problems and what problems need to be addressed."(31) Further, tests do not reveal whether cognitive problems are exacerbated by depression, anxiety, or fatigue. Therefore, behavioral and functional assessments should be administered to complement the information obtained from standardized neuropsychological tests.

Ultimately, the information gathered during the assessment is used to determine if a patient needs treatment to remediate deficits in cognitive functioning and to establish both short- and long-term goals of treatment.(30,32) Reassessment may be necessary at regular intervals to monitor a patient's progress and, if necessary, modify the course and goals of treatment.(24)

Cognitive Rehabilitation Therapy

The Brain Injury Interdisciplinary Special Interest Group (BI-ISIG) of the American Congress of Rehabilitation defines cognitive rehabilitation therapy (CRT) as a "systematic, functionally-oriented service of therapeutic cognitive activities, based on an assessment and understanding of the person's brain-behavior deficits."(32) According to the BI-ISIG, "services are directed to achieve functional changes by 1) reinforcing, strengthening, or reestablishing previously learned patterns of behavior, or 2) establishing new patterns of cognitive activity or compensatory mechanisms for impaired neurological systems." CRT primarily focuses on the alleviation of acquired neurocognitive impairment and disability.(33) However, CRT may be provided as part of a comprehensive, holistic program that focuses on addressing the cognitive, psychosocial, behavioral, and vocational needs of individuals with TBI.

Mechanisms of Action

Approaches to CRT are generally separated into two broad categories—restorative and compensatory.(34)The restorative approach (also called direct intervention or process-specific) is based on the theory that repetitive exercise promotes recovery of damaged neural circuits and restores lost function. Central to the theory and practice of restoration is the potential of the human brain for reorganization (i.e., plasticity), which is not well understood at the cellular level, but hypothetically may involve repetition-based changes in cell connectivity, excitability or

clinical transmission.(35) Restorative CRT typically targets specific internal cognitive processes with the goal of generalizing improvements to real-world settings. Restorative interventions usually involve exercises that are designed to isolate, as clearly as possible, specific components of impaired cognition (e.g., selective attention, visual perception, prospective memory) and to rebuild cognitive skills in a hierarchical manner.(36)

The compensatory approach (sometimes referred to as the functional approach) focuses on teaching patients to use a variety of strategies to cope with underlying cognitive impairments. This approach assumes that lost neurological functioning cannot be restored.(25) Consequently, the primary goal of compensatory CRT is to teach patients strategies to circumvent impaired functioning. Compensatory strategies generally aim to encourage and reinforce patients' intact abilities and strengths.

Restorative Techniques

A number of restorative techniques are currently available. In most cases, these techniques are tailored to meet the individual needs of the patient. An example of a commercially available restorative program for attention deficits is Attention Process Training (APT).(6) This program, developed by Sohlberg and Mateer, consists of treatment tasks that target the following five components of attention: focused attention, sustained attention, alternating attention, selective attention, and divided attention. Exercises within this program require repetitive use of the impaired cognitive system in a graded, progressively more demanding sequence. Examples of tasks within ATP for sustained attention include *Serial Numbers*, which involves having patients count backwards by 2's, 3's, 4's, or 5's with the complexity of the task increasing by adding mathematical computations. An example of a task designed to target deficits in alternating attention is *Odd-Even Number Cancellation*. This task requires patients to first cross out odd numbers on a sheet of paper, and then, when directed, switch to crossing out even numbers. A final example of a task designed to target divided attention is the *Dual Task Performance*. In this task, patients are asked to listen to a sustained-attention training tape and respond to targets by pushing a buzzer while watching a computer screen for a given target.

Another commonly used restorative technique for patients with a primary memory deficit who exhibit difficulty in encoding or recalling new information is prospective memory training.(6) This technique requires a patient to remember a specific activity to perform at a later time, with the goal of systematically extending the amount of time the patient is able to remember to carry out the activity. As the patient begins to demonstrate success at performing the activity after brief time periods (usually in two-minute intervals), the time interval to perform the activity is gradually lengthened. Underlying this technique is the belief that the act of continually updating memory traces, as the target time approaches, exercises both the encoding and retrieval of new information.

Compensatory Techniques

Compensatory approaches typically focus on activities of daily living (ADL's), such as remembering a sequence of events to prepare for work in the morning or a set of structured steps for completing day-to-day activities. For memory rehabilitation, compensatory methods fall into two categories: external and internal.(6) External aids might include memory notebook systems, electronic memory devices, alarms, calendars, reminders posted in different positions around the house, standardized locations for storing regularly needed items (car keys on a hook by the front door). Internal aids usually consist of learning mnemonic strategies, such as acronyms, peg word

systems, and associative imagery. Patients are typically provided with extensive training and practice on how to use compensatory aids.

In some cases, compensatory CRT involves modifying a patient's physical or social environment in such a way that cues for the initiation of behavior, the provision for action sequence, and the elimination of distraction or unwanted behavior are built directly into the their living or work environment. For instance, environmental modifications may include training and coaching work supervisors so that they know how to provide appropriate types and amount of support, and are effective in reducing those supports as the individual regains function.(36)

CRT in Practice

While no generally agreed upon standards of clinical practice currently exists, most CRT programs employ both restorative and compensatory techniques.(28) However, some programs may use only a single approach. A common practice is to start treatment using restorative methods and, in cases where patients fail to respond or have difficulty mastering the exercises within these methods, switch to compensatory techniques.(37) Many clinicians, however, argue that contrasting these two approaches is inappropraite, and that they should be offered simultaneously.(21)

Both approaches have received criticism. Some of the often cited criticisms of restorative methods are that they rely on test materials or tasks that are essentially artificial, are of little relevance to "real-world" functional cognitive challenges, and that the learning does not generalize to performance outside the training environment.(37-39) Criticism of compensatory methods include foremost, that the learning of standard stereotyped behaviors to accomplish ADL's assumes that the person lives in a static world where life demands do not change and that the person will not need to creatively adjust to changing circumstances.(31)

Some clinicians advocate for an approach to CRT that is flexible and contextualized in which both restorative and compensatory strategies are used interchangeably to help patients improve their abilities on functional tasks that are important to them.(28)Within this approach, restoration is task-specific (e.g., practice on meal preparation or grooming routines) and compensation involves modifying the task in ways that allow the patient to achieve their functional goal (e.g., simplifying the overall task or the steps involved in completing the task). Such an approach is thought to help patients better achieve or maintain the goal of independence.

Because many individuals with TBI experience both cognitive and non-cognitive problems (e.g., emotional and behavioral problems), CRT is often provided as part of a comprehensive, holistic program that focuses on treating the cognitive, psychosocial, and behavioral problems associated with TBI. Most holistic programs "include group and individual therapy in which patients are a) encouraged to be more aware of their strengths and weaknesses, b) helped to understand and accept these, c) given strategies to compensate for cognitive difficulties, and d) offered vocational guidance and support."(27) Comprehensive, holistic programs are typically provided by a multidisciplinary team of professionals that may include a psychiatrist, neuropsychiatrist, psychologist, physical, occupational, and speech therapists, social workers, and other counselors. These programs may be offered in either an inpatient or outpatient setting.

When to initiate treatment, the intensity of treatment, and the duration of treatment are topics that continue to be a source of much debate. Some clinicians and researchers advocate for initiating CRT services early during the acute phase of recovery.(21,40) These clinicians suggest that early

intervention may lead to greater overall improvement in cognitive functioning, reduced length of in-hospital stay, and less need for outside support upon returning home. Others suggest that CRT should not be initiated until later in the recovery phase when cognitive deficits are more apparent and treatment can be better targeted.(16) According to High (1995), the evidence for when to initiate treatment is mixed with no clear indication that early intervention leads to better patient outcomes.(41) Similarly, according to High, the evidence for intensity and duration of treatment is also mixed. Based on his review of a few studies that have assessed the effects of intensity and duration of treatment, High suggests that these aspects of treatment depend on the severity of the brain injury, with more severely injured patients requiring longer periods of rehabilitation.

Indications/Contraindications

According to the BI-ISIG, CRT is primarily intended for persons with acquired cognitive deficits resulting from traumatic brain injury, cerebrovascular accidents, or other neurological conditions.(32) While there are no formal contraindications, CRT is typically not recommended for patients who cannot actively participate in the planning and design of their treatment.

Care Setting

CRT may be delivered in an inpatient setting where rehabilitation is provided in the context of 24-hour care. This includes hospitals, long-term care facilities, and specialized rehabilitation centers. CRT may also be provided in outpatient or day treatment settings, which may be in a hospital environment, community health center, or specialized rehabilitation center. Rehabilitation can also be provided in a patient's home.

Training and Credentialing

CRT is provided by various professional groups, including neuropsychologists, psychiatrists, psychologists, speech/language pathologists, physical therapists, and occupational therapists.(32) Currently, however, no discipline provides specific training guidelines for cognitive rehabilitation. According to the BI-ISIG and other professional societies, in order to practice CRT, clinicians must have fulfilled the requirements for professional certification and licensure in their respective medical and allied health disciplines. Further, the BI-ISIG guidelines indicate that qualified clinicians should have documented course work, relevant experience, and formalized training in the understanding of neurological, behavioral, and cognitive functioning.

Ashely & Persel (2003) conducted a recent survey developed to examine the attitudes and practices of allied health professionals involved in brain injury rehabilitation.(42) Surveys were sent to rehabilitation facilities identified from the Brain Injury Association's Resource Directory, which provides access to both hospital and community-based rehabilitation programs across the United States. Of the 464 surveys mailed to unique facilities, only 168 were returned (a return rate of 36%). The survey results indicated that cognitive rehabilitation services were offered in 94% of the facilities surveyed. The majority of the facilities reported that speech pathologists (88%) and occupational therapists (71%) were the professionals primarily involved in providing CRT. Sixty-six percent indicated that neuropsychologists were the primary providers, 34% psychologists, 26% education therapists, and in 19% physical therapists. The results of this survey, however, should be interpreted with caution due to the low response rate, which may limit the validity and generalizability of the results.

Complementary Interventions

Numerous clinical services are needed by individuals who experience a traumatic brain injury. The U.S. Department of Education's National Institute on Disability and Rehabilitation Research (NIDRR) supports a "model system of care" in which a coordinated continuum of care is provided from the onset of injury to long-term follow-up to ensure optimal community integration.(43) The model system of care has been adopted by a number of medical centers located throughout the U.S. The following Web site provides information about the model systems of care and the centers that have adopted this model: http://www.tbindsc.org/Centers/centers.asp.

According to the model system, the first priority for severely head-injured patients is complete and rapid physiologic resuscitation.(43) Signs of impending transtentorial herniation (unilateral posturing and/or unilateral dilated pupil) or of rapid progressive neurological deterioration (without extracranial cause) indicate the presence of significant intracranial hypertension, and measures to control intracranial pressure (ICP) should be immediately instituted. A variety of interventions are used to control ICP. These interventions are commonly used in a stepwise manner, and include hyperventilation, osmotherapy (mannitol or hypertonic saline), cerebral spinal fluid drainage, barbiturates, and decompressive craniectomy. Other less well-studied interventions include hypothermia, normobaric hyperoxia, and hyperbaric oxygen therapy. Once a patient is stabilized, a CT scan is administered to determine the extent of damage to the brain and the need of further treatment.

Once a patient has been medically stabilized, the NIDRR recommends that comprehensive rehabilitation services be provided by an interdisciplinary team of professionals that may include rehabilitation nurses, physical and occupational therapists, speech pathologists, neuropsychologists, social workers, and pharmacists. The specific services and composition of the professional staff should, according to the model systems, be based on the needs of the patient. Further, services may be provided on inpatient or outpatient basis, again depending on the severity of the patient's brain injury and the extent of other injuries.

Cognitive remediation may be one of many rehabilitation services provided within the context of a comprehensive model of care. Other services may include one or more of the following treatments:

- Physical therapy: treatment designed to restore normal physical functioning.
- Therapeutic recreation: treatment that focuses on resuming leisure activities, and community or social skills.
- Occupational therapy: treatment that typically focuses on re-training patients on skills related to daily living tasks, such as dressing, feeding, cooking, and shopping.
- Speech and language therapy: treatment that encompasses re-learning of verbal and non-verbal communication skills.
- Psychotherapy: treatment that targets emotional issues related to experiencing a traumatic brain injury.
- Vocational therapy: treatment designed to help patients reach maximal levels of employment. Vocational therapy may involve re-training on tasks related to a specific

job, job counseling, job placement, and/or making changes to patients' work environment that will help them in their ability to perform their job.

- Pharmacotherapy: medications used during rehabilitation may include stimulants (e.g., methylphenidate and amphetamines) to treat the lethargy, inattention, and distractibility associated with TBI.(44) Neuroleptics, beta-blockers, or anti-depressants may also be used to treat associated restlessness and agitation.

Economic and Regulatory Issues

Charges and Fees

The charges involved in providing CRT vary considerably. For instance, individual therapy provided by occupational therapists ranges from $65.00 to $116.00 for every 15 minutes of therapy.(45) These charges may vary depending on the care setting (e.g., inpatient versus outpatient). Charges may also vary depending on who is delivering the therapy (e.g., occupational therapist, speech-language therapist, or neuropsychologist). Our searches, however, did not identify information that provided a direct comparison of costs by provider or setting.

Similarly, the cost of commercially available CRT software packages, such as Attention Process Training (developed by Sohlberg and Mateer, 2001) and THINKable (developed by IBM in contract with the Psychological Corp, 1990), ranges depending on the materials included in the package. For instance, the APT screening measure costs $95.00, the APT-I-Clinician Tool for Cognitive Remediation costs $425.00, and the APT-II for Persons with Mild Cognitive Dysfunction costs $450.00.(46) The cost of the THINKable multi-media software package lists at $4,800 and runs on an IBM Personal System/2.(47) The software and hardware together cost between $12,000 and $15,000, depending on equipment configuration.

Centers for Medicare and Medicaid Services Coverage Policy

The Centers for Medicare and Medicaid Services (CMS) does not have a national coverage policy for the use of CRT to treat patients with TBI. Coverage decisions are left to the discretion of local Medicare and Medicaid carriers. Information about local coverage decisions (LCD) can be found by searching the CMS Web site at http://www.cms.hhs.gov/mcd/search.asp?clickon=search&. Our searches for information about reimbursement identified a current procedural terminology code for cognitive skills development delivered in 15-minute sessions. Reimbursement rates ranged from $13.57 to $23.75/15 minutes (rates may vary depending on state and care setting).

Third Party Payer Coverage

We searched 12 private third party payers for coverage policies of CRT. Five of the 12 payers cover CRT in patients who experience cognitive deficits as a result of TBI. In general, the policies have similar coverage criteria, which specify that patients are covered if (1) they have been evaluated by a neuropsychiatrist or neuropsychologist; (2) neuropsychological testing has been performed and the results will be used to guide the rehabilitation strategies; and (3) the patient is expected to make sufficient cognitive improvement in a reasonable amount of time. One payer only covers individuals with Medicare HMO or PPO plans in accordance with their local coverage decision, and the remaining six payers either specifically stated that they consider CRT investigational and, therefore, do not cover it at all or they have no specific policy regarding CRT. These coverage policies are summarized in Table 13 of Appendix B.

Key Questions and Outcomes Assessed

For this report, we addressed the following nine Key Questions:

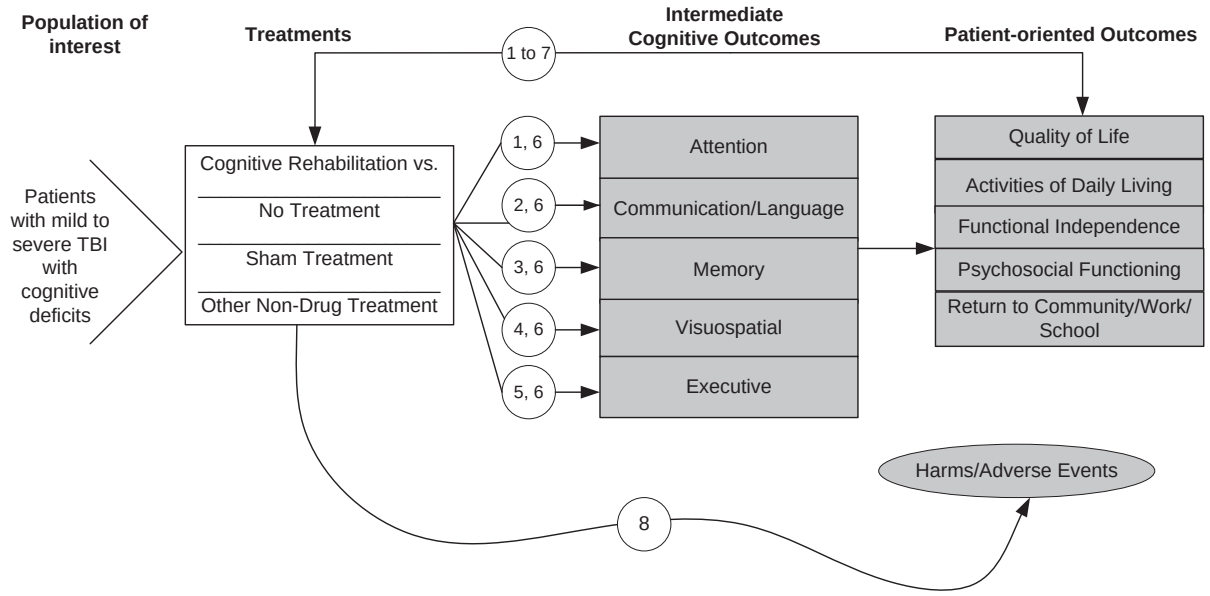
1) In patients with TBI, does cognitive rehabilitation for attention deficits improve attention or other patient-oriented outcomes when compared to no treatment, sham treatment, or other non-pharmacological treatment?
2) In patients with TBI, does cognitive rehabilitation for language and communication deficits improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment, or other non-pharmacological treatment?
3) In patients with TBI, does cognitive rehabilitation for memory deficits improve memory function or other patient-oriented outcomes when compared to no treatment, sham treatment, or other non-pharmacological treatment?
4) In patients with TBI, does cognitive rehabilitation for visuospatial deficits improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment, or other non-pharmacological treatment?
5) In patients with TBI, does cognitive rehabilitation for deficits of executive function (e.g., problem solving and awareness) improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment, or other non-pharmacological treatment?
6) In patients with TBI, does multi-modal CRT (treatment structured to address multiple cognitive deficits) improve cognitive functioning or other patient-oriented outcomes compared to no treatment, sham treatment, or other non-pharmacological treatment?
7) In patients with TBI, does comprehensive, holistic CRT (treatment structured to address the cognitive, emotional, psychosocial, and behavioral deficits of TBI) improve patient-oriented outcomes compared to no treatment, sham treatment, or other non-pharmacological treatment?
8) For persons with TBI, what are the reported harms/adverse events associated with cognitive rehabilitation?
9) For persons with TBI, what is the consensus of experts regarding the efficacy and safety of cognitive rehabilitation?

These questions, along with the treatments and outcomes we evaluated to address these questions, are illustrated in Figure 1 below. This figure portrays the pathway of events that patients experience, starting from when they are first identified (the far left of the figure), to the treatments they receive, to intermediate outcomes resulting from treatment, and finally to patient-oriented outcomes. As such, patients in the population of interest are identified and "enter" the pathway at the left of the figure. The figure illustrates that patients with TBI enter to receive CRT or no treatment, a sham treatment condition, or some other non-pharmaceutical treatment, such as occupational therapy. According to Hart, "a sham treatment is a control method that provides a treatment theoretically irrelevant to the target problem."(48) In the cognitive rehabilitation literature, a sham treatment is used to control for expectancy effects and effects of common treatment factors associated with professional attention and stimulation.

The outcomes we address are shown to the right side of the figure. The pathway through the figure represents both the direct and indirect effect of CRT. The "direct" effect is the effect CRT has directly on patient-oriented outcomes—outcomes that are felt or experienced by the patient in daily life (e.g., quality of life, functional independence). The "indirect" effect refers to a causal chain that relies on intermediate measures.(34) In this report, we consider standardized neuropsychological tests measuring change in cognitive functioning as intermediate measures of CRT. The indirect effect represents two paths—the effect of CRT on test scores measuring cognitive function and the effect of improved test scores on patient-oriented outcomes.[1] Improvement on tests scores may or may not lead to changes in patient-oriented outcomes.

Because Key Question 7 focuses on the effect of comprehensive programs (e.g., programs designed to treat the cognitive, emotional, behavioral, and vocational deficits of TBI), we do not consider intermediate outcomes for this question. Key Question 9 is not depicted in the figure because this question deals with current medical opinion on cognitive rehabilitation and does not address an intermediate or patient-oriented outcome. We address this question by summarizing pertinent information from clinical practice guidelines and consensus or position statements.

Figure 1. Analytic Framework



Note: Circled numbers, e.g., (1) denote Key Questions.

[1] For this report, we only examined outcomes at post-treatment and beyond. Further, we did not consider outcomes that were used as part of the intervention (e.g., performance on tasks used during the cognitive re-training process).

Methods

Identification of Clinical Studies

One characteristic of a good technology assessment is a systematic and comprehensive search for information. Such searches distinguish ECRI Institute's assessments from traditional literature reviews. Traditional reviews use a less rigorous approach to identifying and obtaining literature and allow a reviewer to include only articles that agree with a particular perspective, and to ignore articles that do not. Our approach precludes this potential reviewer bias because we obtained and included articles according to explicitly determined *a priori* criteria. The criteria used for this report is explained in detail below under *Study Selection.*

Often, we exclude some articles that we obtained because of their relatively low methodological quality or because they did not report required results. We document these exclusions in Appendix A of this report. We discuss articles that we included in the *Synthesis of Results* section.

Electronic Database Searches

We searched 17 external and internal databases, including PubMed, Embase, and Pilots, for clinical trials on the use of CRT to treat TBI. To supplement the electronic searches, we examined the bibliographies of included studies, scanned the content of new issues of selected journals, and reviewed relevant gray literature for potential additional relevant articles. Gray literature includes reports and studies produced by local government agencies, private organizations, educational facilities, and corporations that do not appear in the peer-reviewed literature. Although we examined gray literature sources to identify relevant information, we only evaluate published, peer-reviewed literature in this report. All of the databases and the detailed search strategies used in this report are presented in Appendix A.

Study Selection

We selected the studies that we considered in this report using *a priori* inclusion criteria. As mentioned above, arriving at these criteria before beginning the analysis is one way of reducing bias.

We used the following inclusion criteria:

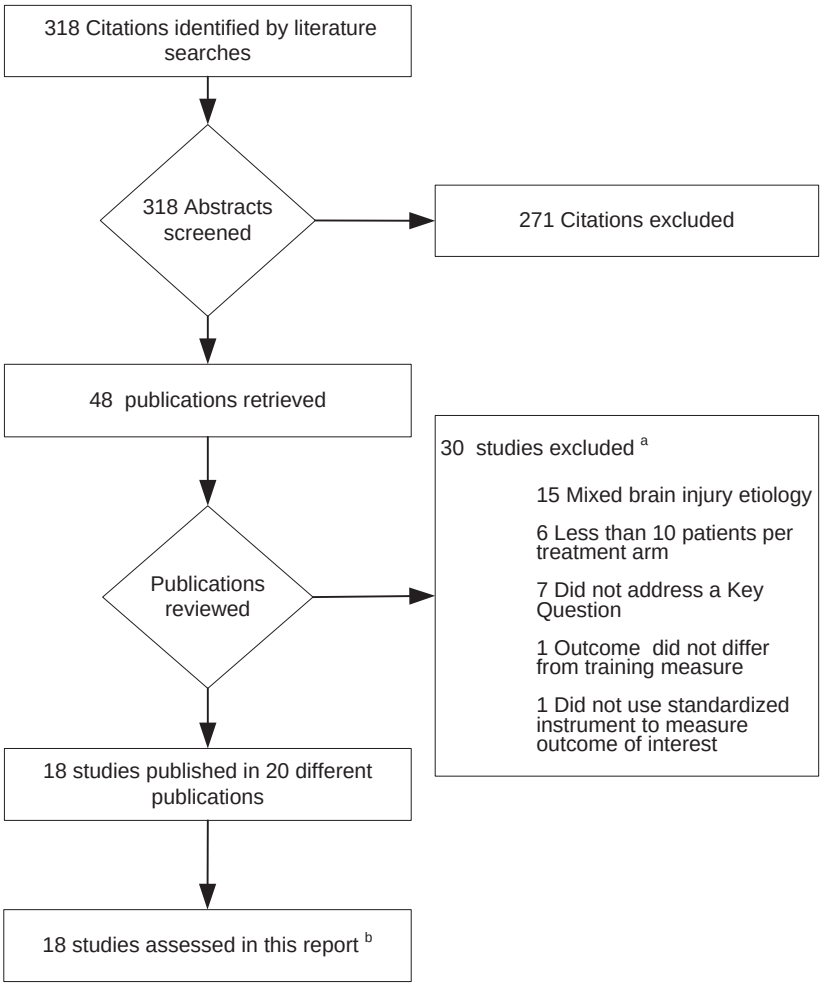
- *Eighty-five percent (85%) of patients in a study must have cognitive deficits resulting from mild, moderate, or severe TBI, or, if not, results for them must have been reported separately.*
  This report only considers cognitive deficits caused by TBI. Cognitive deficits resulting from stroke or some other neurological condition (e.g., Alzheimer's disease) are out of the scope of this technology assessment.
- *Eighty-five percent (85%) of patients in a study were 18 years or older, or, if not, results for different age groups must have been reported separately.*
  Children, adolescents, and adults are likely to have different responses to rehabilitation after a TBI due to differences in the level of cognitive development and inherent differences in brain plasticity.(25) Thus, children and adolescents are out of the scope of this technology assessment.

- *For Key Question 1-8, we only accepted prospective randomized controlled trials. Non-randomized controlled trials, retrospective case-control studies, uncontrolled studies, and historically controlled studies were excluded.* Randomized controlled trials (RCTs) promote comparability of groups, reduce the potential for biased selection of patients, and control for spontaneous recovery. RCTs are particularly important when considering TBI, because a certain degree of spontaneous recovery is likely to occur among patients who experience head trauma, especially within the first three to six months following the injury.(5) Randomization also increases the likelihood that the groups will contain equal proportions of patients with unfavorable prognoses (more severe conditions).
- *Study must have included at least 10 patients per treatment arm.* In very small studies the different arms of the study are likely to differ substantially on important characteristics, simply due to random chance. The effect sizes calculated from these studies may be substantially influenced by the differences between patient arms. Furthermore, such data may only represent a center's initial experience with a treatment, and may therefore misrepresent the effectiveness of a treatment.
- *Patients reported on in the study were not reported on in other included studies.* Double-counting of patients must be avoided, because it inflates and may bias the evidence base. Determinations of overlap between studies were based on comparative examinations of study enrollment dates, patient characteristics, treatment regimens, author names, and author affiliations. If the same study had been published more than once, we used the data from the publication with the most complete information.
- *The reliability and validity of all instruments measuring relevant outcomes (e.g., neuropsychological tests, quality of life, functioning, etc) must have been verified in the published literature.* However, if a study did not use a validated instrument, then the entire study was not necessarily excluded—only its data from instruments in which the psychometric properties were not reported in the published literature.
- *Study was reported in the English-language literature.*
  Moher et al. have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn.(49) Further, Juni et al. found that non-English studies typically were of lower methodological quality and that excluding them had little effect on effect size estimates in the majority of meta-analyses they examined.(50) Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost of translations to identify studies of acceptable quality for inclusion in our reviews.
- *Study was reported as a peer-reviewed full article rather than an abstract or letter.* Published abstracts and letters do not include sufficient details about experimental methods to permit verification and evaluation of study design.(51,52) However, we included data from any abstract that reported additional outcomes from a study and patient group that had been reported in a full-length article that met all inclusion criteria.(53)

Articles Identified by Searches

Our searches identified 318 potentially relevant articles. Most of the articles were excluded at the abstract level because they were not clinical studies or did not address any of the Key Questions. Figure 2 below provides a chart of our study selection process. Eighteen studies, published in 20 different publications, met the inclusion criteria and addressed at least one Key Question. The studies, which are listed in Table 3, enrolled a total of 1,088 patients. Three studies addressed Key Question 1, two studies addressed Key Question 2, four studies addressed Key Question 3, zero studies addressed Key Question 4, four studies addressed Key Question 5, two studies addressed Key Question 6, and three studies addressed Key Question 7. A total of 30 studies were excluded from consideration. The majority of these studies (k = 15) were excluded because they included patients with mixed etiology (e.g., stroke, dementia) of brain injury and did not report outcomes separately for patients with TBI. Table 12 in Appendix A lists the reasons for exclusion of all excluded studies.

Figure 2. Study Attrition Diagram



[a] Table 12. Excluded Randomized Controlled Trials
[b] Table 3. Key Questions Addressed by Included Studies

Table 3. Key Questions Addressed by Included Studies

Reference	Treatment	N Patients	Severity of TBI	Key Questions Addressed					
				Q1 Attention	Q2 Communication	Q3 Memory	Q5 Executive Function	Q6 Multi-modal	Q7 Comprehensive
Cicerone et al. 2008(54)	Intensive Cognitive Rehabilitation	34	Mixed: (68% severe, 18% moderate, 9% mild, and 6% NR)						✓
	Standard Neurorehabilitation	34	Mixed: (50% severe, 29% moderate, 18% mild, and 3% NR)						
McDonald et al. 2008(55)	Social Skills Program	18	Severe		✓				
	Social Activity Alone (placebo control)	17							
	No Treatment	16							
Vanderploeg et al. 2008(56)	Cognitive didactic CRT	180	Moderate to severe					✓	
	Functional-experimental CRT	180							
Bourgeois et al. 2007(57)	Spaced Retrieval Training	22	Mild to moderate			✓			
	Placebo control	16							
Dahlberg et al. 2007(58)	Social Skills Training	26	Moderate to severe		✓				
	No Treatment	26							
Cheng and Man 2006(22)	Awareness Intervention Program (AIP)	11	Moderate to severe				✓		
	Occupational Therapy	10							

Reference	Treatment	N Patients	Severity of TBI	Key Questions Addressed					
				Q1 Attention	Q2 Communication	Q3 Memory	Q5 Executive Function	Q6 Multi-modal	Q7 Comprehensive
Dou et al. 2006(59)	Computer-assisted Memory Rehabilitation	13	Mild to moderate			✓			
	Therapist-assisted Memory Rehabilitation	11							
	No Treatment	13							
Tiersky et al. 2005(60)[1]	Cognitive rehabilitation plus cognitive behavioral therapy	14	Mild: 100%						✓
	No Treatment	15	Mild: 78% Moderate: 22%						
Rath et al. 2003(61)	Problem Solving	27	Mixed: (59% mild, 24% moderate, 41% severe, 6.5% unknown)				✓		
	Standard Rehabilitation	19							
Fasotti et al. 2000(62)	Time Pressure Management (TPM)	12	Severe	✓					
	Control	10							
Levine et al. 2000(63)	Goal Management Training	15	Moderate				✓		
	Control	15							
Salazar et al. 2000(64)	Intensive Cognitive Rehabilitation	67	Moderate to severe						✓
	Limited Home Rehabilitation	53							
Novack et al. 1996(65)	Structured Attention Training	22	Severe	✓					
	Control	22							

Reference	Treatment	N Patients	Severity of TBI	Key Questions Addressed					
				Q1 Attention	Q2 Communication	Q3 Memory	Q5 Executive Function	Q6 Multi-modal	Q7 Comprehensive
Milders et al. 1995(66) & Berg et al. 1991(67)[2]	Cognitive Memory Strategies	17	Moderate to severe			✓			
	Control	11							
	No Treatment	11							
Neistadt, M. 1991(68)	Functional Constructional Training	23	Moderate to severe				✓		
	Remedial Control	22							
Neimann et al. 1990(69)	Attention Training	13	Moderate to severe	✓					
	Memory Control	13							
Ruff and Niemann 1990(70) & Ruff et al. 1989(71)[2]	Structured Cognitive Rehabilitation	20	Moderate to severe					✓	
	Control	20							
Ryan & Ruff 1988(72)	Memory Remediation	10	Mild to moderate (50% mild and 50% moderate)			✓			
	Placebo Control	10							
Total	**---**	**1,088**	**---**	**3**	**2**	**4**	**4**	**2**	**3**

Note: Key Questions 4 is not presented in the table because none of the included studies addressed this question.

[1] Six patients discontinued the study from the control group causing the number of patients to be below 10 for this group. However, this study was included because greater than 10 patients were randomized to the treatment or control group.

[2] Milders et al. 1995(66) reports four year follow-up data for the same patient population in Berg et al. 1991.(67) Ruff and Niemann 1990(70) and Ruff et al. 1989(71) include the same patient population, but report on different outcomes. These studies are presented together in the table to avoid double counting the number of patients that make up the evidence base.

NR Not reported.

Rating the Stability and Strength of Evidence

We used the ECRI Institute strength-of-evidence system to evaluate the stability and strength of a body of literature (shown in Appendix C).(73) ECRI Institute's system employs 13 decision points that collectively yield an overall category that describes the stability of our quantitative estimates of treatment effect and the strength of the evidence supporting our qualitative conclusions. Qualitative conclusions address the question, "Does it work?" Quantitative estimates addresses the question, "How well does it work?" This distinction allows an evidence base to be considered unstable in terms of the quantitative estimate of effect (e.g., if estimates vary widely among studies) yet provide strong or moderate qualitative conclusions (e.g., if all studies nevertheless demonstrate the same direction of effect). Interpretations of the terms that define the strength of evidence (strong evidence, moderate evidence, weak evidence, and inconclusive evidence) and stability ratings (high stability, moderate stability, low stability or unstable) are presented in the *Summary* section of this report in Table 1.

The 13 decision points that comprise the ECRI Institute strength-of-evidence system address five general aspects of the evidence (domains): quality, quantity, consistency, robustness, and magnitude of treatment effect. Quality refers to the degree of potential bias in the design or conduct of studies. Quantity refers to the number of studies and the number of patients enrolled in the studies. Consistency addresses the degree of agreement among the results of available studies. Robustness is the insensitivity of conclusions to minor alterations in the data. Magnitude of treatment effect concerns the quantitative amount of benefit (or harm) that patients experience after treatment. These concepts are described in greater detail in Appendix C.

Quality of Evidence

To aid in assessing the quality of each of the studies included in this assessment, we used the quality assessment instrument developed by ECRI Institute for controlled trials, shown in Appendix C. This instrument examines different factors of study design that have the potential to reduce the validity of the conclusions that can be drawn from a trial. In brief, the tool was designed so that a study attribute that, in theory, protects a study from bias receives a "Yes" response. If the study clearly does not contain that attribute it receives a "No" response. If poor reporting precludes assigning a "Yes" or "No" response for an attribute, then "NR" is recorded (NR = not reported).

To estimate the quality of an individual study, we computed a normalized score so that a perfect study received a score of 10, a study for which the answers to all items was "No" received a score of 0, and a study for which the answers to all questions was "NR" was 5.0. We then classified the overall quality of the evidence base by taking the median quality score. Quality scores were converted to categories as shown in the table below. The definitions for what constitutes low, moderate, or high quality evidence were determined *a priori* by a committee of four ECRI Institute methodologists, and are presented in Table 4 below.

Table 4. Study Quality Categories

	Overall Quality of Evidence Base		
	Low	**Moderate**	**High**
Median Overall Quality Score of the Evidence Base	6.7 or less	6.8 to <8.5	8.5 or higher

Data Synthesis

When the evidence base included three or more studies, we attempted to reach *quantitative* conclusions using a random-effects meta-analysis. Statistical significance was set at $p < 0.05$ and heterogeneity was determined using the I^2 statistic.(74,75) An I^2 greater than or equal to 50% was evidence of substantial heterogeneity among study results.

If a summary effect size could be obtained, we then determined whether or not the summary effect size estimate was informative. The summary effect size estimate was considered informative if it met one of the following criteria: 1) it was statistically significant or 2) it was not statistically significant and the 95% confidence intervals surrounding it did not overlap the boundaries of a clinically significant effect. In this report, a small effect of 0.2 using Hedges' g was considered a clinically important effect.(76) So, for a summary effect size to be considered clinically important, the 95% confidence intervals surrounding the summary statistic could not overlap with -0.2 or +0.2, and the summary effect estimate must have been outside this interval. If the 95% confidence intervals overlapped the boundaries, then the results of the meta-analysis were considered inconclusive, and no evidence-based conclusion was drawn.

We did not attempt to obtain a quantitative summary effect estimate from an evidence base with unexplained heterogeneity. We tested homogeneous meta-analyses for robustness by removal and replacement of each separate study, and by performing cumulative meta-analysis by publication date (oldest to most recent study). These methods are described more fully in Appendix C.

When a quantitative conclusion was not possible, we entered all available data into a random effects meta-analysis to determine the robustness of a qualitative conclusion. We performed the same sensitivity analyses as described above when there were three or more studies in the meta-analysis. The data were considered robust if the summary effect size remained statistically significant (did not cross zero) and the direction of the effect size did not change (go from positive to negative or negative to positive) during the analysis.

The choice of effect size metric depended on whether reported outcome data were continuous or dichotomous. Pre-post treatment differences in outcomes measured using continuous data (e.g., scores on neuropsychological tests) were calculated using Hedges' g.[2](78) We computed baseline-adjusted Hedges' g values using a pre-post correlation of 0.5.(79) For dichotomous outcomes, we used the odds ratio as the measure of effect size; values greater than one favored the experimental group, and values less than one favored the control group.[3] All effect size estimates and meta-analyses were calculated using the Comprehensive Meta-Analysis Statistical Software Package Version 2 (Biostat/ Englewood, NJ).

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[2] The formula for Hedges' g is $g = \left(\frac{M_1 - M_2}{s}\right) * \left(1 - \frac{3}{(4*(N-2))-1}\right)$ where M_1 is the mean pre-post change score for one group, M_2 is the mean pre-post change score for the other group, s is the pooled standard deviation, and N is the total number of patients in both groups. Hedges' g adds a correction factor to adjust for small samples.(77)

[3] The formula for Odds Ratio (OR) = (ad/bc) where a, b, c, and d relate to the following cells in a 2 X 2 table: a = number of events in thexperimental group, b = the number of events in the control group, c = the number of non-events in the experimental group, and d = the number of non-events in the control group.(80)

Synthesis of Results

Key Question 1. In patients with TBI, does CRT for attention deficits improve attention or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?

- **For adults with moderate to severe TBI, the evidence is insufficient to determine if CRT for attention deficits is more effective than a sham treatment control condition for improving intermediate measures of attention and memory or patient-oriented outcomes.**

  None of the studies that made up the evidence base for this question included adults with mild TBI.

Three studies enrolling a total of 92 patients addressed this question.(62,65,69) Each study compared the effects of CRT to remediate deficits of attention to a sham treatment control. Each study also used multiple neuropsychological tests to measure the effects of CRT on patients' attention skills. In addition to tests of attention, all three studies included tests designed to measure various aspects of memory (e.g., short- and long-term memory recall). The specific neuropsychological tests used in each of the studies are presented below in Table 5. The tests are organized by the primary cognitive function they were intended by the study authors to measure.

One of the included studies also considered the effect of CRT on a patient-oriented outcome.(65) This study used the Functional Independence Measure (FIM) to examine patients' functional recovery.(81) The FIM is a widely used instrument that was developed to track patients' progress in functional status from inpatient admission to discharge. The FIM primarily concentrates on measuring motor and self-care skills involved in activities of daily living (ADLs).

The median quality assessment rating for the studies that addressed Key Question 1 was moderate (median score 7.3, range 7.3 to 7.7). Table 16 in Appendix D presents the quality assessment rating for each study. Out of the three studies, only one study reported that the outcome assessor was blinded to treatment.(62) In all of the studies, the patients were either not blinded to treatment(62) or the authors of the study did not report that they were blinded.(65,69)

Table 5. Neuropsychological Tests Reported in Studies Addressing Key Question 1

Test and Associated Cognitive Function		Study		
		Fasotti et al. 2000(62)	Novack et al. 1996(65)	Neimann et al. 1990(69)
Attention				
Attention Test d2(29)	Selective and sustained attention			✓
Digit Span(29)	Selective and immediate attention		✓	
Divided Attention(29)	Visual and auditory divided attention			✓
Paced Auditory Serial Addition Test (PASAT)(29)	Auditory selective and sustained attention; information processing	✓		✓
Ruff 2 & 7(82)	Selective and sustained attention			✓
Ruff-Light Trail Learning Test(82)	Selective and sustained attention			✓
Seashore Rhythm Test(29)	Selective and sustained attention			
Single/Choice Reaction Time(29)	Speed of information processing	✓	✓	
Trail Making Test(29)	Selective and sustained attention ion		✓	✓
Memory				
Benton Sentence Repetition Test(29)	Learning and recall of visual information		✓	
Buschke Selective Reminding Test(83)	Learning and recall of visual material			
Block Span Learning Test(29)	Learning and recall of visual material			✓
Rey's Auditory Verbal Learning Test (AVLT)(29)	Learning and recall of verbal material	✓		✓
Rey's Visual Memory (RVT)(29)	Learning and recall of visual material			
Rivermead Behavioral Memory Test(84)	Everyday memory problems (e.g., remember an appointment)	✓		

Test and Associated Cognitive Function		Study		
		Fasotti et al. 2000(62)	Novack et al. 1996(65)	Neimann et al. 1990(69)
Wechsler Memory Scale(29,85)	Immediate and long-term recall of visual and verbal material		✓	✓

Note: As indicated in the inclusion/exclusion criteria for this report, we did not include data from modified standardized tests or instruments developed by the authors specifically to measure study outcomes.

Note: Some of the tests listed above may measure more than one cognitive domain. We categorized the test depending on the primary domain the authors indicated that the test was measuring.

Patient Baseline Characteristics of Included Studies

Overall, the patients assessed in the studies were similar in terms of age, education level, and severity of TBI. The average age across the studies ranged from 26 to 34 years old. The average years of education indicated that most patients had at least a high school education. The patients' years of education ranged from 11.5 to 13.8 years. As indicated by commonly used measures of TBI severity (scores on Glasgow Coma Scale, length of coma, or duration of PTA), the patients in the three studies experienced moderate to severe TBI.[4] Table 18 in Appendix E presents the baseline characteristics of the patients in the included studies.

The patients, however, differed considerably in terms of the chronicity of their brain injury at the time CRT was initiated. In the Novack et al. (1996) study, patients began CRT while they were in the acute phase of recovery (less than three months post injury).(65) In this study, the average time post-injury of patients in the treatment group was 1.9 months, and the average time for patients in the control group was 2.1 months. In the other two studies, CRT was initiated at a much later stage of recovery.(62,69) Chronicity of brain injury in these studies ranged from 8.3 months post-injury to 37.1 months. While the later studies were designed to minimize the possible effects of spontaneous recovery, the study of patients in the acute phase of recovery was designed to capitalize on this effect. According to the authors of this study, attention deficits can interfere with other areas of recovery and slow overall progress. By initiating cognitive re-training of attention deficits while spontaneous recovery was still a factor, the authors sought to further improve attention skills and potentially expedite patients' overall recovery.

Treatment Characteristics of Included Studies

While in all of the studies CRT was used to remediate deficits in attention, the characteristics of both the treatment and control conditions varied across the studies. In two studies, Novack et al. (1996) and Niemann et al., (1990), CRT was structured to address all five components of attention—focused attention, selective attention, alternating attention, sustained attention, and divided attention.(65,69) In these studies, restorative training strategies were used to assist patients in selecting and focusing on relevant stimuli and to increase the speed and accuracy of information processing. Tasks were delivered in a hierarchical manner, with the complexity of each task increasing over time based on the patient's subsequent performance. In both of the studies, visual tasks were computerized. Patients in the Novack study received a total of ten hours of treatment, and patients in the Neimann study received a total of 36 hours.

In the third study, Fasotti et al. (2000), attention training focused primarily on increasing the speed of information processing.(62) Unlike the other two studies, which addressed mental slowness through repetitive training on computerized tasks, this study used a set of compensatory strategies called Time Pressure Management (TPM). TPM is a set of cognitive strategies developed by the authors of the study to help patients compensate for consequences of slow information processing in daily living tasks. TPM strategies included making patients aware of their mental slowness and performance, giving patients specific tips for allowing more time to process information, and instructing patients on the use of self-instruction and memory aids to help with information recall. Patients in the study practiced TPM strategies by watching videotapes of situations they are likely to encounter in everyday life. Patients in the treatment

[4] Each study reported either scores on the Glasgow Coma Scale that were 8 or below, an average length of coma that was greater than 6 hours, and/or that the average duration of PTA was greater than 7 days.

group received an average of 7.4 hours of training, and patients in the control condition received 6.9 total hours.

Each of the three studies compared CRT directed toward attention deficits to a sham treatment control. In both the Fasotti (2000) and Novack (1996) study, patients were given similar practice tasks as the primary treatment group, but were not provided with the same instructions or treatment structure.(62,65) In the Neimann (1990) study, patients in the control group received training on memory tasks instead of tasks specific to attention.(69) In all three studies, patients in the control condition received the alternate treatment for the same length of time as patients in the primary treatment group. Further information about the characteristics of the treatment and control conditions of the studies addressing Key Question 1 are presented in Table 19 in Appendix E.

In brief, the primary advantage of a sham control is that it can give some of the advantages of a placebo control in that a sham treatment controls for expectancy effects and the effects of common treatment factors.(48) However, according to Hart, there are several drawbacks to using a sham control.(48) One is that the treatment may not be credible to participants, especially those recruited into a study on the basis of having a specific problem which is then ignored. A second is that sham treatments can be expensive, as they require two sets of therapists or double the time of one set. A third potential drawback is that the sham treatment may turn out to be effective for the target problem.

Individual Study Results and Meta-Analysis

As previously mentioned, the authors of the three studies used multiple neuropsychological tests to measure the effects of CRT directed towards remediating deficits of attention. Some of the tests were specific to attention skills, while others measured skills related to memory (see Table 5). Table 36 of Appendix F presents the individual study results for all the neuropsychological tests reported on in the studies. In all three studies, patients in both the treatment and control conditions demonstrated similar pretreatment to post-treatment performance on all neuropsychological tests, and no significant between-group differences were observed in any of the studies at posttreatment. Further, results from the Novack et al. study indicated that there were no statistically significant pre to post-treatment differences on scores of the FIM for either the attention remediation or sham treatment group. There were also no statistically significant between-group differences on the FIM. Individual study results for this outcome are reported in Table 37 of Appendix F.

All three studies reported data on neuropsychological tests of attention and memory in a manner that allowed us to perform random-effects meta-analyses. None of the studies reported long-term follow-up data on any outcome beyond immediate posttreatment evaluation. Because several different measures of attention and memory were used within each of the three studies, we calculated two single effect size estimates for each study—one combining the individual effect size estimates for all tests of attention and one combining the individual estimates for all tests of memory.(86) We then pooled the single effect size estimates in two separate random-effects meta-analyses to obtain an overall summary estimate. This method of obtaining a single result for a set of results from a single study is described more fully by Rosenthal.(86)

ECRI Institute's Conclusions

Heterogeneity testing indicated that the studies included in each meta-analysis were quantitatively consistent (I^2 was 0 for both meta-analyses). However, the estimated random-effects summary statistic for each of the analyses was not statistically significant. Further, the 95% confidence intervals surrounding the summary statistic in each analysis did not exclude the possibility of a clinically significant effect. Therefore, the evidence from intermediate outcomes measuring the effect of CRT directed toward remediating attention deficits was inconclusive, and no evidence-based conclusion could be drawn.The results of our analysis are presented in Figure 9 and Figure 10 in Appendix G.

The small size of the evidence base is the most likely reason why the results of our meta-analysis are inconclusive (i.e., the evidence base has insufficient power to detect a clinically significant difference if one exists). However, the sham control condition used in the three studies may have improved attention deficits and obscured any treatment effect. As previously mentioned, both the treatment and control group demonstrated similar pre to post-treatment performance on all the neuropsychological tests in all three studies. This suggests that the active ingredient in the treatment condition may have been no more effective than the common factors (i.e., professional attention, stimulation) associated with the sham condition. Future studies of CRT directed toward attention or any other cognitive deficit should be based on well-founded hypotheses about the active ingredient(s) of the treatment before testing the treatment against a sham condition. One approach to determining the active ingredients, according to Whyte, would be to compare two treatments "that have different hypotheses about the active ingredients, and that predict change in different outcomes."(87) An example would be to compare restorative treatments to compensatory treatments with the prediction that scores on neuropsychological tests will change for the restorative treatments, while functional abilities will change for compensatory treatments.

Finally, since only one study of moderate quality reported data on a patient-oriented outcome, we drew no conclusion as to whether CRT for attention deficits is more effective than a sham treatment control for improving patient-oriented outcomes.

Key Question 2. In patients with TBI, does CRT for language and communication deficits improve these deficits or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?

- **Patients with moderate to severe TBI who receive social skill training demonstrate improvement on measures of social communication compared to patients who receive no treatment. Strength of evidence: Low**
- **For adults with moderate to severe TBI, the evidence is insufficient to determine if social skill training improves community integration or other patient-oriented outcomes.**

  None of the studies that made up the evidence base for this question included adults with mild TBI.

Two studies enrolling a total of 103 patients addressed this question.(55,58) Both studies evaluated the efficacy of group social skills training for improving and remediating social communication deficits in adults with TBI. In the study by McDonald et al, patients were randomized to social skills training, a placebo control group, or a waitlist control group.(55)

In the other study by Dahlberg et al, patients were randomized to social skills training or a delayed treatment group.(58)

Both studies considered a number of outcomes. The primary outcomes in the McDonald study were social communication skills, social perception, and depression and anxiety. Secondary outcomes included self-reported ratings of psychosocial reintegration and relative-reported ratings of the patient's social behavior and perception. The main outcomes in the Dahlberg study were social communication skills and goal setting over time. Secondary outcomes included self and significant other measures of social and occupational integration and satisfaction with life. Table 6 below describes the outcomes assessed in each study and the instruments used to measure the outcomes.

The average quality rating of both studies across all outcomes was moderate (mean score 7.5). See Table 16 of Appendix D for the quality assessment ratings for each of the studies. Both of the studies used appropriate methods of randomization and, for outcomes rated by trained observers (e.g., social behavior and communication skills), the observers were blinded in both studies. However, only Dahlberg reported concealment of allocation, and less than 85% of the enrolled patients completed the McDonald study (39 of 51 or 76% of patients remained in the study immediately following treatment).

Table 6. Outcomes Assessed in Studies Addressing Key Question 2

Study	Outcome	Method/Instrument Used to Measure Outcome
McDonald et al. 2008(55)	Social communication skills	Trained observers blinded to treatment measured this outcome by rating patients' performance along several communication skills (e.g., social manners, level of reasoning) using the Behaviorally Referenced Rating System of Intermediary Social Skills (BRISS-R).(88)
	Social perception	Social perception was assessed by rating patient's reaction to audiovisual vignettes from The Awareness of Social Inference Test (TASIT).(89)
	Emotional adjustment	Measured via self-report on the Depression, Anxiety and Stress Scale (DASS).(90)
	Community integration	Measured via self-report on the Sydney Psychosocial Reintegration Scale (SPRS).(91)
Dahlberg et al. 2007(58)	Social communication skills	Trained observers blinded to treatment measured this outcome by rating patients' performance along several communication skills (e.g., clarity of expression, social style) using the Profile of Functional Impairment in Communication (PFIC).(92)
	Community integration	Measured via self-report on the Craig Handicap Assessment and Reporting Technique-Short Form (CHART-SF)(93) and the Community Integration Questionnaire (CIQ).(94)
	Satisfaction with life	Measured via self-report on the Satisfaction with Life Scale (SWLS).(95)

Note: Relative or significant other rated outcomes or outcomes for which the reliability and validity of the instrument used to measure the outcome have not been verified in the published literature were not considered in this report. Also not considered in this report was goal attainment in the Dahlberg study because this outcome was measured after the delayed treatment group received treatment.

Patient Baseline Characteristics of Included Studies

The average age of patients across the two studies ranged from 36 to 42 years, and most patients indicated having at least a high school level of education. The patients in the two studies experienced moderate to severe TBI. The average length of PTA across the studies was 63 days (standard deviation 84.0). The average time post-injury to treatment was 4.0 years (standard deviation 5.7) for the McDonald study and 9.7 years (standard deviation 5.6) for the Dahlberg study. Table 21 in Appendix E presents the baseline characteristics of the patients in the included studies.

Treatment Characteristics of Included Studies

In both studies, treatment was delivered in a group setting within an outpatient clinic by speech pathologists and clinical psychologists or social workers. In the McDonald study, patients in the social skills group received 12 weekly group sessions of three hours with 3 to 5 other members. The first two hours of treatment focused on different aspects of social communication and behavior, such as greetings and starting a conversation. The third hour was devoted to "training in decoding of expressions of emotions in face, and gesture, as well as to understanding social inferences." Patients in the treatment group also attended a weekly one-hour individual session with a clinical psychologist to address personal issues related to self-esteem, anxiety, and depression.

In the Dalhberg study, patients in the social skills group participated in 12 weekly group sessions of 1.5 hours with up to eight other members. Treatment focused teaching and practicing various social communication skills, such as conversational strategies and social confidence. Patients in this study did not receive individual psychotherapy.

In both studies the social skills group was compared to a waitlist (or no-treatment) control group. In the McDonald et al. study, the social skills group was also compared to a placebo control group. Patients in the placebo group participated in group social activities, such as cooking, crafts, and games with no explicit therapeutic goals. Further information about the characteristics of the treatment and control conditions of the studies addressing Key Question 2 are presented in Table 22 in Appendix E.

Individual Study Results and Meta-Analysis

Table 38 in Appendix F presents the individual study results of the studies that addressed this question. In the McDonald study, outcomes were measured shortly after treatment completion with no further follow-up data reported in the study. Outcomes in the Dahlberg study were reported at posttreatment and at three, six, and nine months follow-up. However, for both the three and six month follow-up, data for both study groups were collapsed, and only data for the social skills group were reported for the nine month follow-up. Thus, we only report on the posttreatment findings, which are presented separately for each study group in the Dalhberg study.

In the McDonald study, no significant between-group differences were observed between the social skills group and the placebo group on social communication scales (i.e., BRISS-R and TASIT). However, significant differences were observed in favor of the social skills group compared to the waitlist control group on the following subscales of the BRISS—partner involvement and self-centered behavior. No differences were observed at posttreatment between the social skills group and placebo or waitlist control group on measures of depression and anxiety or community integration.

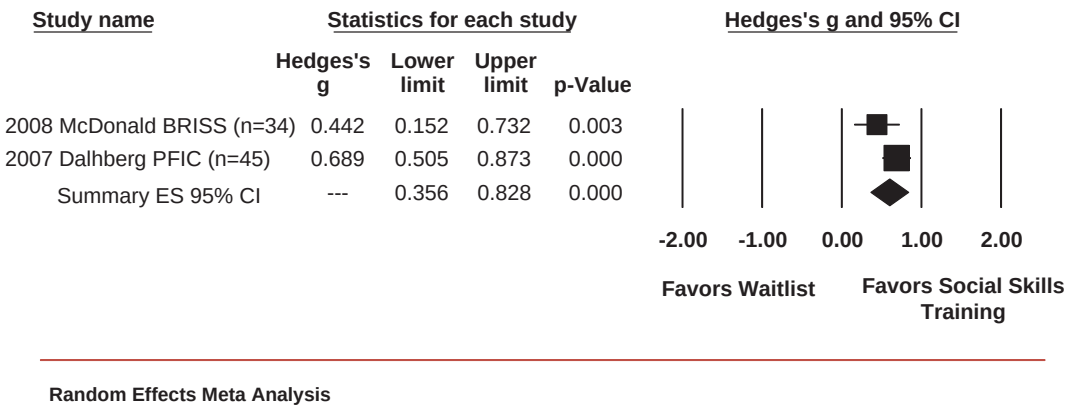
Compared to the waitlist control group, patients in the social skills group in the Dahlberg study demonstrated significant improvement on several subscales of the PFIC, including general participation in conversation (general participation), quantity of conversation (quantity), expressing ideas within speaking turns (internal relation), acknowledging the participation of the other speaker (external relation), clarity of expression, social style, subject matter, and non-verbal elements of conversation (aesthetics). No differences, however, were observed between groups on measures of community integration or satisfaction with life.

We pooled data from the social communication and community integration measures used in each study in two separate random-effects meta-analyses to determine if any qualitative conclusions could be reached about the effect of social skills training on social communication skills and community integration. The instruments used in the studies to measure social communication—the BRISS-R and PFIC—consider similar aspects of social communication in a similar manner. Both instruments use trained observers to rate patients' performance along several areas of social communication. Likewise the two community integration measures—SPRS and CIQ—consider similar aspects of integration, such as work, leisure activities, relationships, and independent living. In both analyses, we only pooled data from the social skills and waitlist group from the McDonald study (not the placebo group). Further, all analyses were performed using the combined effect size estimate of each of the subscales measured in each instrument.

ECRI Institute's Conclusions

The results of our meta-analyses indicated that patients who received social skills training performed significantly better on measures of social communication than patients who received no treatment. The 95% confidence intervals surrounding the summary effect size estimate did not overlap zero (95% CI: 0.356 to 0.828) and were clearly above the minimum threshold for a clinically significant difference (0.2). However, because the results of our analysis were based on the findings of two small studies of moderate quality, we rated the strength of evidence supporting our conclusion as low. The results of our analysis are presented below in Figure 3.

Figure 3. Key Question 2: Meta-Analytic Results of Measures of Social Communication Skills



The results of our second analysis on measures of community integration were inconclusive—the 95% confidence intervals surrounding the summary statistic overlapped zero (95% CI: -0.326 to 0.470) and did not exclude the possibility of a clinically significant effect. Thus, the evidence was considered insufficient for this outcome, and no evidence-based conclusion was drawn.

Key Question 3. In patients with TBI, does CRT for memory deficits improve memory function or other patient-oriented outcomes when compared to no treatment, sham treatment control, or other non-pharmacological treatment?

- **For adults with TBI, the evidence was insufficient to determine if CRT for memory deficits is more effective than a sham or no treatment control for improving intermediate outcomes of memory or patient-oriented outcomes.**

Four studies enrolling a total of 134 patients addressed this question.(57,59,66,67,72) The findings of one study were reported in two separate publications, each presenting results at different follow-up times.(66,67) Berg et al. reported outcomes at post-treatment and Milders et al. reported outcomes at four years follow-up.(66,67) In all four studies patients were randomized to receive CRT or a sham treatment, and two of the four studies also included a no treatment group.(59,66,67) Patients in the CRT group in the four studies participated in various cognitive strategies and exercises intended to improve deficits in memory. The studies considered a wide range of outcomes including performance on neuropsychological assessments of memory, patient ratings of memory problems, and other measures, such as community integration and employment status.

The results of our assessment of the quality of the publications that addressed Key Question 3 can be found in Table 16 of Appendix D. The overall quality rating of the studies was moderate (median score of 7.3, range 6.1 to 7.7). The primary reason for the moderate quality rating was lack of blinding or not reporting whether the patients or outcome assessors were blinded, not reporting the method used to randomize patients, not reporting whether there was concealment of allocation, and the subjective nature of the instruments used to measure the outcomes.

Table 7. Outcomes Assessed in Studies Addressing Key Question 3

Study	Treatment	Outcomes/Instrument Used to Measure
Bourgeois et al. 2007(57)	Spaced retrieval vs. placebo control	Goals mastered (correct response to prompt question), generalization (use of therapy techniques in other settings), frequency of reported memory problems, Cognitive Difficulties Scale (CDC)(96), and Community Integration Questionnaire (CIQ)(94)
Dou et al. 2006(59)	Computer assisted vs. therapist assisted rehabilitation vs. no treatment	Rivermead Behavioral Memory Test (RBMT, Cantonese Version)(84) and Neurobehavioral Cognitive Status Examination (NCSE)(97)
Milders et al. 1995(66) & Berg et al. 1991(67)[1]	Memory training vs. placebo vs. no treatment	Neuropsychological tests include Rey's 15 Word Test, Face-Naming, and Shopping List. Other outcomes functional status (percent patients reporting improvement in day to day functioning and employment status (percent of patients in paid employment).
Ryan & Ruff 1988(72)[1]	Memory training vs. placebo control	Neuropsychological tests include Benton Visual Retention Test, Rey-Osterrieth Complex Figure Test, the Tylor Complex Figure, the Selective Reminding Test(83), the Ruff-Light Trail Learning Test(98), and the Wechsler Memory Scale, Logical Memory Subtest.

Note: Relative or significant other rated outcomes or outcomes for which the reliability and validity of the instrument used to measure the outcome have not been verified in the published literature were not considered in this report. Measures for which we could not identify literature about their psychometric properties include the Hong Kong List Learning Test (Dou et al.).

Note: Unless provided with specific reference, a description of all other neuropsychological tests can be found in Lezak, MD.(29)

Patient Baseline Characteristics of Included Studies

The average age of the patients across the four studies ranged from 31 to 43 years. The average years of education indicated that most patients in all of the studies had at least a high school education. The severity of TBI varied across the studies. In the study by Berg et al.(67)and Milders et al.(66), the patients had moderate to severe TBI as evidenced by the average length of PTA—30 days for the treatment group (range 1 to 60 days), 35 days for the placebo group (range 1 to 90 days), and 37 days for the no treatment group (range 7 to 120). The other three studies included patients with mild to moderate TBI. However, only one of these studies, Ryan & Ruff, reported the number of patients with either mild or moderate TBI.(72) In this study 50% of patients had mild TBI and 50% had moderate TBI.

The chronicity of the patients' brain injury at the time CRT was initiated also varied across the studies, ranging from 5.4 months to 155.3 months (or 13 years). The study with the shortest duration from injury to treatment was Dou et al.(59) In this study, the time post injury was 9.0 months for the treatment group, 5.4 months for the alternate treatment group, and 7.5 months for the no treatment group. The study with the longest length of time was Bourgeois et al., with the time post injury for treatment group being 116.2 months and for the placebo group 155.2 months.(57) Table 24 of Appendix E presents further information about the baseline characteristics of the patients.

Treatment Characteristics of Included Studies

The amount of treatment, treatment setting, delivery method, and cognitive strategies varied across the studies. Table 25 in Appendix E presents key information about the nature of the treatment the patients received. In the Bourgeois et al. study, patients in the treatment group received spaced retrieval (SR) training delivered over the telephone for 30 minutes at a time four to five days per week.(57) SR is a method of learning and retaining information by recalling that information over increasingly longer periods of time. In this study, SR training involved recording memory problems, selecting specific memory goals (e.g., remember to take medications), and having a clinician use prompt questions, which were gradually delivered in increasing intervals, to help patients master their goal. SR training was compared to a placebo control condition in which patients simply received information about common memory strategies, such as written reminders and verbal rehearsal. This information was delivered over the telephone by a clinician for 30 minutes at a time four to five days each week.

In the Dou et al. study, patients in the primary treatment group received computerized assisted memory rehabilitation (CAMR).(59) Treatment in this group emphasized human-computer interaction and the use of multi-media presentations. Patients received training to improve sensory, working, and semantic memory, and were provided with mnemonic strategies to practice in everyday life. The CAMR treatment was compared to therapist assisted memory rehabilitation (TAMR) and to a no treatment group. Patients in the TAMR group received the same treatment as patients in the CAMR group, with the only difference being the method of delivery. Patients in both the TAMR and CAMR group received 20, 45-minute training sessions for six days per week (a total of 4 weeks of training).

In the Berg et al. and Milders et al. study, patients in the memory training group received extensive training on the use of compensatory strategies that included a mix of both internal and external memory aids.(66,67) Internal memory aids included mnemonic strategies, such as associative imagery, and external aids including the use of memory notebooks or diaries. Memory training was compared to a sham treatment control group and a no treatment control group. Patients in the sham treatment group were given various memory tasks and games without any suggestions about how to manage or complete the tasks more efficiently. Treatment was provided in a laboratory setting, and patients in both groups received a total of 18 hours of training.

Finally, in the Ryan and Ruff study the main focus of treatment in the experimental group was on retraining memory. Patients in this group participated in associational tasks, chaining tasks (i.e., task that require patients to link information together sequentially), visual imagery tasks, and personalized emotional techniques (i.e., using real life experiences in tasks of recall). The memory training was compared to a placebo control in which patients participated either individually or in small groups in an assortment of board or card games with no structured feedback. Treatment in both groups took place in a laboratory setting over a six week period (4 days a week, 5.5 hours a day) for a total of 132 hours of memory or placebo training.

Individual Study Results

The individual study results for all the studies addressing Key Question 3 are presented in Table 39 to Table 42 of Appendix F. The primary purpose of the Bourgeois et al. study was to evaluate the effects of spaced retrieval training on the frequency of reported memory problems in weekly memory logs. According to the authors, memory problems in both the treatment group

(SR training) and the control group (information only) decreased at posttreatment and one month follow-up. However, the changes between groups were not significant at either timepoint. The second purpose of this study was to determine the extent to which SR training produced generalized effects on other non-targeted everyday memory problems and had a positive effect on quality of life (as measured by the Cognitive Difficulties Scale (CDS) and Community Integration Questionnaire (CIQ). Both groups reported some generalized strategy use to other non-targeted memory problems at one month, but no statistically significant between-group differences were observed. Similarly, both groups reported significantly fewer problems over time on the CDS, but no significant between-group differences were observed at posttreatment or follow-up. Finally, no within group or between groups differences were demonstrated on the CIQ at posttreatment or follow-up.

Compared to patients in the waitlist control group, patients in the computer and therapist assisted memory rehabilitation groups in the Dou et al. study demonstrated statistically significant improvement at posttreatment in scores on the Rivermead Behavioral Memory Test (RBMT, Cantonese Version) and the Neurobehavioral Cognitive Status Examination (NCSE). However, no differences were observed between patients in the computer assisted group and the therapist assisted group. According to the authors, these findings suggest that computer aided memory rehabilitation may be a viable alternative to therapist led rehabilitation.

Berg et al. & Milders et al. measured the effects of memory training on patients' memory skills using the following neuropsychological tests: Rey's 15-word Verbal Memory Test, Face Naming, and Shopping List. These tests are described in detail in Lezak (1983).(29) Additionally, the authors of the four year follow-up study reported on patient employment status and patient-rated change in memory and work performance. According to the study authors, patients in the memory group demonstrated significant pre- to post-treatment improvement on measures of memory, and also improved significantly more than patients in both the control and no-treatment group at post-treatment. However, in the four-year follow-up study, only the control group demonstrated significant post-treatment to follow-up improvement on memory test summary scores.(66) The authors of both studies did not report data in a manner (i.e., no measure of dispersion reported) that allowed us to calculate individual study effect size estimates for summary scores on neuropsychological tests at post-treatment or four-year follow-up.

In the four year follow-up study, patients were asked about whether or not they had participated in paid employment since their last evaluation at post-treatment. Twenty percent of patients in the memory training group, 12.5 percent in the control group, and 37.5 percent of patients in the no treatment group indicated that they had not participated in paid employment. Patients were also asked if they had experienced improvement, deterioration, or no change in their memory or work performance since their last evaluation at post-treatment. Since the authors did not use standardized instruments to obtain patient ratings, we do not discuss the results of these outcomes in this section. However, we do present them in Table 40 of Appendix F.

Finally, the results of the Ryan and Ruff study indicated that both patients in the memory retraining group and the placebo group improved over time on measures of memory. However, the memory retraining group did not demonstrate significantly greater improvement than the placebo group. Additional analyses conducted by the authors of this study revealed a highly significant interaction between treatment effect and level of TBI severity. Patients with mild TBI appeared to benefit more from memory retraining than patients who were more severely impaired.

ECRI Institute's Conclusions

Because none of the studies that addressed Key Question 3 measured the same or similar outcomes, data from the studies could not be pooled in any analyses. Further, in two studies, data were not reported in a manner that allowed us to calculate individual study effect size estimates. Thus, the evidence was considered insufficient, and no evidence-based conclusions were drawn. However, the study results reported by the authors of the studies addressing this question suggest that memory training in general benefits patients with TBI compared to no treatment. But, in studies that compared memory training to a sham/placebo treatment group, no significant between-group differences were observed. These findings may indicate that the sham control condition used in the studies had some kind of effect on the target problem (memory deficits).

Key Question 4. In patients with TBI, does CRT for visuospatial deficits improve these deficits when compared to no treatment, placebo or alternate treatment control, or other non-pharmacological treatment?

- **None of the studies that met the inclusion criteria for this report addressed this question.**

Key Question 5. In patients with TBI, does CRT for deficits in executive function (e.g., problem solving and awareness) improve these deficits when compared to no treatment, placebo or alternate treatment control, or other non-pharmacological treatment?

- **For adults with TBI, the evidence is insufficient to determine if CRT for deficits in executive functioning is more effective than standard care or a sham treatment for improving intermediate or patient-oriented outcomes.**

Four studies enrolling 157 patients addressed this question. Cheng and Man randomized patients with TBI to receive either a new program developed by the authors to address impaired self-awareness called Awareness Intervention Program (AIP) or to standard care.(22) Rath et al. randomized patients to receive problem solving training or standard care(61), and Levine et al. randomized patients to Goal Management Training (GMT) or Motor Skills Training (MST).(63) Finally, Neistadt randomized patients to receive either functional skills training in meal preparation or remedial training involving practice on a block assembly task.(68) Three of the four studies assessed executive functioning using various neuropsychological tests, ranging from a single test to a series of tests.(61,63,68) Two studies measured patient-oriented outcomes, such as functional independence, problem solving, and psychosocial functioning.(22,61) However, none of the studies used the same or similar instruments to measure the outcomes. Table 8 below lists the outcomes and instruments of the four studies.

Table 8. Outcomes Assessed in Studies Addressing Key Question 5

Study	Treatment	Outcomes/Instrument Used to Measure
Cheng & Mann 2006(22)	AIP vs. standard care	Functional Independence Measure (FIM)(81), Lawton's Instrumental Activities of Daily Living Scale (IADL, Chinese version)(99), and the Self-Awareness of Deficits Interview (SADI)(23)
Rath et al. 2003(61)	Problem solving training vs. standard care	Logical and visual memory (measured using tests of recall); Watson-Glasar Critical Thinking measure(100); symptom complaints (Problem Checklist)(101); self-esteem (Rosenberg Self-Esteem Scale)(102); and problem solving (using the Wisconsin Card Sorting Task(28) and other problem solving measures, such as the Problem Solving Inventory)(103)
Levine et al. 2000(63)	GMT vs. MST	Stroop procedure, Trails Making A and B, and Digit Span subtests of the Wechsler Adult Intelligence Scale (WAIS)(29)
Neistadt, 1991(68)	Functional training vs. remedial training	Block Design subtest of the Wechsler Adult Intelligence Scale (WAIS)(29)

Note: Levine measured performance on training tasks (accuracy and speed of completion) at posttreatment. Since these tasks were used during the treatment phase of the study, we did not consider data from these tasks. Similarly, Neistadt evaluated CRT using a modified version of the Rabideau Kitchen Evaluation, which requires subjects to prepare a simple meal or beverage. Since this is a non-standardized test, we did not consider any data from the test. We also did not consider data measuring each group's performance on the Parquetry Block Test at post-treatment, since this was the training task given to the control group.

The results of our assessment of the quality of the studies that addressed Key Question 5 can be found in Table 16 of Appendix D. The median quality assessment rating for the studies was moderate (7.0, range 6.8 to 7.5). Overall, the primary reasons for the moderate quality rating were not blinding or not reporting whether the outcome assessors or patients were blinded to treatment, not reporting whether appropriate methods of randomization were used, and not reporting whether or not randomization was concealed. Further, in two studies the patients in the study groups were not comparable in terms of age.(22,68) Patients in the control group in both of these studies were significantly older than patients in the experimental group.

Patient Characteristics of Included Studies

The patients in the studies differed in terms of age, TBI severity, and time post injury. The average age of patients across the studies ranged from 29 to 58 years old. The average age of patients in the Levine and Neistadt studies was significantly younger than patients in the Cheng & Man and Rath studies (29 to 33 years versus 44 to 58 years, respectively). However, the majority of patients across all the studies indicated having at least a high school education. The severity of TBI in the Rath study ranged from mild (59%) to moderate (24%) to severe (41%), while the severity of TBI in the other three studies ranged from moderate to severe. Patients in the Cheng and Man study were in the acute phase of recovery, with an average post-injury time for the AIP group of 1.2 months and the standard care group 1.5 months. In the other studies, the average post injury time ranged from 44 to 94.8 months, with patients in the Neistadt study having the longest time post injury. Table 27 of Appendix E presents further information about the characteristics of the patients enrolled in these studies.

Treatment Characteristics of Included Studies

Information about the treatment and control conditions of the studies addressing this Key Question 5 are presented in Table 28 of Appendix E. Briefly, in the Cheng and Mann study, the initial focus of AIP was on educating patients about their injury and resultant deficits (e.g., physical, functional, and cognitive deficits). During this phase of treatment, patients were asked to assess their condition using both a standard item checklist and by discussing their condition with the therapist. Feedback was given immediately to reinforce the patient's true situation. During the second phase of treatment, patients performed a number of functional tasks selected by the therapists. Patients were asked to monitor and rate their own performance of each task. Again, patients were provided with immediate feedback about their evaluation. Finally, patients were asked to set short-term goals based on their performance on the functional tasks. The remaining time in therapy was spent on working toward accomplishing these goals. Training was delivered on an individual basis for two sessions a day, five days a week for four weeks (a total of 20 hours). Patients in the standard care group received treatment that included the physical, functional and cognitive aspects of occupational therapy. Training was delivered in a group format, with patients receiving two to three daily sessions, five days a week for four weeks.

In the Rath study, treatment in the problem solving group was divided into two components, each lasting for 12 weeks. The first component focused on problem orientation, which involved accurately recognizing problematic situations, applying problem-solving skills, and teaching self-efficacy. The second component focused on teaching and practicing specific problem-solving strategies. Treatment was delivered in two hour weekly sessions for a total of 24 sessions. Patients in the control group received group cognitive remediation that focused on five skill areas: awareness of strengths and deficits, attention, note taking, and social skills. Patients also received group psychosocial therapy devoted to psychological and social issues. Like the problem solving group, treatment was delivered in weekly two hour sessions for a total of 24 weeks.

In the Levine study, the overall purpose of Goal Management Training was to help patients stay on task. GMT was delivered in five stages. The first stage involved orienting and alerting the patients to the task at hand. The second and third stage involved goal setting and dividing goals into manageable subgoals. The final two stages involved retention of subgoals and monitoring progress. Training was delivered during one, one-hour session. Patients in the control condition received Motor Skills Training. The MST procedural processes were unrelated to goal management. Training in this group involved reading and tracing mirror-reversed text and designs. Patients in the MST group received instruction and encouragement similar to that provided to patients in the GMT group. Training in this group was also provided in a single one-hour session.

Finally, in the Neistadt study, patients in functional skills group were given training in the preparation of snacks and hot beverages. The treatment involved deciding on what snacks to prepare and, with the help of a therapist, developing a plan for preparing the snack or beverage (e.g., selecting ingredients). The therapist guided patients in the problem-solving process by asking leading questions about what next steps were needed to complete the task. Patients received three, 30-minute individual sessions per week for six weeks (a total of nine hours training). Patients in the remedial group received training in parquetry block design construction. The expectation in this group was that skills acquired through training in block design would

transfer to other functional tasks. The remedial skills group received the same amount of treatment as the functional skills group and was provided with some guidance from a therapist. In both groups, training was delivered in gradations of difficulty.

Individual Study Results

Table 43 and Table 44 in Appendix F presents the individual study results for the outcomes reported on in these studies. In the Cheng & Man study, both the AIP and standard care group demonstrated statistically significant pre- to post-treatment improvement on all outcome measures. However, the AIP group showed significantly more improvement in self awareness (as measured by the SADI) than the standard care group.

While the differences were not statistically significant, the GMT group in the Levine study preformed slower than the control group (MST group) on timed neuropsychological tests (the Stroop inference procedure and Trails Making Part B). However, according to the authors of the study, patients in the GMT group, but not in the MST group, demonstrated significant gains on everyday paper-and-pencil tasks designed to mimic tasks that are difficult for patients with goal neglect.

Results of the Rath study were mixed. Both the problem solving group and the standard care group showed significant pre to posttreatment improvement on logical memory tests of immediate and delayed recall and visual memory tests of delayed recall. However, only the problem solving group showed improvement on visual memory tests of immediate recall, whereas on the standard care group demonstrated improvement on the Watson-Glaser Critical Thinking Test. In terms of psychosocial functioning, the standard care group reported less severe symptoms after treatment, but the problem solving group reported increased self-esteem. The problem solving group showed significant pre to posttreatment gains on all measures of problem solving, including the Wisconsin Card Sorting Task, the Problem Solving Inventory, Problem Solving Questionnaire, and the Problem Solving Role Play Test.

Finally, results of the Neistadt study indicated that patients in the functional skills group demonstrated significant pre- to post-treatment improvement in scores on the WAIS Block Design task. No statistically significant pre- to post-treatment differences were observed among patients in the remedial group. Further, there were no statistically significant between-group differences in test scores at post-treatment. The author of this study suggests that patients in both the remedial and functional skills group may have relied heavily on association learning. In both groups, cuing was used as a means of helping subjects learn a general strategy of problem solving in approaching difficult tasks. The lack of difference between the groups may be due to patients not learning a general strategy, but instead learning a series of responses to specific stimuli in the treatment environments. Changing the environments/tasks at post-treatment may have affected patient performance.

ECRI Institute's Conclusion

Because none of the studies that addressed Key Question 5 measured the same or similar outcomes, data from the studies could not be pooled in any analyses. Further, the moderate quality and small size of the individual studies precluded us from drawing any qualitative conclusions. In general, however, few significant differences were observed between patients in the experimental group and patients in the sham control group, suggesting that the sham control condition used in the studies had some kind of effect on the target problem (deficits of executive function).

Key Question 6. In patients with TBI, does multi-modal CRT (treatment structured to address multiple cognitive deficits) improve cognitive functioning or other patient-oriented outcomes compared to no treatment, sham treatment control, or other non-pharmacological treatment?

- **For adults with moderate to severe TBI, the evidence is insufficient to determine whether CRT used to treat multiple cognitive deficits is more effective than alternative treatment focused on general or functional activities in improving intermediate measures of cognitive functioning or patient-oriented outcomes.**

  None of the studies that made up the evidence base for this question included adults with mild TBI.

For this question, we considered studies in which CRT was intended to treat multiple cognitive deficits. Two studies, enrolling a total of 400 patients, met our inclusion criteria.(56,70,71) One study that was described in two separate publications, Ruff and Niemann and Ruff et al., reported on different outcomes. In this study, adults with severe TBI were randomized to receive either a cognitive remediation program that focused on the following areas of cognitive functioning: attention, visuospatial integration, memory, and problem solving, or to an alternate treatment program that focused on general activities and psychosocial issues. The other study, by Vanderploeg et al, was a multicenter study in which active duty military members or veterans admitted to an inpatient brain injury program at four participating Veterans Administration Medical Centers (Minneapolis, Palo Alto, Richmond, and Tampa) were randomized to receive one of two forms of CRT—cognitive-didactic (CD) treatment or functional-experimental (FE) treatment. The CD treatment focused on four cognitive domains: attention, memory, executive function, and pragmatic communication.

The Ruff et al. study assessed the effects of multi-modal CRT using a battery of neuropsychological tests developed to measure the various aspects of cognitive functioning targeted during treatment.(71) The only patient-oriented outcome assessed in the Ruff study was emotional adjusted measured using the Katz Adjustment Scale (KAS). The results of which were reported in Ruff & Niemann.(70) The following posttreatment outcomes were measured in the Vanderploeg study: functional impairment status (measured using the FIM motor and cognitive scale), disability status (measured using the Disability Rating Scale (DRS)), and patient reported employment status, independent living status, and satisfaction with life. Neuropsychological tests were only used as baseline measures in the Vanderploeg study. Results of neuropsychological testing indicated that patients in both study groups scored at least two standard deviation points below normative values on all tests, but no statistically significant between-group differences were observed.

The results of our quality assessment can be found in Table 16 of Appendix D. The median quality assessment rating was moderate (median score 7.4, range 6.8 to 8.4). The primary reasons for the moderate quality rating were lack of comparability of patients in the Ruff and Niemann and Ruff et al. study and lack of blinding of outcome assessors in both studies. The number of days spent in a coma and the chronicity of the patients in the CRT group was significantly less than patients in the control group ($p = 0.03$) in the Ruff study.

Patient Characteristics of the Included Studies

Patients in both studies were similar in age and in number of years of education. The average age ranged from 30 to 33 years old, and the average years of education indicated that the majority of patients had at least a high school diploma. The TBI severity of patients in both studies ranged from moderate to severe. In the Ruff study, the average length of coma was 27 days in the treatment group and 49 days in the control group. Patients in the CRT group in this study spent significantly fewer days in a coma. In the Vanderploeg study, the majority of patients in didactic group (33%) and functional group (27%) spent between one and seven days in a coma. Vanderploeg also reported that 42% of patients in the didactic group and 37% of patients in the functional group experienced between seven and 30 days of PTA. Finally, time from injury to treatment was close to two months for both study groups in the Vanderploeg study. Time post injury was substantially higher in the Ruff study. In this study, time post injury was 38 months for the CRT group and 52 months for the control group. Table 30 of Appendix E presents further information about the characteristics of the patients enrolled in these studies.

Treatment Characteristics of Included Studies

Information about the treatment provided in both studies can be found in Table 32 of Appendix E. Briefly, in the Ruff study, the CRT program consisted of four, two-week treatment modules, with each module focusing on a different cognitive deficit (e.g., attention, visuospatial, memory, and problem solving). Each treatment module was delivered independently in consecutive order starting with the attention module and ending with the problem solving module. Both remediating and compensatory CRT strategies were used in each treatment module. In each module, training was delivered in four 50-minute group sessions per day for a total of eight days (a total of about 26.6 hours of training). The entire program lasted for eight weeks (a total of about 106 hours training). Patients in the control condition received treatment that emphasized psychosocial adjustment, leisure, and activities of daily living. Each day, the control patients attended four, 50-minute sessions, four days a week for a total of eight weeks (a total of about 106 hours of treatment). Both the CRT and control group also received 50 minutes of group psychotherapy per treatment day.

In the Vanderploeg study, elements of treatment in the CD group included trial-and-error learning, building self-awareness, and using mostly cognitive remediating strategies to target the following areas: attention, working and prospective memory, communication problems, and executive self-awareness. Patients in this group participated in progressively more difficult pen and paper or computerized tasks. Treatment was delivered in one to one sessions for 1.5 to 2.5 hours a day of protocol specific training and an additional 2.0 to 2.5 hours of physical and occupational therapy. The CD interventions did not included functional, real life tasks or treatment in real-life settings. The duration of treatment ranged from 20 to 60 days depending on the needs of the patients.

Elements of treatment in the FE group included errorless learning, experiential interventions, developing useful functional abilities and skills, and targeting the following functional behaviors: compensation techniques, environmental management, and functional task-specific checklists. Treatment did not involve any self-analytic interventions or any focus on self-awareness. Patients in the FE group received the same amount and duration of treatment as patients in the CD group, but unlike the CD group, treatment was provided in a group setting in real-life environments.

Individual Study Results

Individual study results for each outcome measured in the studies addressing this question are presented in Table 46 to Table 48 of Appendix F. Ruff et al. used the San Diego Neuropsychological Test Battery to measure the effect of the CRT program on cognitive functioning. This test battery includes a variety of tests designed to measure different aspects of cognitive functioning.(71) Table 9 presents the individual tests included in the battery, the area of cognitive functioning the tests are designed to measure, and the qualitative results of the study. See Lezak for a complete description of each tests included in the battery.(29) All tests included in the battery have been standardized and normed. The test battery was administered to patients before treatment began and immediately following the eight-week treatment program. Tests were not administered after the completion of each module of the program.

Table 9. Results of Neuropsychological Tests and Associated Cognitive Function from Ruff et al.

Cognitive Function	Tests	Study Results
Attention	Digit Span Forward, Digit Symbol, Digits Total, Block Span, Letter Span, Ruff 2 & 7 Selective Attention test, Seashore Rhythm test	Patients in the CRT program demonstrated significant pre- to post-treatment improvement on the following tests: Digit Symbol, Digits Total, and Ruff 2 & 7 Selective Attention test. No significant pre- to post-treatment differences were observed for the control condition, and no between-group differences were observed on any of the tests of attention at post-treatment.
Visuospatial	Benton Facial test, Picture Completion, Rey Complex Figure, Block Design	Patients in the control group demonstrated significant improvement from pre- to post treatment on the Rey Complex Figure placement score. No statistically significant pre- to post-treatment differences were observed for the CRT group. Further, there were no statistically significant between-group differences on any of the tests at post-treatment.
Memory	Wechsler Short Stories, Rey's Visual Memory, Bushke Long-Term Memory, Trails Learning	Both groups demonstrated significant pre- to post-treatment improvement on the Rey's Visual Memory (RVM) three and 60-minute presentation tests. However, no significant between-group differences were observed on these tests. Similarly, both groups demonstrated significant improvement on the three and 60-minute placement subscales of the RVM test. Significant between-group differences in favor of the CRT group were also observed on these subscales. No other significant between-group differences were observed.
Problem Solving	Wisconsin Card Sorting, Figure Fluency	Patients in the CRT group demonstrated significant pre- to post-treatment improvement on both the Wisconsin Card Sorting Test (completed categories) and the Figure Fluency task (mean number of designs). No statistically significant pre- to post-treatment differences were observed among patients in the control condition. Significant between-group differences were only observed on the post-treatment scores of the Wisconsin Card Sorting test.
Emotional Adjustment	KAS	No significant pre- to post-treatment differences were observed for the CRT or control group, and no between-group differences were observed at post-treatment.

Note: Because the authors of the study did not measure outcomes after patients completed each module of the CRT program, the results do not necessarily indicate that a particular module had a direct effect on any one of the cognitive areas addressed. In other words, improvements observed in any one area of cognitive functioning (e.g., attention, memory) do not indicate that the module directed toward that area was independently responsible for the observed improvements. A description of all the tests can be found in Lezak, MD.(29)

To measure the overall impact of treatment, Ruff et al. used the full Wechsler Adult Intelligence Scale (WAIS)(104), which is an overall measure of intelligence, and also compared the average pretreatment score of all the neuropsychological tests administered to each of the study groups to the average post-treatment score.[5](71) No statistically significant pre- to post-treatment differences were observed for either the CRT or control group on the Full-Scale IQ score, Verbal-IQ score, or Performance-IQ score. Further, no between-group differences were observed on any of the tests. According to the authors, a comparison between the average pretreatment and post-treatment composite test scores indicated that overall cognitive functioning improved for both groups. No between-group differences on composite scores were reported. According to the authors of the study, these findings suggest that both general stimulation activities (control group) and cognitive remediation (treatment group) have positive effects on neurocognitive functioning, indicating that an enriched environment alone may yield some benefits for patients with TBI.

Overall, patients in both the CD and FE groups in the Vanderploeg study showed similar improvement from pretreatment to one year follow-up on all outcome measures. No between group-differences were observed at any of the treatment sites at one year follow-up on either of the primary outcome measures—return to work or independent living. Percent returned to work was 38.9% for the CD group and 35.4% for the FE group. Similarly, 56.3% of the CD group and 61.6% of the FE group reported living independently. Further, no between-group differences were observed for measures of disability. Small differences were observed in favor of the CD group on reported frequency of memory problems. Subgroup analyses performed by the authors did find that age and education led to differential treatment effects. Younger patients in the CD group had a higher rate of returning to work or school than younger patients in the FE group at one year posttreatment. In contrast, patients older than 30 years and those with more education in the FE group had higher rates of independent living at one year follow-up.

ECRI Institute's Conclusion

No pooled analyses were performed on the data reported from the studies addressing Key Question 6, because the studies did not include similar outcomes. Overall, the individual study results did not indicate statistically or clinically significant differences between patients who received multi-modal CRT (treatment addressing multiple cognitive deficits) and patients who received an alternate form of treatment (general activities or FE). Thus, we considered the evidence for this question insufficient, and no evidence based conclusions were drawn.

[5] The average pre and post treatment scores were calculated by the authors by combining scores of all the neuropsychological tests given to each study group at pretreatment and again at post-treatment. The mean and standard deviation of the pretreatment or post-treatment composite scores are not reported on in the study.

Key Question 7. In patients with TBI, does comprehensive-holistic CRT (treatment structured to address the cognitive, emotional, psychosocial, and behavioral deficits of TBI) improve cognitive functioning or other patient-oriented outcomes compared to no treatment, sham treatment, or other non-pharmacological treatment?

- **Patients with TBI who receive comprehensive, holistic CRT report significant improvement on measures of quality of life compared to patients who receive a less intensive form of therapy. Strength of evidence: Low**
- **For adults with TBI, the evidence is insufficient to determine if comprehensive, holistic CRT is more effective than less intensive care in improving patients' employment status or other patient-oriented outcomes.**

Three studies enrolling a total of 208 patients addressed this question. In two of the studies, patients were randomized to receive either inpatient, comprehensive CRT or a less intense form of treatment.(54,64) In the third study, patients were randomized to receive either outpatient, comprehensive CRT or delayed treatment.(60) The studies considered a number of outcomes. Table 10 below lists the outcomes and instruments used in each of the studies. For this question, we only considered patient-oriented outcomes as these are the primary outcomes of interest in most comprehensive CRT programs. However, we present the results of any neuropsychological tests administered in the studies in Table 50 of Appendix F.

Table 10. Outcomes Assessed in Studies Addressing Key Question 7

Study	Outcomes/Instruments
Cicerone et al. 2008(54)	Return to work, Community Integration Questionnaire (CIQ)(94), Perceived Quality of Life (PQOL)(105), Self Efficacy for Management of Symptoms Scale(54), and various neuropsychological tests
Tiersky et al. 2005(60)	Symptom Checklist-90 Revised(106), Coping Response Inventory(107), and neuropsychological tests of attention
Salazar et al. 2000(64)	Return to work, fitness for duty, Katz Adjustment Scale (KAS), and various neuropsychological tests

The results of our quality assessment of the studies can be found in Table 16 of Appendix D. The median quality assessment rating was moderate (median score 7.7, range 7.5 to 8.4). The primary reasons for the moderate quality rating were lack of blinding of patients in all three studies, lack of blinding of outcome assessors in one study(64), and the subjective nature of most of the outcomes.

Patient Characteristics of the Included Studies

The average age of patients in the three studies ranged from 25 to 47 years old, and the average years of education indicated that the majority of patients had at least a high school diploma. Two of the studies included patients with mild TBI. In the study by Cicerone et al., 9.0% of patients in

the experimental group and 18% of patients in the control group had mild TBI.(54) The rest of the patients in this study had moderate to severe TBI. In the Tiersky et al. study, 100% of patients in the experimental group and 78% of patients in the control group had mild TBI.(60) Patients in the Salazar study had moderate to severe TBI.(64) Time post injury to the start of treatment varied across the three studies. In the Salazar study, the average time post injury was 1.3 months. The patients in this study were military personnel who had been admitted to the Walter Reed Army Medical Center shortly before consenting to participate in the study. The post injury duration in the other two studies was substantially longer, with the average time ranging from 37 to 65 months. Patients in these studies were recruited through community referrals. Table 34 of Appendix E presents further information about the characteristics of the patients enrolled in these studies.

Treatment Characteristics of Included Studies

Information about the treatment provided in the studies can be found in Table 35 of Appendix E. In the Cicerone study, treatment in the comprehensive program emphasized the integration of interventions for cognitive deficits, emotional difficulties, interpersonal behaviors, and functional skills. Treatment was organized around specific themes (e.g., group process, acquisition and practicing skills, and carryover of strategies) delivered in phases both individually and within a group setting. The core structure of the comprehensive program consisted of 15 hours of individual and group therapies conducted three days a week for a total of 16 weeks. Patients received 11 hours of group training in various skills, three hours of individual therapy with a primary therapist that involved cognitive remediation and psychological counseling, and one hour of time with a neuropsychologist each week. Patients in the control group received standard neurorehabilitation that involved discipline-specific interventions targeting specific deficit areas, including retraining of discrete cognitive functions. The structure of the control treatment consisted of individual therapies including physical therapy, occupational therapy, and speech therapy. Patients in this group received the same hours and duration of treatment as the experimental group, and also met with a neuropsychologist for one hour a week.

In the Tiersky study, patients in the experimental group received treatment that focused on improving neuropsychological functioning, emotional well-being, and functional status. Treatment involved cognitive remedial therapy focusing mostly on deficits of attention and memory and cognitive behavioral therapy to increase effective coping, reduce stress, prevent relapse, and help cope with loss. Patients received five hours of treatment per week over the course of three days/week. The treatment lasted for a total of 11 weeks. Patients in the control group in this study were placed on a waitlist for treatment, during which time they did have minimal contact with the principal investigator. The contact, however, did not involve providing any treatment.

Finally, patients in the Salazar study were randomized to receive inpatient, comprehensive CRT or home-based rehabilitation. Treatment in the CRT program combined individual and group therapies that used a milieu-oriented approach and were modified to fit into a military framework. The treatment structure included physical fitness training and group and individual cognitive, speech, occupational, and coping skills therapy. Specific group therapies were planning and organization, cognitive skills, pragmatic speech, milieu, psychotherapy, and community reintegration. Patients also received vocational rehabilitation in various work settings that were similar to their previous military position. Therapy in this group was provided for 7.5 hours per day for five days a week over the course of eight weeks. Patients in the control

group received treatment in their home by a psychiatric nurse. Most of the treatment took place over the telephone and consisted of education, individual counseling, and vocational encouragement. Patients received weekly 30-minute phone calls from the psychiatric nurse for a total of eight weeks.

Individual Study Results and Meta-Analysis

Individual study results for the outcomes assessed in the studies that addressed this question are presented in Table 49 to Table 51. In the Cicerone study, both the comprehensive program and standard care program were associated with significant pre to post treatment differences on measures of neurocognitive functioning. However, only patients in the comprehensive program demonstrated significant pre to post differences on measures of community functioning, perceived quality of life, and life satisfaction. Between-group differences in favor of patients in the comprehensive program were only observed on measures of overall community functioning immediately following treatment. These differences were no longer significant at the one year follow-up. Finally, significantly more patients in the comprehensive group were engaged in community-based employment at posttreatment than patients in the standard care group (47% versus 21%). However, this difference was no longer significant at the one year follow-up (59% versus 41%).

In the Tiersky study, patients in the comprehensive group demonstrated improvement from pretreatment to posttreatment on measures of global symptom functioning, depression, anxiety, and problem solving. However, the only significant between-group difference was on the Coping Response Inventory (CRI, problem solving). Scores on the CRI at post treatment indicated significant improvement in problem solving for patients in the comprehensive group compared to patients in the waitlist group.

Finally, Salazar et al. did not find any overall differences at one year after treatment (post treatment outcomes not reported in this study) between patients who received comprehensive rehabilitation and those who received limited in home treatment in terms of return to work (90% versus 94%, respectively), fitness for military duty (73% versus 66%, respectively), or on measures of quality of life, neurocognitive functioning, or mood and behavior.[6] The authors of the study suggest that the high rate of return to work and fitness for duty may have been due to the emphasis placed on these outcomes in both study groups. However, in a post-hoc subset analysis of patients who were unconscious for more than one hour (n = 75) following TBI, the authors found that the patients in the comprehensive group had a greater return to duty rate than patients in the home treatment group (80% versus 58%). In addition to reporting on patient-oriented outcomes, this study also provided information about the cost of treatment. According to the authors, "the estimated cost for each patient in the hospital group was $51,840 based on the standard [Walter Reed Army Medical Center] psychiatry service cost of $864 per day. In contrast, home program rehabilitation costs were estimated at $504 per patient based on therapist time for the weekly home telephone calls ($63 per hour)."

From the data reported on in the studies, we performed two separate random effects meta-analyses—one pooling data on return to work status from the Cicerone and Salazar studies and the other on measures of quality of life from the same two studies. Return to work in Cicerone

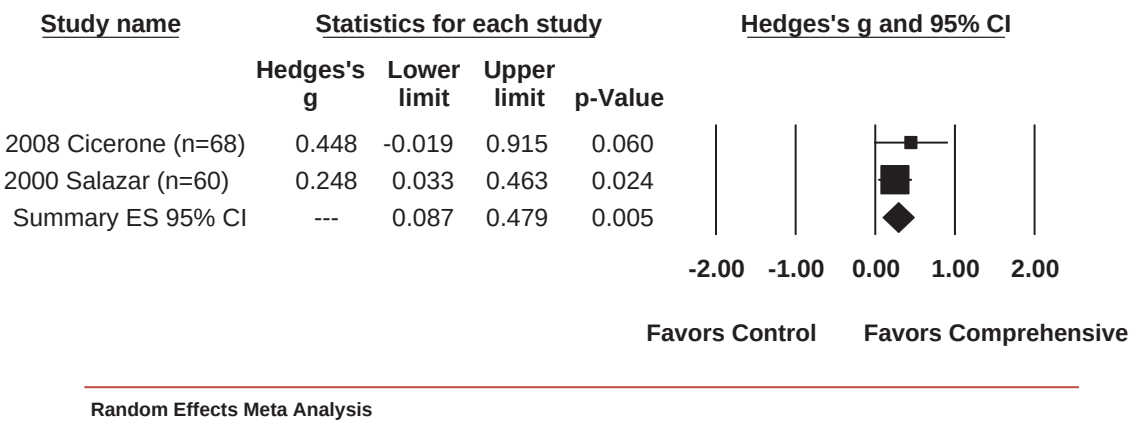
[6] Fitness for military duty included all patients who were still on active military duty or had received a normal discharge from the service. Excluded were patients who had a medical discharge or whose discharge was pending.

study was defined as engaging in supported, transitional (e.g., education, job coaching), or competitive community-based employment. In the Salazar study, return to work was defined as either full-time (≥35 hours/week) or part-time (≤35 hours/week) gainful military or civilian employment. The quality of life measures varied in the two studies. Cicerone measured quality of life using the Perceived Quality of Life Scale (PQoLS)(54) and Salazar used the Katz Adjustment Scale (KAS). These instruments are similar in that they both ask patients to rate their functioning and behavior within a broad range of areas including psychological/emotional functioning, thinking and remembering, and physical health. Both analyses were done using one-year follow-up data from each study, as both studies reported data at this timepoint.

ECRI Institute's Conclusion

The results of our meta-analyses indicated that adults with TBI who receive comprehensive CRT report significant improvement on measures of quality of life compared to adults who receive a less intense form of therapy. However, the estimated effect of treatment was small (0.28) and possibly not clinically significant (the 95% confidence intervals overlapped the bounds of clinical significance). Thus, the strength of the evidence supporting this conclusion was considered low. Figure 4 below presents the results of our analysis.

Figure 4. Key Question 7: Meta-Analytic Results for Measures of Quality of Life



For return to work the results were inconclusive. The estimated summary odds ratio for the analysis of the number of patients who returned to work at one year was not statistically significant and the 95% confidence intervals surrounding the summary statistic did not exclude the possibility of a clinically significant effect. The results of our analysis are presented in Figure 12 of Appendix G.

Key Question 8. What are the harms associated with CRT when used in the treatment of TBI?

- **None of the studies included in this review reported on any harms associated with CRT or any of the comparative treatments.**

Key Question 9. What is the consensus among experts about the safety and efficacy of CRT in the treatment of TBI?

ECRI Institute's search of the National Guideline Clearinghouse™ (NGC) and the Healthcare Standards database identified treatment guidelines for TBI that included recommendations for the use of CRT to treat cognitive deficits from the following organizations:

- New Zealand Guidelines Group (NZGG, 2006)(108)
- European Federation of Neurological Society (EFNS, 2005)(109)

The NZGG published a comprehensive set of guidelines for the management of patients with TBI that included recommendations for diagnosing, acute care management, and rehabilitation. The guidelines include the following recommendations for providing CRT:

- In the acute phase, CRT should include structured and targeted programs for patients with executive difficulties that are provided in a distraction-free environment.
- In later phases of rehabilitation, CRT should include attempts to improve attention and information-processing skills, and teaching of compensatory techniques (e.g., memory aids)

The NZGG also recommends that errorless learning methods, instead of trial and error learning, be used in patients with memory problems. As the name implies, errorless learning involves learning without errors or mistakes.(31) In this method of learning, information is presented in such a way as to avoid or significantly reduce mistakes. Research conducted by Baddeley and Wilson (1994) suggests that patients with severe memory deficits learn better if prevented from making mistakes during the learning process.(31) The reason for this, however, remains unclear.

The EFNS developed a set of guidelines to be used in the management of adult patients with cognitive deficits. In general, the guidelines recommended the use of neglect and apraxia rehabilitation after stroke, attention training after TBI in the post-acute stage, and memory rehabilitation with compensatory training in patients with mild amnesia.

Our searches also identified position and consensus statements from the following organizations:

- Brain Injury Association of America (BIAA, 2006)(110)
- The Society for Cognitive Rehabilitation (SCR, 2004)(30)
- The Academy of Neurologic Communication Disorders and Sciences (ANCDS, 2004)(111)
- National Academy of Neuropsychology (NAN, 2002)(112)
- British Society of Rehabilitation Medicine (BSRM, 1998)(113)
- The National Institute of Health (NIH, 1998)(111)
- The Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ISIG, 1992)(32)

In general, the organizations listed above support the use of CRT to remediate cognitive deficits resulting from acquired brain injury (e.g., TBI, stroke). The positions of these organizations are based on a mix of expert opinion, consensus panels, and empirical evidence. The most recent document, the position paper published by the BIAA, offers several recommendations specific to the delivery and practice of CRT. Below, we summarize these recommendations:

- CRT should be a covered benefit for persons with brain injury.
- CRT should be based on sound scientific theoretical constructs and, when available, evidence for best practices, with clearly stated goals.
- CRT should be provided by qualified practitioners (i.e., clinicians who fulfilled the requirements for professional certification and licensure in their respective field).
- CRT strategies and goals, and the duration, scope, intensity, and interval of treatment should be determined based on appropriate diagnosis and prognosis, the individual functional needs of the person with brain injury and reasonable expectations of continued progress with treatment.
- Treatment planning, case management and health insurance coverage for CRT should respect the possible long-term scope and changing needs of the patient.
- Future research should focus on how cognitive rehabilitation interventions improve recovery and functioning. Specific priorities should include questions about what interventions are effective for what particular problems, at what intensities.
- There should be an increased emphasis on proper education, training, and certification and continuing education for professionals and support staff involved in CRT.
- The health care system needs to address the particular needs of children with TBI and their families.
- CRT should be integrated into and coordinated with vocational services, special education, and community based programs, such as supported living, support networks, and recreation groups.
- All states should have a medical review process for all claims.

Findings of Other Systematic Reviews

Our searches identified 11 previous systematic reviews that evaluated the efficacy of CRT. The reviews were all published between 1999 and 2009. Table 52 presents important information about the search strategy, patient populations, methodology, results, and authors' conclusions of the previous reviews. In as much as possible, we present data from the reviews that included studies of mixed etiology that are specific to individuals with TBI. Below, we briefly describe the results of the two most recent systematic reviews.

The first, published by Rohling et al. in 2009(114), provided a meta-analysis of the CRT literature that was reviewed by Cicerone et al. in 2000 and 2005.(33) The Cicerone reviews summarized the findings of 258 articles on the use of CRT to treat deficits resulting from brain injury caused by various etiologies, including TBI. To reduce the number of studies included in the Cicerone reviews, Rohling et al. excluded studies that measured the following outcomes: motor deficits (e.g., apraxia), emotionality (e.g., depression, anxiety, or irritability), social interactions (e.g., marital status or social skills), and hard to define outcomes of real world function (e.g., employment status or measures of self-sufficiency). They also excluded single-case studies or multiple-case studies with less than three patients and studies that did not report data in a manner that allowed the calculation of an effect size estimate. The final sample of studies included in this review consisted of 97 articles reporting on 115 studies. Of the 115 studies, 70 were single group pre-post studies (case series studies) and 45 were independent group pre-post studies (non-randomized and randomized studies). The authors of this review primarily considered intermediate outcomes that addressed the following cognitive domains: 1) attention/executive function, 2) visuospatial, 3) language, 4) memory, and 5) comprehensive (multiple domains or holistic CRT programs). They also considered the following moderator variables: study design, treatment variables (e.g., duration of treatment), and patient variables (e.g., age, etiology, and chronicity).

Overall, the meta-analytic results of the Rohling review demonstrated a small treatment effect directly attributable to CRT. The small effect observed by the authors was corrected for improvement demonstrated by the nontreatment control groups. According to the authors of this review, treatment effects were moderated by cognitive domain treated, time postinjury, type of brain injury, and age. The final meta-analytic results revealed sufficient evidence for the effectiveness of attention training after TBI and for language and visuospatial training after stroke. Based on their review, the authors highlighted the following limitations in CRT literature: strong reliance on single group designs, heterogeneity of the control conditions (ranging from no treatment to placebo to sham treatment), variability in the treatment delivered, and variability in the outcomes and relevant information reported in the studies.

The second review, published by the Blue Cross Blue Shield Technology Evaluation Center (TEC) in 2008, focused on whether there is adequate evidence to demonstrate that CRT results in improved health outcomes among patients with TBI.(115) Health outcomes in this review included results from instruments assessing daily functioning or quality of life. This review did not consider evidence from intermediate outcomes (i.e., neuropsychological tests). The review relied mainly on evidence from randomized controlled studies, but did include evidence from one non-randomized controlled study. In total, the evidence base for this review included

13 studies (12 RCTs and 1 non-RCT), 10 of which considered health related outcomes. Two of these studies considered comprehensive, holistic CRT, while the remaining 11 considered CRT for specific cognitive defects. All the studies included in this review are also included in the review by ECRI Institute, except for the one non-randomized study.

According to the authors of the TEC review, the results of the two studies on comprehensive CRT demonstrated inconsistent findings. One study found no differences in outcomes of return to work, fitness for military duty, quality of life, and on measures of cognitive and psychological function, while the other non-randomized study showed greater improvements for the CRT group on measures of community integration. Three of the 11 studies on specific cognitive defects showed statistically significant differences in favor of the CRT groups. However, the authors of the TEC review comment that two of the three studies were extremely small and the findings were no longer present at six months follow-up. The authors concluded that the "randomized trial literature of [CRT] does not show strong evidence for efficacy in the treatment of [TBI]." They further stated that demonstration of effectiveness of CRT requires prospective randomized trials that include validated measures of health outcomes.

In general, ECRI Institute's review differed from the reviews described above and those presented in Table 53 in terms of scope, study inclusion/exclusion criteria, assessment of the quality and strength of the evidence, and analytic methods employed. In contrast to the review by Rohling et al, ECRI Institute's review was specific to CRT for the treatment of patients with TBI, did not include single group studies, and considered both the quality and strength of the evidence. Further, ECRI Institute's review included both intermediate (scores on neuropsychological tests) and patient-oriented outcomes (employment status, etc.) and, instead of attempting to draw general conclusions about the overall effect of CRT, we considered its effect on different outcomes. Drawing conclusions at the outcome level takes into account differences in terms of the clinical relevance of outcomes (e.g., intermediate versus patient-oriented) and potential risk of bias in how outcomes are measured. ECRI Institute's review differed from the TEC review in that we did not exclude studies that reported only intermediate outcomes.

Ongoing Clinical Trials

To locate recently conducted and ongoing clinical trials of CRT for TBI, we searched two databases: http://clinicaltrials.gov and http://www.controlled-trials.com. In addition to these two databases, we also searched the grey literature for possible ongoing studies. Our searches identified nine trials. Important information about these trials is presented in Table 53 of Appendix G. In four of the nine studies, CRT was being delivered outside of the hospital or clinic either within the home or workplace. Two of the four studies specifically indicated that CRT was being provided through tele-visits.

Conclusions and Discussion

This report examined the efficacy of cognitive rehabilitation therapy (CRT) in the treatment of adult patients with traumatic brain injury (TBI). The efficacy of CRT was addressed through seven Key Questions. Key Question 1 through 5 considered the effects of CRT for one of the five following cognitive deficits: attention deficits (Key Question 1), language and communication deficits (Key Question 2), memory deficits (Key Question 3), visuospatial deficits (Key Question 4), and deficits of executive function (Key Question 5). In Key Question 6, we considered the effects of multi-modal CRT (i.e., treatment structured to address multiple cognitive deficits), and in Key Question 7 we considered the effectiveness of comprehensive, holistic CRT programs (programs designed to address the cognitive, behavioral, emotional, and vocational problems associated with TBI). We compared the efficacy of CRT to no treatment, a sham treatment control condition, or another non-pharmacological treatment (e.g., occupational therapy), and considered both intermediate outcomes (scores on neuropsychological tests) and patient-oriented outcomes (quality of life, functional status).

The evidence base for this report consisted of 18 studies published in 20 different publications that met our inclusion criteria. A description of the evidence base for each Key Question, along with a summary of our findings, is presented below in Table 11. The overall quality of the studies that made up the evidence base for this report was moderate. The primary reasons for the moderate quality of the studies were lack of blinding or not reporting that the patients or outcome assessors were blinded, lack of reporting about the methods used to randomize patients, lack of reporting about whether randomization was concealed, the subjective nature of most of the outcomes assessed, lack of comparability between the study groups, and attrition.

Overall, the evidence base for CRT permitted us to draw the following conclusions: 1) Adults with moderate to severe TBI who receive social skills training perform significantly better on measures of social communication than patients who receive no treatment and 2) Adults with TBI who receive comprehensive, holistic CRT report significant improvement on measures of quality of life compared to patients who receive a less intense form of therapy. Both conclusions, however, are based on the meta-analytic results of two small studies of moderate quality. Thus, the strength of the evidence supporting these conclusions is low. We were unable to draw any definitive conclusions about the effectiveness of CRT used to treat deficits related to the following cognitive areas: attention, memory, visospatial, and executive function. We were also precluded from drawing conclusions about the effectiveness of CRT used to treat multiple areas of cognitive functioning. The following factors limited our ability to draw conclusions for these areas: inconclusiveness of meta-analytic results (no clear indication of whether CRT is more effective than the control condition), differences in the outcomes assessed in the studies, or insufficient number of studies addressing an outcome.

The inconclusiveness of the results of our meta-analyses is most likely due to the small size of the evidence base (i.e., the evidence base has insufficient power to detect a clinically significant difference). However, another possible reason for the lack of conclusiveness is that the sham control condition used in many of the studies had some kind of effect on the target problem. In general, individual results of studies that included a sham control condition indicated that both the treatment and control groups demonstrated similar pre- to post-treatment performance

on most outcomes. This suggests that the active ingredient in the treatment condition may have been no more effective than the common factors (i.e., professional attention, stimulation) associated with the sham condition. Thus, in addition to more studies with larger sample sizes, future studies of CRT should be based on well-founded hypotheses about the active ingredient(s) of the treatment before testing the treatment against a sham condition. One approach to determining the active ingredients, according to Whyte, would be to compare two treatments "that have different hypotheses about the active ingredients, and that predict change in different outcomes." An example would be to compare restorative treatments to compensatory treatments with the prediction that scores on neuropsychological tests will change for the restorative treatments, while functional abilities will change for compensatory treatments.

Table 11. Summary of Evidence-Base and Findings

Decision Point	**Key Question 1:** Attention Deficits	**Key Question 2:** Language and Communication Deficits	**Key Question 3:** Memory Deficits	**Key Question 4:** Visuospatial Deficits	**Key Question 5:** Executive Function Deficits	**Key Question 6:** Multi-Modal CRT	**Key Question 7:** Comprehensive CRT
Number of included studies (number of patients)	3 (n = 92)	2 (n = 103)	4 (n = 134)	0	4 (n = 157)	2 (n = 400)	2 (n = 208)
Quality of evidence base	Moderate	Moderate	Moderate	---	Moderate	Moderate	Moderate
Quantitative analysis allowed	Yes	No	No	---	No	No	No
Homogeneous meta-analysis (I^2 <50)	Yes	Studies qualitatively consistent	---	---	---	---	Studies qualitatively consistent
Potentially Informative	No	Yes for measures of social communication and no for measures of community integration and other outcomes	No	---	No	No	Yes for measures of quality of life and no for work status and other outcomes

Decision Point	**Key Question 1:** Attention Deficits	**Key Question 2:** Language and Communication Deficits	**Key Question 3:** Memory Deficits	**Key Question 4:** Visuospatial Deficits	**Key Question 5:** Executive Function Deficits	**Key Question 6:** Multi-Modal CRT	**Key Question 7:** Comprehensive CRT
Overall Conclusion	Inconclusive: Summary effect size estimate not statistically significant and 95% CI were too wide to rule out possible clinical significance	Patients with moderate to severe TBI who receive social skill training demonstrate improvement on measures of social communication compared to patients who receive no treatment	No conclusion: Evidence was insufficient due to differences in the outcomes measured across studies and inadequate reporting of data	No studies addressed this question	No conclusion: Evidence is insufficient due to differences in the outcomes measured across studies	No conclusion: Insufficient quantity of evidence	Patients who receive comprehensive, holistic CRT report improvement on measures of quality of life compared to patients who receive less intense forms of therapy
Strength	---	Low	---	---	---	---	---

Note: The decision points are described in detail in Appendix C.

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Appendix A. Literature Search Methods

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1983 through June 1, 2009	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2009, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2009, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2009, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2009, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through June 1, 2009	OVID
Health Technology Assessment Database (HTA)	Through 2009, Issue 2	www.thecochranelibrary.com
MEDLINE	1950 through June 1, 2009	OVID
PreMEDLINE	Searched May 19, 2009	OVID
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2009, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched May 2009	www.ngc.gov

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE and MEDLINE. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), Emtree, PsycINFO and Keywords

Conventions:

OVID

$	=	truncation character (wildcard)
exp	=	"explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.de.	=	limit controlled vocabulary heading
.fs.	=	floating subheading
.hw.	=	limit to heading word
.md.	=	type of methodology (PsycINFO)
.mp.	=	combined search fields (default if no fields are specified)
.pt.	=	publication type
.ti.	=	limit to title
.tw.	=	limit to title and abstract fields

PubMed

[mh]	=	MeSH heading
[majr]	=	MeSH heading designated as major topic
[pt]	=	publication type
[sb]	=	subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)
[sh]	=	MeSH subheading (qualifiers used in conjunction with MeSH headings)
[tiab]	=	keyword in title or abstract

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Attention	Attention disturbance.de. Attention.de. Concentration.de. Distractability.de. Distraction.de. Exp attention/	Attention$ Concentrat$ Distract$
Brain injury	Concussion/ Exp acquired brain injury/ Exp brain injuries/ Exp brain injury/ Exp traumatic brain injury/	Abi Acquir$ brain injur$ concussion Post brain injur$ Tbi Traum$ brain injur$
Cognitive rehabilitation	Cognitive rehabilitation.de. Cues.de. Learning strategies.de.	Cognitive rehab$ Cognitive$ remediat$ Cognitive$ train$ Compensatory rehab Compensatory remediat$ Compensatory train$ Memory$ rehab$ Memory$ remediat$ Memory$ train$ Neuropsych$ rehab$ Neuropsych$ remediat$ Neuropsych$ train$ Restorative rehab$ Restorative remediat$ Restorative train$
Communication disorders	Exp apraxia/ Exp communication disorders/	Apraxia$ Communication disorder$ Dysprax$ Language disorder$

Concept	Controlled Vocabulary	Keywords
Executive Function	Awareness.de. Exp cognitive ability/ Exp metacognition/ Metacognition.de. Problem solving.de.	Cognitive function$ Executive function$ Intellectual function$
Memory	Exp memory/ Forgetting.de. Memory disorders.de. Recall learning.de. Retention/	Memory$
Perception	Exp perception/ Exp visuospatial ability/	Visuo-spatial Visuospatial
Rehabilitation	Exp rehabilitation/ Rehabilitation.fs.	Rehab$
Self-help devices	Augmentative communication.de. Self-help devices/	Assistive device$ Cell$ phone Keyboard$ Mobile phone Pager$ PDA$ Personal digital assistant$ Typewriter$
Thought	Exp thinking/ Exp thought disorder/	Think$ Thought$

EMBASE/MEDLINE

English language, human, remove overlap

Set Number	Concept	Search Statement
1	Traumatic brain injury	Exp Traumatic brain injury/ or exp brain injury/ or exp brain injuries/ or exp acquired brain injury/ or exp brain injury, chronic/ or exp brain damage, chronic/ or exp brain concussion/
2	Traumatic brain injury	((post or trauma$ or acquir$ or mild or moderate or severe) adj2 brain injur$) or ((mild or moderate or severe) adj3 (traumatic brain injur$)).ti,ab. or ("mild TBI" or "moderate TBI" or "severe TBI" or concussion).ti,ab.
3	Combine sets	1 or 2
4	Limit by publication type	3 not ((letter or editorial or news or comment or case reports or review or note or conference paper).de. or (letter or editorial or news or comment or case reports or review).pt.)
5	Cognitive rehabilitation	(cognitive rehabilitation/de or neuropsychological rehabilitation/de or memory training/de or learning strategies/de or cues/de) or (cognitive rehabilitation or neuropsychological rehabilitation or memory training or learning strategies or cues).mp.)
6	Combine sets	4 and 5
7	Rehabilitation	Exp rehabilitation/ or rehab$.ti,ab,sh. or rh.fs.
8	Cognitive	((Cognitive$ or neuropsych$ or memory or compensatory or restorative) adj2 (remediat$ or rehab$ or train$))
9	Attention	(Exp attention/ or (attention or attention disturbance or distraction or concentration or distractibility).de. or (attention$ or distract$ or concentrat$).ti.)
10	Memory	(exp memory/ or exp retention or (Memory disorders or recall learning or forgetting).de. or memory$.ti.)
11	Communication disorders	(Exp communication disorders/ or exp communication disorder/ or exp apraxias/ or (apraxia$ or dyspraxia$ or language disorder$ or communication disorder$))
12	Thought	exp thought disorder/ or exp thinking/ or think$.ti. or thought$.ti.
13	Perception	Visuospatial or exp perception/ or exp visuospatial ability/
14	Executive function	(exp metacognition/ or exp cognitive ability/ or (Problem solving or awareness or metacognition).de. or ((executive or cognitive or intellectual) adj2 function$).ti,ab.)
15	Self-help	Exp self-help devices/ or Augmentative communication.de. or (keyboard$ or typewriter$ or device$ or pager$ or PDA$ or personal digital assistant$ or assistive device$ or mobile phone or cell$ phone).ti,ab.
16	Combine sets (cognitive elements)	or/8-14

Set Number	Concept	Search Statement
17	Combine sets (cognitive elements & rehabilitation)	(4 and 7) and 16
18	Combine sets (cognitive rehab for TBI)	6 or 17
19	Eliminate overlap	Remove duplicates from 18
20	Holistic care	Exp complementary therapies/ or exp holistic care/ or exp holistic health/ or combination therapy/ or exp alternative medicine/
21	Therapy programs	((therap$ or treat$ or care or program$ or center$ or group$ or rehab$) adj5 (holistic or complementary or comprehensive or combination or multi-disciplin$ or multiple therap$)).ti,ab.
22	Combine	Or/19-20
23	Limit by publication type	21 not ((letter or editorial or news or comment or case reports or review or note or conference paper).de. or (letter or editorial or news or comment or case reports or review).pt.)
24	Eliminate overlap	Remove duplicates from 22
25	Combine concepts: CRT for TBI or holistic CRT programs for TBI	18 or (24 and 18)
26	Eliminate overlap	Remove duplicates from 25
27	Limit to human	Limit 26 to human or humans
28	Limit by study type	27 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN) or randomized controlled trial.pt.
29	Limit by study type	27 and ((research synthesis or pooled).mp. or (systematic review or meta analysis or meta-analysis).de. or ((evidence base$ or methodol$ or systematic or quantitative$ or studies$ or search$).mp. and (review.de. or review.pt.)))
30	Combine sets	28 or 29

CINAHL

Set Number	Concept	Search Statement
1	Traumatic brain injury	Explode brain injuries
2	Traumatic brain injury	((post or trauma$ or acquir$) AND brain injur$) or (tbi or abi)
3	Combine sets	1 or 2
4	Limit by publication type	3 AND (clinical trial or journal article or research or review or systematic review)
5	Cognitive rehabilitation	(cognitive rehabilitation or neuropsychological rehabilitation or memory training or learning strategies or cues)
6	Combine sets	S4 and S5
7	Rehabilitation	Exp rehabilitation/ or rehab$.ti,ab,sh. or rh.fs.
8	Combine sets	S4 and S7
9	Cognitive	((Cognitive$ or neuropsych$ or memory or compensatory or restorative) adj2 (remediat$ or rehab$ or train$))
10	Attention	(Exp attention/ or (attent$ or distract$ or concentrate$)
11	Memory	(exp memory/ or exp retention or (Memory disorders or recall learning or forgetting).de. or memory$.ti.)
12	Communication disorders	(Exp communication disorders/ or (apraxia$ or dyspraxia$ or language disorder$ or communication disorder$))
13	Thought	think$.ti. or thought$.ti.
14	Perception	exp perception/
15	Executive function	(exp cognition/ or exp cognitive therapy/ or (Problem solving or awareness) or ((executive or cognitive or intellectual) adj2 function$).ti,ab.)
16	Self-help	(device$ or keyboard$ or typewriter$ or pager$ or PDA$ or personal digital assistant$ or assistive device$ or mobile phone or cell$ phone)
17	Combine sets	S8 and (S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16)
18	Combine sets	S17 or S6
19	Limit by publication type/Exclude MEDLINE Records	S18 and (clinical trial or journal article or review or systematic review) and (Exclude MEDLINE records)

PsycInfo

Set Number	Concept	Search Statement
1	Traumatic Brain Injury	TRAUMATIC BRAIN INJURY/DE OR BRAIN CONCUSSION/DE OR HEAD INJURIES/DE OR BRAIN DAMAGE/DE
2	Traumatic Brain Injury	(POST OR TRAUMA? OR ACQUIR? OR CHRONIC OR MILD OR MODERATE OR SEVERE) AND BRAIN INJUR?
3	Traumatic Brain Injury	"MILD TBI" OR "MODERATE TBI" OR "SEVERE TBI" OR CONCUSSION
4	Combine sets	S1 OR S2 OR S3
5	Cognitive rehabilitation	COGNITIVE REHABILITATION/DE OR NEUROPSYCHOLOGICAL REHABILITATION/DE OR MEMORY TRAINING/DE OR LEARNING STRATEGIES/DE OR CUES/DE
6	Combine sets	S4 AND S5
7	Rehabilitation for TBI	S4 AND (REHABILITATION/DE OR REHAB?)
8	Cognitive	S7 AND ((COGNITIV? OR NEUROPSYCH? OR MEMORY OR COMPENSATORY OR RESTORATIVE) (2N) (REMEDIAT? OR REHAB? OR TRAIN?))
9	Attention	S7 AND (ATTENTION/DE OR ATTENTION DISTURBANCE OR DISTRACTION OR CONCENTRATION OR DISTRACTABILITY OR ATTENTION? OR DISTRACT? OR CONCENTRAT?)
10	Memory	S7 AND (MEMORY/DE OR RETENTION/DE OR RECALL/DE OR FORGETTING/DE OR MEMORY DISORDER? OR MEMORY?)
11	Communication Disorders	S7 AND (COMMUNICATION DISORDERS/DE OR APRAXIAS/DE OR SPEECH DISORDERS/DE)
12	Thought	S7 AND (THOUGHT DISORDER/DE OR THINKING/DE OR THINK?)
13	Perception	S7 AND (PERCEPTION/DE OR VISUOSPATIAL ABILITY/DE OR VISUOSPATIAL?)
14	Executive functions	S7 AND (METACOGNITION/DE OR COGNITIVE ABILITY/DE OR PROBLEM SOLVING/DE OR AWARENESS/DE OR ((EXECUTIVE OR COGNITIVE OR INTELLECTUAL) (2N) FUNCTION?))
15	Self-help	S7 AND (SELF-HELP DEVICES/DE OR AUGMENTATIVE COMMUNICATION/DE OR (KEYBOARD? OR TYPEWRITER? OR DEVICE? OR PAGER? OR PDA? OR PERSONAL DIGITAL ASSISTANT? OR ASSISTIVE DEVICE?))
16	Combine sets	S8 OR S9 OR S10 OR S11 OR S12 OR S 13 OR S14 OR S15
17	Treatment outcomes	REHABILITATION OUTCOMES OR MEASUREMENT OR PROGNOSIS OR TREATMENT EFFECTIVENESS
18	Holistic therapy	MULTIMODAL TREATMENT APPROACH/DE OR INTEGRATED SERVICES/DE OR HOLISTIC HEALTH/DE OR ALTERNATIVE MEDICINE/DE OR INTERDISCIPLINARY TREATMENT APPROACH/DE OR (INTERDISCIPLINARY OR MULTI-THERAP? OR COMBIN? OR HOLISTIC OR COMPREHENSIVE OR INTEGR?
19	Combine sets	S18 AND S16

Set Number	Concept	Search Statement
20	Combine sets	S18 AND S6
21	Combine sets	S18 AND S8
22	Combine sets	S19 OR S20 OR S21
23	Limit by publication type	S22 AND ((RANDOMIZED CONTROLLED TRIAL? OR RANDOM ALLOCATION OR DOUBLE-BLIND METHOD OR SINGLE-BLIND METHOD OR PLACEBO? OR CROSS-OVER STUD? OR RANDOM? OR CROSSOVER? OR CROSS OVER) OR ((SINGL? OR DOUBL? OR TRIPL? OR TREBL?) AND (BLIND? OR MASK
24	Limit by publication type	S22 AND (RESEARCH SYNTHESIS OR POOLED OR (SYSTEMATIC REVIEW OR META ANALYSIS OR META-ANALYSIS) OR ((EVIDENCE BASE? OR METHODOL? OR SYSTEMATIC OR QUANTITATIVE? OR STUDIES OR SEARCH?) AND (REVIEW/DE OR REVIEW)))
25	Limit by publication type	ME=LITERATURE REVIEW OR LONGITUDINAL STUDY OR META ANALYSIS OR PROSPECTIVE STUDY OR QUANTITATIVE STUDY OR RETROSPECTIVE STUDY OR SYSTEMATIC REVIEW OR TREATMENT OUTCOME
26	Combine sets	S22 AND S25
27	Combine sets	S24 OR S26
28	Combine sets	S23 OR S27
29	Limit to English language	S28 AND LA=ENGLISH
30	Limit by publication date	S29 AND PY=1967:2009
31	Identify population	S30 AND (CHILD? OR ADOLESCENT? OR PEDIATRIC? OR TEEN? OR PAEDIATR?)
32	Identify adult	S31 AND ADULT?
33	Eliminate adult	S31 NOT S34
34	Eliminate pediatric	S30 NOT S33
35	Eliminate publication type	S34 NOT PT=BOOK
36	Eliminate publication type	S35 NOT PT=DISSERTATION
37	Eliminate publication type	S35 NOT PT=DISSERTATION ABSTRACT
38	Eliminate publication type	S37 NOT PT=CHAPTER
39	Eliminate publication type	S38 NOT (BOOK OR CHAPTER OR DISSERTATION? OR CONFERENCE?)
40	Identify major topic	(TRAUMATIC BRAIN INJURY/MAJ) OR (S2 OR S3)
41	Identify major topic	COGNITIVE REHABILITATION/MAJ OR NEUROPSYCHOLOGICAL REHABILITATION/MAJ OR MEMORY TRAINING/MAJ OR LEARNING STRATEGIES/MAJ OR CUES/MAJ OR ((COGNITIV? OR NEUROPSYCH? OR MEMORY OR COMPENSATORY OR RESTORATIVE) (2N) (REMEDIAT? OR REHAB? OR TRAIN?))
42	Combine sets	S40 AND S41
43	Combine sets	S40 OR S41

Set Number	Concept	Search Statement
44	Combine sets	S43 AND S39
45	Limit by publication year	S44 AND PY=1967:2000
46	Limit by publication year	S44 AND PY=2001:2003
47	Limit by publication year	S44 AND PY=2004:2006
48	Limit by publication year	S44 AND PY=2007:2009
49	Combine sets	S45 OR S46 OR S47 OR S48

Total Search Count

Database	Total Identified	Total Downloaded
EMBASE	180	37
MEDLINE	125	64
Pre-MEDLINE	173	21
CINAHL	450	47
PsychInfo	654	149
Total	**1,582**	**318**

Table 12. Excluded Randomized Controlled Trials

Study	Primary Cognitive Deficit	Experimental Treatment	Reason for Exclusion
Evans et al. 2009(116)	Cognitive-motor dual tasking	Combination of walking with increasingly demanding cognitive tasks versus treatment as usual	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Bornhofen & Skye 2008(117)	Executive functioning	Errorless learning training and self-instruction training versus waitlist control	Study had less than 10 subjects per treatment arm.
Goverover et al. 2007(118)	Executive functioning	Self-awareness training versus conventional therapy	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Zhu et al. 2007(119)	Functional independence	High-intensity In-hospital rehabilitation versus normal intensity rehabilitation	Study does not address any of the key questions of interest to this report and does not describe the treatments with sufficient detail to determine if or what CRT approaches were used.
Man et al. 2006(120)	Executive functioning	Computer-assisted problem-solving training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Man et al. 2006(121)	Executive functioning	Computer-assisted problem-solving training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Bell et al. 2005(122)	Not applicable	Scheduled telephone follow-up compared to standard follow-up of patients with TBI	Study did not report what type CRT was provided to patients in the study groups.
Hewitt et al. 2005(123)	Executive functioning	Intervention designed to help patients recall specific memories from their own personal experience with the goal of adding in problem solving	The instrument used to measure the outcome of interest was modified by the authors of the study, and not validated.
Soong et al. 2005(124)	Executive functioning	Computer-assisted problem-solving training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.

Study	Primary Cognitive Deficit	Experimental Treatment	Reason for Exclusion
Barreca et al. 2003(125)	Communication skills	Enriched environment with additional yes/no training versus standard hospital care	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI and less than 10 patients per treatment arm.
Tam et al. 2003(126)	Memory	Computer-assisted memory training	Study had less than 10 subjects per treatment arm.
Kaschel et al. 2002(127)	Memory	Imagery training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Powell et al. 2002(128)	Activities of daily living	Community outreach treatment versus provision of information regarding community resources for TBI	Treatment in experimental group not described in sufficient detail to determine if or what CRT approaches were used.
Wilson et al. 2005(129) & Wilson et al. 2001(130)	Memory and executive functioning	Paging system	The 2001 study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI. The 2005 study included patients outside the age range for this report.
Sheil et al. 2001(131)	Functional independence	High-intensity In-hospital rehabilitation versus normal intensity rehabilitation	Study does not address any of the key questions of interest to this report and does not describe the treatments with sufficient detail to determine if or what CRT approaches were used.
Paniak et al. 2000(132) & Paniak et al. 1998(133)	Non-specified problems associated with mild TBI	Single session of brain injury education and consultation versus neuropsychological assessment and treatment as needed (same treatment offered in the single session group)	Not assessing efficacy of CRT.
Sohlberg et al. 2000(134)	Attention	Attention process training (ATP)	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.

Study	Primary Cognitive Deficit	Experimental Treatment	Reason for Exclusion
Dirette et al. 1999(135)	Visual processing	Compensatory CRT strategies versus remedial CRT strategies	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Grealy et al. 1999(136)	Attention, memory, and reaction time	Virtual reality physical exercise versus no-exercise control	Study did not assess efficacy of CRT.
Ownsworth and McFarland 1999(137)	Memory	Diary training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Watanabe et al. 1998(138)	Temporal orientation	Calenders in room	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Kasten et al. 1998(139)	Visual processing	Computer-assisted visual restitution training (VRT)	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Schmitter and Fahy 1995(140)	Memory	Notebook training	Study included less than 10 patients per treatment arm.
Thomas-Stonell et al. 1994(141)	Cognitive-communication	TEACHware™	Study included less than 10 patients per treatment arm and mostly adolescents.
Twum and Parente 1994(142)	Memory	Imagery versus verbal labeling to improve memory	Outcome measures did not differ from the training measures.
Webb & Glueckauf 1994(143)	Executive functioning	High involvement in goal setting training versus low involvement	Study does not address one of the key questions in this report and has less than 10 patients per treatment arm.
Ruff et al. 1992(144)	Attention and memory	THINKable™	Study included less than 10 patients per treatment arm.
Gray and Robertson 1992(145)	Attention	Computer-assisted attention retraining	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.

Study	Primary Cognitive Deficit	Experimental Treatment	Reason for Exclusion
Lincoln et al. 1985(146)	Visual processing	Visual perceptual training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with TBI.
Helffenstein and Wechsler 1982(147)	Cognitive-communication	Interpersonal process recall (IPR)	Study included less than 10 patients per treatment arm.

Appendix B. Coverage Policies

Table 13. Commercial Coverage Policies

Third Party Payer	Web site	Coverage Policy	Date of Last Review	Policy/ Bulletin Number
Policies that cover CRT for TBI				
Aetna	http://www.aetna.com	Covered when: (1) the cognitive deficits are the result of impairment due to trauma, stroke, or encephalopathy; (2) the member has been seen and evaluated by a neuropsychiatrist or neuropsychologist; (3) neuropsychological testing has been performed and results will used to guide rehabilitation strategies; (4) and the member is expected to make sufficient cognitive improvement (not in coma or custodial state). CRT may be performed by an occupational or physical therapist, speech/language pathologist, neuropsychologist, or a physician.	05/06/09	0214

Third Party Payer	Web site	Coverage Policy	Date of Last Review	Policy/ Bulletin Number
Anthem BlueCross/BlueShield	http://www.anthem.com	CRT is covered in patients with significant impairment in cognitive functioning after TBI when the following criteria are met: (1) The service is prescribed by the attending physician as part of the care plan; (2) The service is so complex it requires a licensed professional to provide it; (3) The patient is capable of actively participating in CRT; (4) The patient's condition prior to the injury indicates that there is potential for improvement; (5) The patient is expected to demonstrate measurable functional improvement in a predetermined length of time; (6) The treating physician periodically assesses and documents progress	08/28/08	MED.00081
Wellmark BlueCross/BlueShield	http://www.wellmark.com	Covered when: (1) impairment due to stroke or TBI; (2) care plan documents specific diagnosis-related goals; (3) patient has reasonable expectation of achieving measurable improvements in a reasonable and predictable period of time.	02/2008	08.03.01

Third Party Payer	Web site	Coverage Policy	Date of Last Review	Policy/ Bulletin Number
Cigna	http://www.cigna.com	Covered when: (1) impairment due to acute brain insult, TBI, or CVA; (2) documented cognitive impairment with compromised functional status exists; (3) the patient can actively participate in treatment plan; (4) significant improvement is expected and can be demonstrated by documentation submitted weekly.	12/15/08	0124
Humana	http://apps.humana.com	Patients are eligible for CRT when it is provided by a licensed professional and all the following criteria are met: (1) Presence of cognitive deficits following moderate to severe TBI or stroke; (2) Patient can actively participate in treatment; (3) Patient has the potential for improvement.	01/22/09	CPD-0426-001
United Healthcare, Inc.	http://www.unitedhealthcareonline.com	CRT is covered when the patient can interactively participate in the program (e.g., is not comatose or at a level of consciousness that would preclude such interaction) and includes one of the following modalities: "specific interventions for the treatment of communication deficits, including pragmatic conversational skills, or compensatory memory strategy training."	11/13/08	NR

Third Party Payer	Web site	Coverage Policy	Date of Last Review	Policy/ Bulletin Number
Policies that do not cover CRT for TBI/or do not have a specific policy				
BlueCross/BlueShield of Alabama	http://www.bcbsal.org	Does not have a specific coverage plan for CRT, and does not mention that it is covered under PT or OT.	NR	NR
BlueCross/BlueShield of Massachusetts	http://www.bcbsma.com	Only covers individuals with Medicare HMO or PPO plans in accordance with their local coverage decision. Otherwise, coverage is determined on an individual basis.	06/08/09	439
BlueCross/BlueShield of North Carolina	http://www.bcbsnc.com	CRT not covered because it is thought to be investigational.	06/2008	0TH8040
BlueCross/BlueShield of Tennessee	http://bcbst.com	CRT not covered because it is thought to be investigational.	02/12/09	NR
Regence BlueCross/BlueShield	http://www.regence.com	CRT not covered because it is thought to be investigational.	03/01/09	20

NR Not reported.
OT Occupational therapy.
PT Physical therapy.

Appendix C. Quality of Literature and Evidence Strength Rating

Determining the Quality of Individual Studies

To aid in assessing the quality of each of the studies included in this assessment, we used a quality scale that was developed by ECRI Institute. This instrument examines twenty-two different factors of study design that have the potential to reduce the validity of the conclusions that can be drawn from a trial.

Study Quality Evaluation Scale

Comparability of Groups at Baseline

1. Were patients randomly assigned to the study's groups?
2. Did the study use appropriate randomization methods?
3. Was there concealment of group allocation?
4. Were any methods other than randomization used to make the patients in the study's groups comparable?
5. Were patients assigned to groups based on factors other than patient or physician preference?
6. Did patients in the different study groups have similar levels of performance on all of the outcome variables at the time they were assigned to groups?
7. Were the study groups comparable for important characteristics at the time they were assigned to groups?

Comparability of Groups at Baseline

8. Did the study enroll all suitable patients or consecutive suitable patients within a time period?
9. Was the comparison of interest prospectively planned?

Treatment

10. If patients received ancillary treatment(s), was there ≤5% difference between groups in the proportion of patients receiving each specific ancillary treatment?
11. Were all of the study's groups concurrently treated?
12. Was compliance with treatment ≥85% in both of the study's groups?

Blinding

13. Were subjects blinded to the treatment they received?
14. Was the healthcare provider blinded to the groups to which the patients were assigned?
15. Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
16. Was the integrity of blinding of patients, healthcare providers, or outcome raters tested and found to be preserved?

Outcome and Follow-up

17. Was the outcome measure of interest objective and was it objectively measured?
18. Was the instrument used to measure the outcome standard?
19. Was there ≤15% difference in the length of follow-up for the two groups?
20. Did ≥85% of the patients complete the study?
21. Was there a ≤15% difference in completion rates in the study's groups?

Investigator Bias

22. Was the funding for this study derived from a source that does not have a financial interest in its results?

Evaluating the Strength and Stability of Evidence System

Ideally, the body of evidence to support a conclusion would be strong. Often, however, the evidence suffers from various limitations concerning the possible risk of bias in available studies, small numbers of studies and patients, and/or inconsistent effects. These limitations often mean that the strength of the evidence is only moderate, low, or even insufficient to permit any conclusion. In order to gauge the impact of these possible limitations, we applied a formal rating system developed at ECRI Institute.(73)

Our system allows one to separate the question "is the treatment effective" (leading to a yes or no conclusion) from the question "how effective is the treatment" (leading to a quantitative conclusion with an estimate of the magnitude of effect). Thus, even if the evidence for a precise quantitative effect may be low, the same evidence may have high strength with respect to the direction of the effect. The interpretation of the strength of the evidence for qualitative and quantitative conclusions is shown in Table 1.

The system employs 13 decision points (Table 14). Four of them are listed in the General section because they apply to both quantitative conclusions as well as qualitative conclusions. The other 9 apply specifically to either quantitative conclusions (numbers 5-9) or qualitative conclusions (numbers 10-13). The rest of this appendix defines these decision points and describes how we resolved them for this report. After these descriptions, the pathways for the full system appear in Figure 5 through Figure 8.

Note that we applied this system separately for each outcome of interest. This is because many aspects of the evidence (quality, consistency, etc.) can vary by outcome.

Table 14. The ECRI Institute Evidence System

Category	Decision Point
General	1) Is each study of acceptable quality?
	2) What is the overall quality of evidence?
	3) Is a quantitative estimate potentially appropriate?
	4) Are data informative?
Quantitative	5) Are data quantitatively consistent?
	6) Are data quantitatively robust?
	7) Are there sufficient data to perform meta-regression?
	8) Does meta-regression explain heterogeneity?
	9) Is the meta-regression model robust?
Qualitative	10) Are data qualitatively robust?
	11) Are data qualitatively consistent?
	12) Was at least one study a multicenter study?
	13) Is the magnitude of effect extremely large?

1: Is each study of acceptable quality?

To aid in assessing the quality of each of the studies included in this assessment, we used a quality scale developed by ECRI Institute for interventional trials. This instrument examines different factors of study design (attributes) that have the potential to reduce the validity of the conclusions that can be drawn from a trial (see above for the complete scale). For example, one attribute is whether patients were randomly assigned to treatment groups. In brief, the scale was designed so that a study attribute that, in theory, protects a study from bias receives a "Yes" response. If the study clearly does not contain that attribute it receives a "No" response. If poor reporting precludes assigning a "Yes" or "No" response for an attribute, then "NR" is recorded (NR = not reported).

To estimate the quality of an individual study, we computed a normalized score so that a perfect study received a score of 10, a study for which the answers to all items was "No" received a score of 0, and a study for which the answers to all questions was "NR" was 5. Quality scores were converted to categories as shown in Table 15 below. The definitions for what constitutes low, moderate, or high quality evidence were determined *a priori* by a committee of four methodologists. Since the quality was determined separately for each outcome, a study that scored as high quality for one outcome might score as moderate quality for another outcome.

2: What is the overall quality of evidence?

After assigning quality scores to each individual outcome, we then classified the overall quality of the evidence base by taking the median quality score of the individual studies. We used the median because it is the appropriate measure of central tendency to represent the "typical" quality score, and is less sensitive to outliers than the mean. Depending on the overall quality

scores for each outcome, we then followed the high, moderate, or low quality branch of the strength of evidence system.

The quality of the evidence base sets an upper limit on judgments of the strength and stability of the evidence. For example, the strength of evidence can be weak, moderate, or strong if the evidence base is of high quality, but the strength can never be strong if the evidence base is of moderate or low quality.

Table 15. Categorization of Quality

	Overall Quality of Evidence Base		
	Low	**Moderate**	**High**
Median Overall Quality Score of the Evidence Base	6.7 or less	6.8 to <8.5	8.5 or higher

3: Is a quantitative estimate potentially appropriate?

The answer to Decision Point 3 depends upon the adequacy of reporting in available studies as well as the number of available studies. In order to conduct a quantitative analysis of a given outcome, the data for that outcome must be reported in at least three studies in a manner that allows the data to be pooled in a meta-analysis. If less than three studies are available, no quantitative analysis is usually possible regardless of reporting. Another situation that does not allow a quantitative analysis is when three or more studies are available, but fewer than 75% of them permit determination of the effect size and its dispersion, either by direct reporting from the trial or calculations based on reported information. If no quantitative analysis is possible, then one moves directly to Decision Point 10 to begin a qualitative analysis.

4: Are Data Informative?

For this question, we determined whether the precision of an evidence base was sufficient to permit a conclusion. Statistically significant results are informative because they mean that a treatment effect may exist. Statistically non-significant results are also potentially informative, but only if they exclude the possibility that a clinically significant treatment effect exists.

When a meta-analysis is performed, a key concern is the confidence interval around the random-effects summary statistic. If this interval is so wide that it is includes a clinically significant (or substantial) effect in one direction *and also an effect in the opposite direction*, then the evidence is inconclusive, and therefore uninformative.(148,149)

Thus, when considering the summary effect size from a meta-analysis (or the effect size from a single study), there are three ways in which the effect can be "informative":

1) The effect size is statistically significantly different from 0. This would be indicated whenever the confidence interval does not overlap 0.
2) The confidence interval is narrow enough to exclude the possibility that a *clinically significant difference* exists.
3) The confidence interval is narrow enough to exclude the possibility that a *substantial difference* exists. This possibility is included to address situations when even a very small effect can be considered "clinically significant" (e.g., a difference in mortality rates), but the effect may not be "substantial."

The second possibility requires definitions of a minimum "clinically significant difference" for each outcome. In this report, a small effect of 0.2 using Hedges' g was considered a clinically important effect.(76) So, for a summary effect size to be considered clinically important, the 95% confidence intervals surrounding the summary statistic could not overlap with -0.2 or +0.2, and the summary effect estimate must have been outside this interval. If the 95% confidence intervals overlapped the boundaries, then the results of the meta-analysis were considered inconclusive, and no evidence-based conclusion was drawn.

5: Are data quantitatively consistent?

Quantitative consistency (also referred to as lack of heterogeneity) refers to the extent to which the effect sizes of studies in an evidence base were statistically similar.(150) To measure quantitative consistency, we used Higgins and Thompson's I^2 statistic.(74) For this report, we considered an evidence base to be quantitatively consistent when I^2 <50%.

6: Are data quantitatively robust?

Robustness of findings refers to whether the evidence for a summary estimate is both *precise* and *stable*. A precise estimate is one for which the evidence permits a narrow confidence range for possible values of the parameter. A stable estimate is one that does not change substantially in response to minor alterations in the analysis. In this report, we considered an estimate to be quantitatively robust if all of the following conditions were met:

1. The overall estimate is sufficiently precise
2. The estimate remains sufficiently precise after the removal of any single study

Test #1: Sufficient precision. An important component of the evidence for a summary estimate is the precision of that estimate. Specifically, we refer to the 95% confidence interval (CI) around the estimate as a measure of precision. This is an objective measure of the quantity of evidence that *simultaneously incorporates* 1) the number of studies; 2) the number of patients in those studies; 3) within-study variability of effect sizes; and 4) between-study variability of effect sizes (because we only perform random-effects meta-analyses). An imprecise estimate is one that could easily change when future evidence becomes available (i.e., a wide confidence interval), whereas a precise estimate is unlikely to change (i.e., a narrow confidence interval).

To assess whether precision is "sufficient," we refer to the minimum difference that is considered to be clinically significant. Specifically, we defined a "sufficiently precise" estimate as one where the lower and upper confidence bounds were *each within one clinically significant difference* from the summary estimate. If not, then the evidence base is not precise enough to locate the effect within a clinically equivalent range. For example, suppose the summary effect size is 10, with a CI of 8.5 to 11.5. Further suppose that the definition of clinical significance is 2 units. This indicates that data *are* sufficiently precise to provide an estimate that is within 1 clinically significant difference, and so the estimate would pass this test. However, suppose the CI had been 7 to 13. Then the interval suggests that the true effect could be a full three units above or below the estimate of 10. Three units is greater than the minimum clinically significant difference of 2, therefore a 7 to 13 interval would fail this test.

For some variables (e.g., mortality), any difference at all can be considered clinically significant. In this case, we then define the magnitude of a "substantial difference," which corresponds to a "small" effect size as defined by Cohen.(76) Thus, if the effect size metric is Hedges' d or

Hedges' g, we defined a "substantial difference" as d = 0.2, or if the effect size metric is the log odds ratio, we defined a "substantial difference" as ln(OR) = 0.4.

Test #2: Removal of one study at a time. The summary estimate should not depend heavily on the inclusion of any particular study in the evidence base. To test this, we perform a series of subsequent analyses, each with one study removed. In order to pass this test, the lower and upper bounds of the 95% CI in all analyses should be within one clinically significant difference from the *all-study* summary estimate. Thus, this test produces a new set of CIs (one CI for each study removal), and each CI is compared to the all-study summary estimate.

7: Are there sufficient data to perform meta-regression?

We required a minimum of five studies before attempting meta-regression.

8: Does meta-regression explain heterogeneity?

This question provides decision rules for the conduct of a meta-regression analysis and the interpretation of its results. The project internal review committee must determine *a priori* what methods will be used in performing a meta-regression should one be necessary. In addition, the committee must define the rules that will be used for interpretation of the findings of the meta-regression analysis. We use the permutation test for all meta-regressions. This test was developed by Higgins and Thompson in attempt to control the Type I error rate for meta-regression.(75)

For this topic, we chose the following covariates as potential explanations of heterogeneity:

- Severity of TBI
- CRT setting
- Duration of CRT
- Time to intervention of CRT
- Intensity of CRT
- Type of control condition

In order to determine that a given covariate "explains" the heterogeneity, the resulting I^2 must have been less than 50%, and the beta coefficient for the covariate must have been statistically significant by the permutation test.

9: Is the meta-regression model robust?

The purpose of this question is to test the robustness of any quantitative findings that may emanate from meta-regression analysis. The only necessary robustness test involves removing one study at a time to determine whether this alters the findings of the meta-regression. If removal of one study results in heterogeneity that is greater than or equal to $I^2 = 50\%$, or caused the covariate to become statistically non-significant by the permutation test, then the meta-regression model is not robust.

10: Are data qualitatively robust?

If the evidence base for an outcome had three or more studies, we determined whether the qualitative findings could be overturned by sensitivity analyses. We considered findings to be overturned only when a sensitivity analysis altered the conclusion (e.g., a statistically significant

finding becomes non-significant as studies are added to the evidence base). The same sensitivity analyses used to test quantitative robustness were used to test qualitative robustness (except for the sufficient precision test, which does not apply to this decision point).

The system allows for several general types of qualitative conclusions:

a) A conclusion that the effect is statistically significant
b) A conclusion that the effect is clinically significant (see definition of clinical significance in question #4 above).
c) A conclusion that the effect is not clinically significant
d) A conclusion that the effect is not "substantial." (see definition of "substantial" in question #4 above)

For each of these types of conclusions, the qualitative robustness test will depend critically on a different threshold. For conclusion **a**, the question is whether the statistical significance of the finding is preserved across all qualitative robustness tests. In practical terms, this means that the lower bound of the 95% confidence interval must not overlap with 0 in any of the robustness tests. For conclusion b, the issue is whether the lower bound of the confidence interval stays consistently *above* the level of clinical significance across all robustness tests. For conclusion c, the issue is whether the lower bound of the confidence interval stays consistently *below* the level of clinical significance across all robustness tests. Finally, for conclusion d, the issue is whether the lower bound of the confidence interval stays consistently *below* the level of a substantial difference across all robustness tests.

Note that more than one qualitative conclusion could apply to the same outcome. For example, a treatment could be both statistically and clinically significantly better than an alternative (conclusions a and b). Or, a treatment could be statistically better than an alternative but clearly not clinically better (conclusions a and c). Conclusions b, c, and d, however, are mutually exclusive. Conclusions b and c are opposites; conclusion d only applies when the notion of "clinical significance" is inappropriate (see question #4 for further explanation).

11: Are data qualitatively consistent?

This question is used only when the evidence base for an outcome consists of two studies.

For the purposes of this question, studies are considered qualitatively consistent unless each study has a statistically significant effect size in opposite directions (e.g., Study 1 shows a statistically significant effect of Treatment A compared to Treatment B, but Study 2 shows a statistically significant effect of Treatment B compared to Treatment A). Meta-analysis is never appropriate in this situation, and the strength of evidence is insufficient.

12: Was at least one study a multicenter study?

Multicenter trials may increase the strength of a one study evidence base because they demonstrate partial replication of findings; they have shown that different investigators at different centers can obtain similar results using the same protocol. We defined a multicenter trial as any trial that met the following two conditions: 1) ≥3 centers and 2) either ≥100 patients or at least 3 centers enrolled ≥20 patients/center.

13: Is the magnitude of effect extremely large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. If a single study finds a large effect with a narrow confidence interval, then new evidence is unlikely to overturn the qualitative conclusion. To resolve this question, we consulted the effect size and the 95% confidence interval around the effect size for the study (with two studies, we consulted the interval around the random effects summary statistic). If this interval was fully above +0.5 (or if it was fully below -0.5) and the effect size was ≥0.8 (or ≤-0.8), we considered the effect to be large. Otherwise, we considered it to be not large. For example, an interval from +0.6 to +1.1 would be considered a large effect, whereas an interval from +0.4 to +1.3 would not be considered a large effect. Another effect that would be considered large is an interval from -1.1 to -0.6 (large in the negative direction). The choice of 0.5 and 0.8 is based on Cohen,(76) who stated that an effect size of 0.5 was "moderate" and 0.8 was "large"; thus the decision rule required that the effect be statistically significantly larger than "moderate." The use of 0.5 and 0.8 applies to Hedges' d or Hedges' g as measures of effect size. These correspond roughly to odds ratios of 2.5 and 4.5, respectively.

Figure 5. General Section of Strength-of-Evidence System

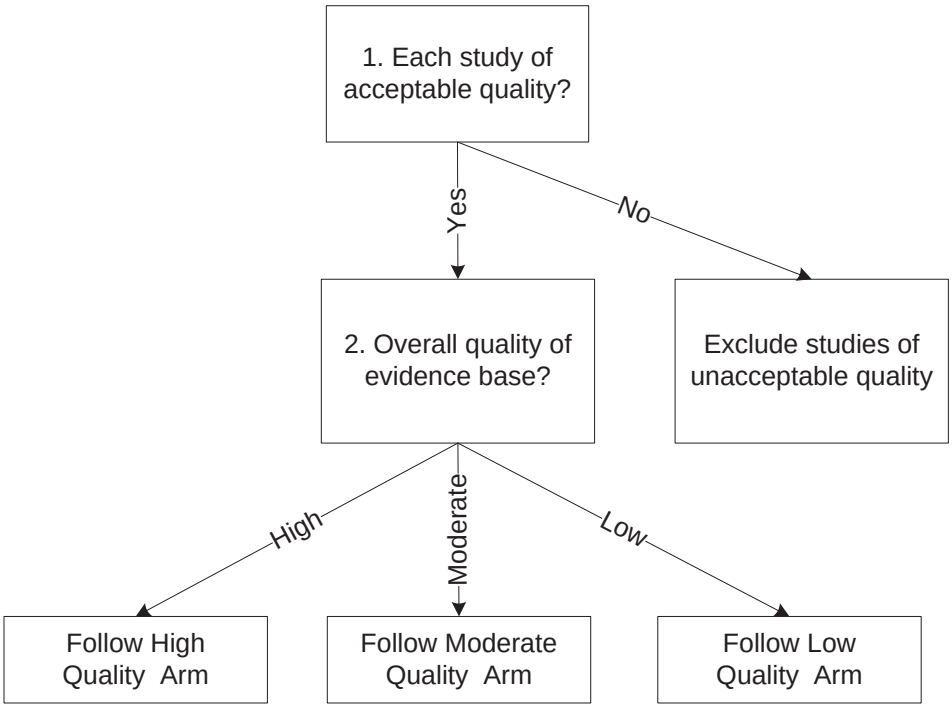


Figure 6. Highest Quality Pathway of Strength-of-Evidence System

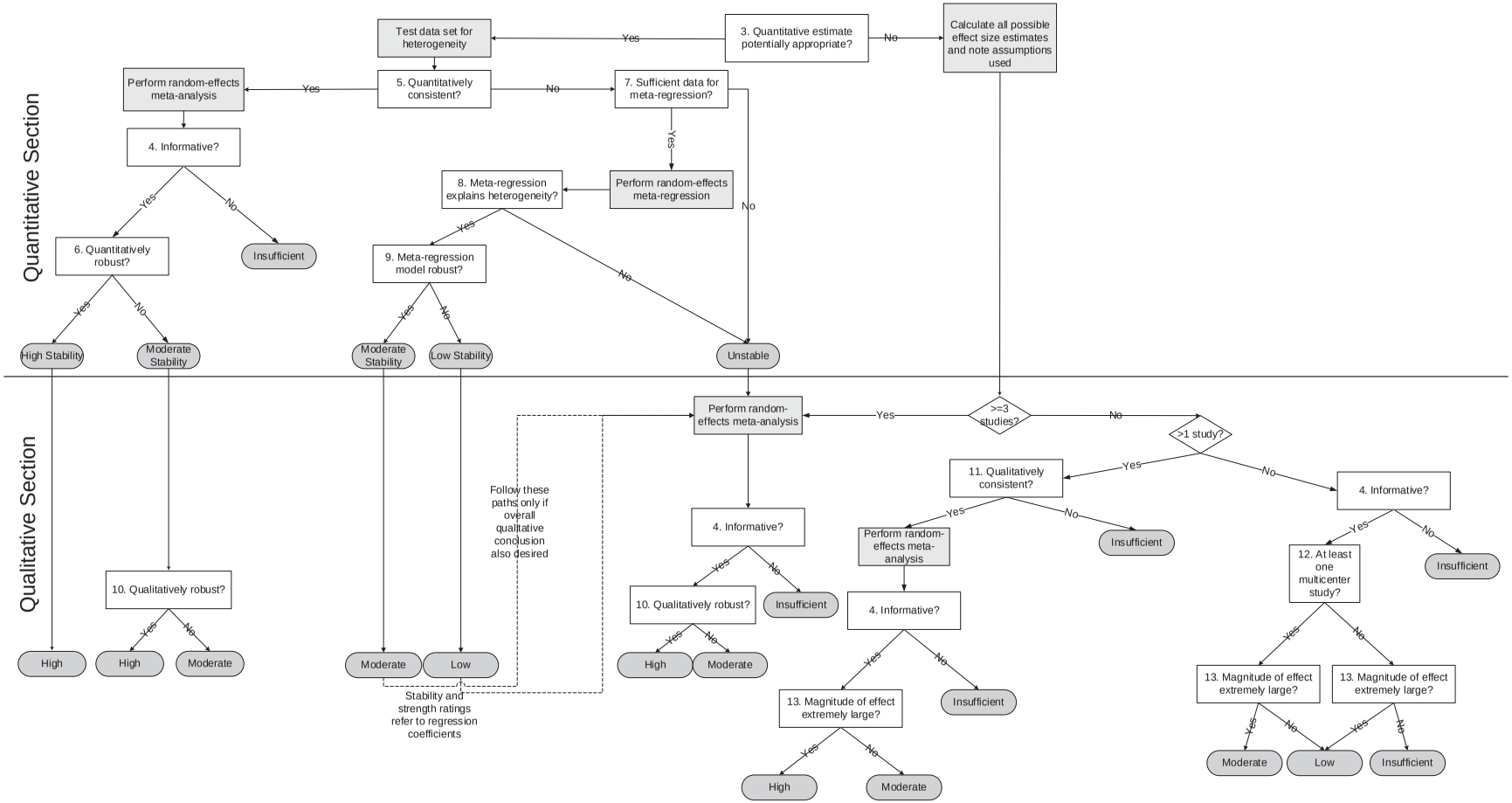


Figure 7. Moderate Quality Pathway of Strength-of-Evidence System

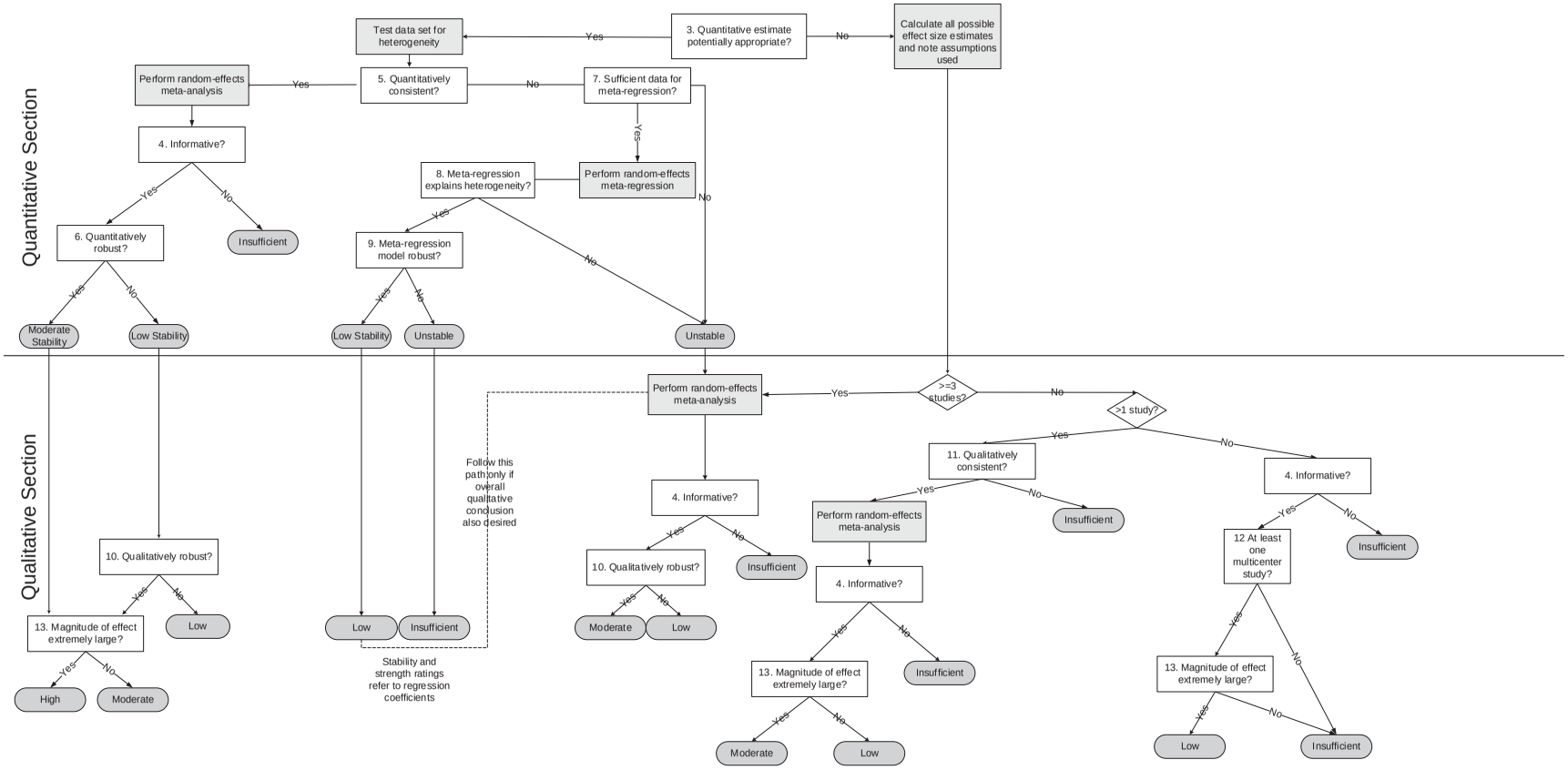
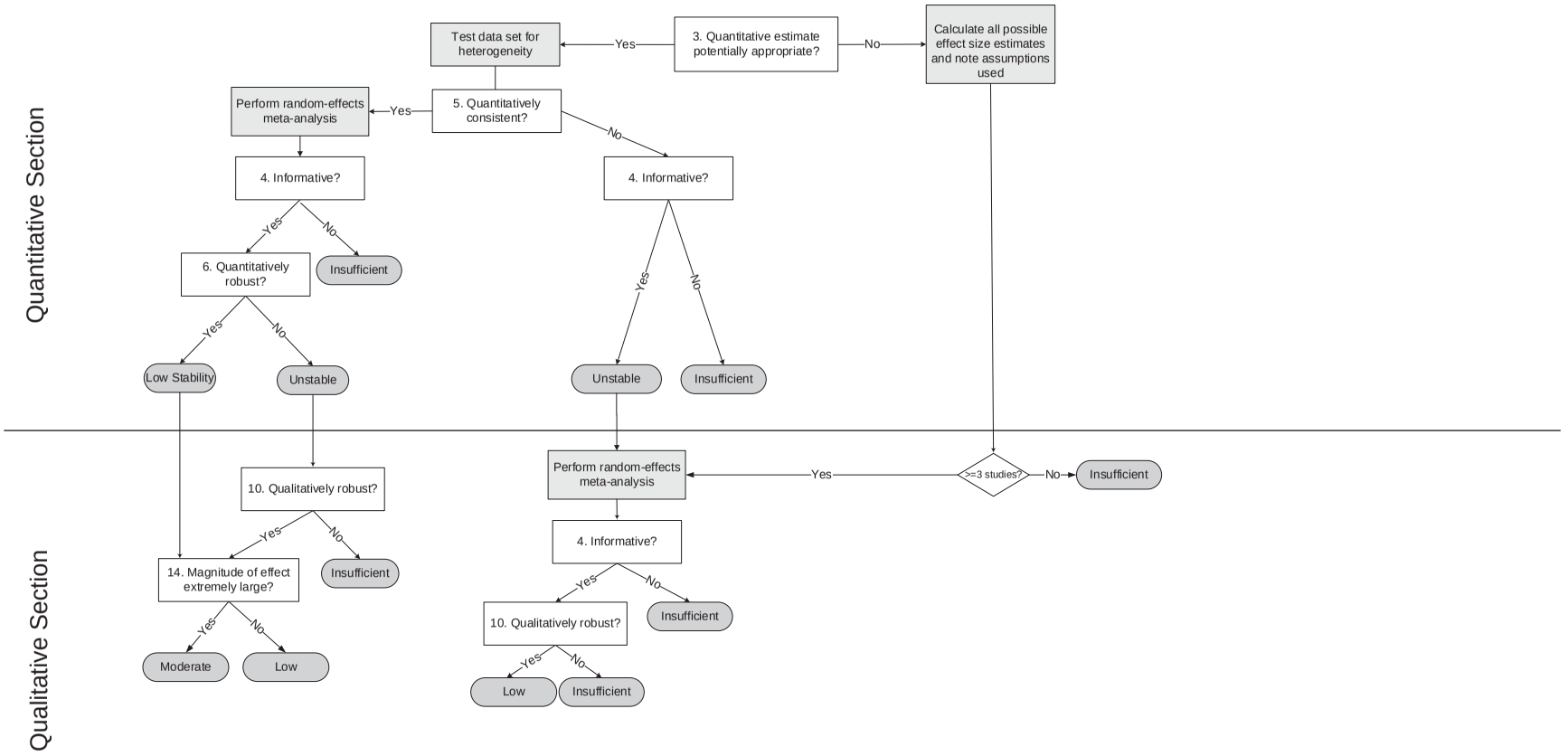


Figure 8. Lowest Quality Pathway of Strength-of-Evidence System



Appendix D. Quality Assessment Scores

Table 16. Quality Assessment of Included Studies by Outcome of Interest

Studies	**Q1.** Were pts randomly assigned to study groups?	**Q2.** Did the study use appropriate methods of randomization?	**Q3.** Was there concealment of allocation?	**Q4.** Were methods other than randomization used to make groups comparable?	**Q5.** Were pts assigned to groups based on factors other than pt or phy preference?	**Q6.** Did pts in different study groups have similar scores on all outcome measures at assignment?	**Q7.** Were characteristics of pts in different groups comparable at assignment?	**Q8.** Were all suitable pts or consecutive suitable pts enrolled in a time period?	**Q9.** Was comparison of interest prospectively planned?	**Q10.** Were all study groups concurrently treated?	**Q11.** Was there a ≤5 difference between groups in ancillary treatment(s)?	**Q12.** Was compliance with treatment ≥85% in both groups?	**Q13.** Were subjects blinded?	**Q14.** Was the treating phy blinded?	**Q15.** Were outcome assessors blinded?	**Q16.** Were tests performed to ensure blinding?	**Q17.** Was the outcome objective and objectively measured?	**Q18.** Was the instrument used to measure the outcome standard?	**Q19.** Was there ≤15% difference in the length of follow-up between groups?	**Q20.** Did ≥85% of the pts complete the study?	**Q21.** Was there a ≤ difference in completion rates in the study groups?	**Q22.** Was funding free of financial interest?	**Overall Quality Score**
Subjective Outcomes (e.g., cognitive outcomes measured using neuropsychological or other tests, functional/disability status, psychosocial outcomes, quality of life, and assessment of fitness to return to duty/work)																							
Key Question 1 (Attention)																							
Fasotti et al. 2000(62)	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	No	Yes	Yes	Yes	Yes	NR	**7.3**
Novack et al. 1996(65)	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	No	Yes	Yes	Yes	Yes	NR	**7.7**
Niemann et al. 1990(69)	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	No	NR	NR	No	Yes	Yes	Yes	Yes	NR	**7.3**

Studies	**Q1.** Were pts randomly assigned to study groups?	**Q2.** Did the study use appropriate methods of randomization?	**Q3.** Was there concealment of allocation?	**Q4.** Were methods other than randomization used to make groups comparable?	**Q5.** Were pts assigned to groups based on factors other than pt or phy preference?	**Q6.** Did pts in different study groups have similar scores on all outcome measures at assignment?	**Q7.** Were characteristics of pts in different groups comparable at assignment?	**Q8.** Were all suitable pts or consecutive suitable pts enrolled in a time period?	**Q9.** Was comparison of interest prospectively planned?	**Q10.** Were all study groups concurrently treated?	**Q11.** Was there a ≤5 difference between groups in ancillary treatment(s)?	**Q12.** Was compliance with treatment ≥85% in both groups?	**Q13.** Were subjects blinded?	**Q14.** Was the treating phy blinded?	**Q15.** Were outcome assessors blinded?	**Q16.** Were tests performed to ensure blinding?	**Q17.** Was the outcome objective and objectively measured?	**Q18.** Was the instrument used to measure the outcome standard?	**Q19.** Was there ≤15% difference in the length of follow-up between groups?	**Q20.** Did ≥85% of the pts complete the study?	**Q21.** Was there a ≤ difference in completion rates in the study groups?	**Q22.** Was funding free of financial interest?	**Overall Quality Score**
Key Question 2 (Communication)																							
McDonald et al. 2008(55)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	No	Yes	Yes	No	Yes	Yes	**7.5**
Dahlberg et al. 2007(58)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	No	Yes	Yes	Yes	Yes	Yes	**7.5**
Key Question 3 (Memory)																							
Bourgeois et al. 2007(57)	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	No	Yes	Yes	No	Yes	Yes	**7.3**
Dou et al. 2006(59)	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	No	Yes	Yes	Yes	Yes	Yes	**7.7**
Milders et al. 1995(66)	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	NR	No	No	No	No	No	Yes	Yes	No	Yes	NR	**6.1**
Berg et al. 1991(67)	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	No	No	No	Yes	Yes	Yes	Yes	NR	**6.6**
Ryan & Ruff 1988(72)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	NR	NR	Yes	No	NR	NR	No	Yes	Yes	Yes	Yes	Yes	**7.7**

Studies	**Q1.** Were pts randomly assigned to study groups?	**Q2.** Did the study use appropriate methods of randomization?	**Q3.** Was there concealment of allocation?	**Q4.** Were methods other than randomization used to make groups comparable?	**Q5.** Were pts assigned to groups based on factors other than pt or phy preference?	**Q6.** Did pts in different study groups have similar scores on all outcome measures at assignment?	**Q7.** Were characteristics of pts in different groups comparable at assignment?	**Q8.** Were all suitable pts or consecutive suitable pts enrolled in a time period?	**Q9.** Was comparison of interest prospectively planned?	**Q10.** Were all study groups concurrently treated?	**Q11.** Was there a ≤5 difference between groups in ancillary treatment(s)?	**Q12.** Was compliance with treatment ≥85% in both groups?	**Q13.** Were subjects blinded?	**Q14.** Was the treating phy blinded?	**Q15.** Were outcome assessors blinded?	**Q16.** Were tests performed to ensure blinding?	**Q17.** Was the outcome objective and objectively measured?	**Q18.** Was the instrument used to measure the outcome standard?	**Q19.** Was there ≤15% difference in the length of follow-up between groups?	**Q20.** Did ≥85% of the pts complete the study?	**Q21.** Was there a ≤ difference in completion rates in the study groups?	**Q22.** Was funding free of financial interest?	**Overall Quality Score**
Key Question 5 (Executive Function)																							
Cheng and Man 2006(22)	Yes	No	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NR	No	No	Yes	NR	No	Yes	Yes	Yes	Yes	NR	**6.8**
Rath et al. 2003(61)	Yes	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	No	Yes	Yes	No	Yes	Yes	**7.0**
Levine et al. 2000(63)	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	NR	NR	No	Yes	Yes	NR	Yes	Yes	**7.5**
Neistadt 1991(68)	Yes	NR	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	NR	NR	NR	No	No	NR	No	Yes	Yes	Yes	Yes	NR	**7.0**
Key Question 6 (Multi-Modal)																							
Vanderploeg et al. 2008(56)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	No	Yes	Yes	Yes	Yes	Yes	**8.0**
Ruff and Niemann 1990(70)	Yes	NR	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	NR	NR	Yes	No	No	NR	No	Yes	Yes	Yes	Yes	NR	**6.8**
Ruff et al. 1989(71)	Yes	NR	NR	Yes	Yes	Yes	No	Yes	Yes	Yes	NR	NR	Yes	No	No	NR	No	Yes	Yes	Yes	Yes	NR	**6.8**

Studies	**Q1.** Were pts randomly assigned to study groups?	**Q2.** Did the study use appropriate methods of randomization?	**Q3.** Was there concealment of allocation?	**Q4.** Were methods other than randomization used to make groups comparable?	**Q5.** Were pts assigned to groups based on factors other than pt or phy preference?	**Q6.** Did pts in different study groups have similar scores on all outcome measures at assignment?	**Q7.** Were characteristics of pts in different groups comparable at assignment?	**Q8.** Were all suitable pts or consecutive suitable pts enrolled in a time period?	**Q9.** Was comparison of interest prospectively planned?	**Q10.** Were all study groups concurrently treated?	**Q11.** Was there a ≤5 difference between groups in ancillary treatment(s)?	**Q12.** Was compliance with treatment ≥85% in both groups?	**Q13.** Were subjects blinded?	**Q14.** Was the treating phy blinded?	**Q15.** Were outcome assessors blinded?	**Q16.** Were tests performed to ensure blinding?	**Q17.** Was the outcome objective and objectively measured?	**Q18.** Was the instrument used to measure the outcome standard?	**Q19.** Was there ≤15% difference in the length of follow-up between groups?	**Q20.** Did ≥85% of the pts complete the study?	**Q21.** Was there a ≤ difference in completion rates in the study groups?	**Q22.** Was funding free of financial interest?	**Overall Quality Score**
Key Question 7 (Comprehensive)																							
Cicerone et al. 2008(54)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	No	Yes	Yes	Yes	Yes	Yes	**8.0**
Tiersky et al. 2005(60)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	No	Yes	Yes	No	Yes	Yes	**7.5**
Salazar et al. 2000(64)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	**7.5**
Non-subjective Outcomes Return to Work or School																							
Key Question 6 (Multi-Modal)																							
Vanderploeg et al. 2008(56)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	**8.4**

Studies	Q1. Were pts randomly assigned to study groups?	Q2. Did the study use appropriate methods of randomization?	Q3. Was there concealment of allocation?	Q4. Were methods other than randomization used to make groups comparable?	Q5. Were pts assigned to groups based on factors other than pt or phy preference?	Q6. Did pts in different study groups have similar scores on all outcome measures at assignment?	Q7. Were characteristics of pts in different groups comparable at assignment?	Q8. Were all suitable pts or consecutive suitable pts enrolled in a time period?	Q9. Was comparison of interest prospectively planned?	Q10. Were all study groups concurrently treated?	Q11. Was there a ≤5 difference between groups in ancillary treatment(s)?	Q12. Was compliance with treatment ≥85% in both groups?	Q13. Were subjects blinded?	Q14. Was the treating phy blinded?	Q15. Were outcome assessors blinded?	Q16. Were tests performed to ensure blinding?	Q17. Was the outcome objective and objectively measured?	Q18. Was the instrument used to measure the outcome standard?	Q19. Was there ≤15% difference in the length of follow-up between groups?	Q20. Did ≥85% of the pts complete the study?	Q21. Was there a ≤ difference in completion rates in the study groups?	Q22. Was funding free of financial interest?	Overall Quality Score
Key Question 7 (Comprehensive)																							
Cicerone et al. 2008(54)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	**8.4**
Salazar et al. 2000(64)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	**7.7**

NR Not reported.

Appendix E. Patient and Treatment Characteristic Tables

KEY QUESTION 1: CRT for Attention Deficits

Table 17. Patient Eligibility Criteria of Studies Addressing Attention Deficits

Study	Inclusion Criteria	Exclusion Criteria
Fasotti et al. 2000(62)	Patients had to 1) sustain a severe to very severe closed head injury at least 3 months prior to randomization; 2) show evidence of slow speed of information processing (demonstrated by PASAT, ACT, and RT); score equal to or greater than 75 on the WAIS; 3) be between the ages of 18 and 50 years; 4) have no severe intellectual, aphasic, agnosic, or personality disorders; 5) implicitly state interest in participating in study.	NR
Novack et al. 1996(65)	Patients had to have the ability to communicate in some fashion.	NR
Niemann et al. 1990(69)	Patients had to 1) be between 16 and 60 years; 2) have TBI in the moderate to severe range with a minimum coma duration of 1 hour; 3) have sustained head injury 12 to 72 months prior to randomization; 4) demonstrate no evidence of severe disorientation and confusion (GOAT Score of at least 75); 5) have sufficient cognitive functioning (DRS score of at least 100); 6) have no severe aphasia; 7) have sufficient vision to read text on computer screen; 8) have at least one functional hand; 9) have no substance abuse or premorbid psychiatric disorders.	NR

ACT Auditory concentration task.
DRS Disability rating scale.
GOAT Galveston orientation and amnesia test.
NR Not reported.
PASAT Paced auditory serial attention task.
RT Reaction time.
WAIS Wechsler adult intelligence scale.

Table 18. Baseline Patient Characteristics of Studies Addressing Attention Deficits

Study	Group	N	Mean Age (SD)	Gender (% Male)	Race (% White)	Education (Mean Years, SD)	% Prior Substance Abuse	Admission Glasgow Coma Score (Mean, SD)	Length of Coma (Days, SD)	Length of Post-trauma Amnesia (Mean Days, SD)	Time Post Injury (Mean Months, SD)
Fasotti et al. 2000(62)	TPM	12	26 (8.1)	66	NR	5.3 (0.9)*	NR	NR	27.1 (19.3)	64.3 (46.8)	9.8 (11.2)
	Control	10	30 (5.5)	70	NR	5.0 (0.7)*	NR	NR	27.0 (21.0)	64.2 (46.1)	8.3 (5.3)
Novack et al. 1996(65)**	Structured Attention Training	22	28.7 (13.2)	NR	NR	11.5 (2.4)	NR	8 or below	NR	NR	1.9
	Control	22	26.4 (10.9)	NR	NR	11.8 (1.6)	NR	8 or below	NR	NR	2.1
Niemann et al. 1990(69)***	Attention Training	13	28.9 (8.2)	NR	NR	13.8 (1.8)	NR	NR	15.0	NR	41 (21.5)
	Memory Control	13	34.3 (12.0)	NR	NR	13.7 (2.5)	NR	NR	20.0	NR	37.1 (20.1)

* Uses Verhage's Dutch coding system for years of education.

** The authors indicate that the patients had severe TBI and that the majority of patients had a Glasgow Coma Score of 8 or below.

*** Niemann et al.(69) did not report Glasgow coma scores, but did report Galveston Orientation and Amnesia Test Scores— 94.4(5.5) and 90.7(6.8), respectively for the treatment and control group.

NR Not reported.
TPM Time Pressure Management (a compensatory strategy).

Table 19. Treatment Characteristics of Studies Addressing Attention Deficits

Study	Treatment Group	N	Provider and Setting	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Fasotti et al. (2000)(62)	TPM	12	Provider not reported Study takes place in a rehabilitation center in the Netherlands	TPM is a set of cognitive strategies used to compensate for consequences of slow information processing in daily living tasks. TPM strategies include making patients aware of their mental slowness and performance, giving them specific tips for allowing more time to process information, and instruction on the use of self-instruction and memory aids to help with recollection. Patients practiced using TPM strategies by watching videotapes of short stories of situations they were likely to encounter in daily life. Patients were then asked to repeat as much as they could about the videos.	NR	1 hour group sessions, with a maximum of 3 hours per week	3 to 4 weeks Total of 7.4 (SD = 2.5) hours of training	6 month	10
	Control	10	Provider not reported Study takes place in a rehabilitation center in the Netherlands	Patients in this group watched the same videos and were instructed to remember as much as they could about the video. Patients were given generic tips to help them remember.	NR	30 minute group sessions/day, with a maximum of 2-5 hours per week	3 to 4 weeks Total of 6.9 (SD = 2.1) hours	6 months	9

Study	Treatment Group	N	Provider and Setting	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Novack et al. 1996(65)	Structured Attention Training	22	Master's degree level educator Study takes place in a rehabilitation center in the United States	Treatment was based on a hierarchy of attention skills. Patients were given both restorative and compensatory tasks directed at lower levels of attention (focused and sustained) first and then moved to tasks of more difficult levels of attention (alternating and divided attention).	NR	30 minute individual sessions/day for 5 days a week.	3 weeks 20 sessions for 10 hour total treatment.	Post-treatment only	22
	Un-structured Control	22	Master's degree level educator Study takes place in a rehabilitation center in the United States	This intervention was atheoretical with no attempt to present material in structured or hierarchical manner. Patients were given tasks focused on memory or reasoning skills and included orientation questions, games and verbal reasoning tasks (categorization, similarities, and cause/effect relationship) None of the tasks that comprised the structured attention training were used in the unstructured control group.	NR	30 minute individual sessions/day for 5 days a week.	3 weeks 20 sessions for 10 hour total treatment.	Post-treatment only	22

Study	Treatment Group	N	Provider and Setting	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Niemann et al. 1990(69)	Attention Training	13	Provider not reported Outpatient laboratory setting in the United States	Attention training focused on the major components of attention: visual, auditory, and divided attention. Tasks were ordered along these components, and were subdivided into focused and alternating tasks. The focused tasks required the correct identification of targets, whereas the divided tasks demanded shifting from one dimension to another. All visual tasks were computerized.	NR	Patients received six, 2 hour individual sessions for each attention component.	Patients were seen on an individual basis 2 times/week for about 14 weeks Total treatment time = 36 hours	Post-treatment only	13
	Memory Control	13	Provider not reported Outpatient laboratory setting in the United States	Patients received approaches to treatment that included both internal (visual imagery and verbal strategies) and external memory aids (diaries, notebooks, and routines). Training was delivered using a number of paper and pencil tasks and computer software programs.	NR	Patients received six, 2 hour individual sessions for each attention component.	Patients were seen on an individual basis 2 times/week for about 14 weeks Total treatment time = 36 hours	Post-treatment only	13

NR Not reported.
TPM Time pressure management.

KEY QUESTION 2: CRT for Language and Communication Deficits

Table 20. Patient Eligibility Criteria of Studies Addressing Communication Deficits

Study	Inclusion Criteria	Exclusion Criteria
McDonald et al. 2008(55)	Patients had 1) severe TBI (PTA >3 days); 2) were in chronic stage of recovery (12-months post injury and living in the community); 3) were referred to study due to deficits in social skills; and 4) had time to attend 12-weeks of therapy	Severe or extensive cognitive impairment, limited English, significant aphasia, active psychosis, and severe depression
Dahlberg et al. 2007(58)	Patients had 1) moderate to severe TBI; 2) been discharged from inpatient TBI rehabilitation (evidence of moderate to severe TBI); 3) were at least 1-year post-injury; 4) were between 18 and 65 years of age; 5) had a Rancho Los Amigos Level of Cognitive Function VI; 6) enough receptive and communication skills to participate in group treatment; 7) sufficient memory and recall to participate in group; 8) demonstrated impairment in social communication skills; 9) provide informed consent.	Significant behavioral problems, diagnosis of significant psychiatric or psychological disorder prior to or after TBI, history of or current substance abuse, significant motor disorder, and non-English speaking

PTA Post-traumatic amnesia.

Table 21. Patient Characteristics of Studies Addressing Communication Deficits

Study	Group	n	Mean Age (SD)	Gender (% Male)	Race (% White)	Education (Mean Years, SD)	% Prior Substance Abuse	Admission Glasgow Coma Score (Mean, SD)	Length of Coma (Days, SD)	Length of PTA (Mean Days, SD)	Time Post Injury (Mean Years, SD)
McDonald et al. 2008(55)	Social skills training	18	36.3 (10.7)	72	NR	11.9 (1.9)	NR	NR	NR	52 (6 to 547)	4.3 (1 to 20.5)
	Placebo control	17	33.1 (11.7)	72	NR	11.6 (3.4)	NR	NR	NR	72 (5 to 180)	4.8 (2 to 39)
	No-treatment control	16	35.2 (11.3)	86	NR	12.4 (2.6)	NR	NR	NR	77 (4 to 410)	3.3 (1 to 20)
Dahlberg et al. 2007(58)	Social skills training	30	42.4 (11.86)	73	88.5	Percent some college: 50	NR	*Percent severe TBI: 72.7 *Percent moderate to mild TBI: 27.3	NR	68.8 (72.8)	9.18 (5.89)
	No-treatment control	30	39.9 (11.40)	96	92.3	Percent some college: 56	NR	*Percent severe TBI: 79.2 *Percent moderate to mild: 20.8	NR	58.7 (76.3)	10.12 (5.37)

*Percents were presented by the authors and were based on initial scores of Glasgow Coma Scores (3 to 8 severe and 9 to 15 moderate)

PTA Post-traumatic amnesia.
NR Not reported.

Table 22. Treatment Characteristics of Studies Addressing Communication Deficits

Study	Treatment Group	N	Primary Provider and Setting of Treatment	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
McDonald et al. 2008(55)	Social skills training	18	Speech pathologists and psychologists Outpatient clinic	Patients participated in a group setting with 3 to 5 members in which they focused on addressing social behavior, social perception, and emotional adjustment	NR	12 weekly sessions at 4 hours/week	12 weeks	Post-treatment only following treatment	13
	Placebo-control	17	Speech pathologists and psychologists Outpatient clinic	Patients participated in group social activities, such as cooking, crafts, and games with no explicit therapeutic goals	NR		12 weeks	Post-treatment only following treatment	13
	No-treatment control	16	---	---	NR	---	---	Second baseline administered at post-treatment for the treated groups	13

Study	Treatment Group	N	Primary Provider and Setting of Treatment	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Dahlberg et al. 2007(58)	Social skills training	30	Speech pathologist and social worker Outpatient clinic	Patients participated in a group setting with 8 other members. Treatment focused on learning and practicing good communication skills, self-assessment, goal setting and social confidence.	NR	Weekly sessions lasting 1.5 hours	12 weeks	Post-treatment	26
	No-treatment control	30	---	---	NR	---	---	Second baseline administered at post-treatment for the treated group	26

NR Not reported.

KEY QUESTION 3: CRT for Memory Deficits

Table 23.Patient Eligibility Criteria of Studies Addressing Memory Deficits

Study	Inclusion criteria	Exclusion criteria
Bourgeois et al. 2007(57)	Patients had a documented closed head injury more than 1 year previously, persistent memory problems, and a caregiver willing to participate in study.	Patients excluded if currently receiving CRT for memory impairment.
Dou et al. 2006(59)	Patients had to 1) be between 18 to 55 years of age; with a history of TBI (closed or open head injury); 2) be at least three-months post-operative stage; 3) have a basic attention span of at least 5 minutes; 4) fair verbal comprehension and expression; and 5) be medically stable.	Patients excluded if had a previous history of psychiatric problems, computer-phobic, or had received similar treatment in the past.
Milders et al. 1995(66) & Berg et al. 1991(67)*	Patients had to 1) sustain a closed-head injury more than 9 months prior to randomization; 2) have subjective memory complaints in everyday life; 3) have no severe intellectual, aphasic, apraxic, agnosic, or personality disturbances; 5) have no previous neurological or psychiatric admissions; and 6) be between 18 and 60 years of age.	NR
Ryan & Ruff 1988(72)	Patients had to 1) be between one and seven years (at least one year) post-injury; 2) have a medical and CT scan documentation of serious head trauma; 3) have an expressive and receptive language ability that allowed for interpersonal communication; 4) have at least one functional hand; 5) have adequate visual acuity; 6) be between 16 and 65 years of age; 7) have motivation and availability for a 14-week period; and 8) no premorbid history of psychiatric disorder.	NR

NR Not reported.

Table 24. Patient Characteristics of Studies Addressing Memory Deficits

Study	Group	n	Mean Age (SD)	Gender (% Male)	Race (% White)	Education (Mean Years, SD)	% Prior Substance Abuse	Admission Glasgow Coma Score (Mean, SD)	Length of Coma (Days, SD)	Length of Post-trauma Amnesia (Mean Days, SD)	Time Post Injury (Mean Months, SD)
Milders et al. 1995(66) & Berg et al. 1991(67)*	Memory Strategy training	17	36 (19 to 58)	NR	NR	5.1 (3 to 7)**	NR	NR	NR	30 (1 to 60)	63.6
	Control (Drill and Practice)	11	33 (18 to 57)	NR	NR	4.5 (3 to 6)**	NR	NR	NR	35.0 (1 to 90)	75.6
	No treatment	11	35 (20 to 60)	NR	NR	4.5 (3 to 6)**	NR	NR	NR	37.0 (7 to 120)	81.6
Bourgeois et al. 2007(57)	Spaced retrieval training	22	43 (16.2)	64	77	NR	NR	11.5 (7.0)***	NR	NR	116.2
	Placebo control (didactic instruction)	16	40 (14.5)	63	87	NR	NR	13.3 (6.6)***	NR	NR	155.3
Dou et al. 2006(59)	CAMR	13	39 (11.9)	69	NR	46% primary education (some college)	NR	NR	NR	NR	9
	TAMR	11	38 (13.8)	73	NR	18% primary education	NR	NR	NR	NR	5.4
	No treatment	13	37 (12.6)	77	NR	24% primary education	NR	NR	NR	NR	7.5

Study	Group	n	Mean Age (SD)	Gender (% Male)	Race (% White)	Education (Mean Years, SD)	% Prior Substance Abuse	Admission Glasgow Coma Score (Mean, SD)	Length of Coma (Days, SD)	Length of Post-trauma Amnesia (Mean Days, SD)	Time Post Injury (Mean Months, SD)
Ryan & Ruff 1988(72)	Memory remediation	10	34 (23 to 60)	70	NR	13.5 (12 to 15)	NR	NR	22.7 (1 to 42)	NR	54.5 (18 to 85)
	Placebo control	10	31 (19 to 43)	70	NR	15 (12 to 18)	NR	NR	67.8 (21 to 122)	NR	57.3 (27 to 89)

* Same patient population. Milders et al.(66) reports 4-year follow-up data, and the patients' level of education is based on the Verhage's Dutch coding system for years of education.

**Reported as level of education, which can range between 1 (primary school only) to 7 (university degree)

***Severity of memory deficit measured using the Rivermead Behavioral Memory Test. The scores indicate moderate impairment.(84)

CAMR Computer assisted memory rehabilitation.
NR Not reported.
TAMR Therapist assisted memory rehabilitation.

Table 25. Treatment Characteristics of Studies Addressing Memory Deficits

Study	Treatment Group	N	Primary Provider and Setting of Treatment	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Milders et al. 1995(66) & Berg et al. 1991(67)*	Strategy training	17	Provider not reported Outpatient laboratory setting in the Netherlands	Patients received individual sessions focusing mostly on compensatory cognitive strategies expected to improve memory. These strategies included helping patients accept their deficit and make more efficient use of remaining capacities, training on the use of external memory aids, and techniques to improve information processing (e.g., spend more time on task, make associations). Patients were periodically given homework.	NR	1 hour individual sessions, 3 times/week for 6 weeks	6 weeks Patients received a total of 18, 1 hour sessions (or 18 hours)	4 years	15

Study	Treatment Group	N	Primary Provider and Setting of Treatment	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
	Control (drill and practice)	11	Provider not reported Outpatient laboratory setting in the Netherlands	Patients received various memory tasks and games to practice in the laboratory and at home. Patients were not given any specific instructions or suggestions in ways of dealing with the tasks.	NR	18, 1 hour individual sessions (three times a week for 6 weeks	6 weeks A total of 18 hours	4 years	8
	No treatment	11	---	---	NR	---	---	4 years	8
Bourgeois et al. 2007(57)	Spaced retrieval training (SR)	22	Clinicians trained to provided SR Therapy delivered over the telephone	Treatment involved recording memory problems, selecting specific memory goals, and having the clinician use prompt questions to help patients master their goal. Gradually, the prompt questions were delivered at increasing intervals.	NR	30 minute telephone sessions on 4 to 5 days each week	Average 11.8 sessions	1 month	22
	Placebo control	16	Same clinicians as in the SR group Therapy delivered over the telephone	Clinicians provided patients with information about common memory strategies, such as written reminders and verbal rehearsal.	NR	30 minute telephone sessions on 4 to 5 days each week	Average 10.2 sessions	1 month	16

Study	Treatment Group	N	Primary Provider and Setting of Treatment	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Dou et al. 2006(59)	CAMR	13	Computer delivered treatment, emphasizing human-computer interaction and the use of multi-media presentations	Patients received training to improve sensory memory, working memory, and semantic memory. Patients also provided with mnemonic strategies to practice and use in everyday life.	NR	20, 45 minute training sessions for 6 days/week	4 weeks	1 month	13
	TAMR	11	Therapist delivered treatment	Same treatment as above, but delivered face-to-face by a therapist.	NR	20, 45 minute training sessions for 6 days/week	4 weeks	1 month	11
	No treatment	13	---	---	NR	---	---	1 month	13
Ryan & Ruff 1988(72)	Memory remediation	10	NR Outpatient laboratory setting	Patients participated in a number of memory tasks, including associational tasks, chaining, and personalized emotional techniques.	NR	4 days/week for 5.5 hours a day	6 weeks A total of 132 hours	Post-treatment	10
	Placebo control	10		Patients participated individually or in small groups in an assortment of video, board, or card games with no structured feedback.	NR	4 days/week for 5.5 hours a day	6 weeks A total of 132 hours	Post-treatment	10

*Same patient population. Milders et al.(66) report 4-year follow-up data.

CAMR Computer assisted memory rehabilitation.
NR Not reported.
TAMR Therapist assisted memory rehabilitation.

KEY QUESTION 5: CRT for Executive Function Deficits

Table 26. Patient Eligibility Criteria of Studies Addressing Executive Function Deficits

Study	Inclusion Criteria	Exclusion Criteria
Cheng & Man 2006(22)	Patients had to be stable and mentally alert as evidenced by normal range in language sub-test of the Neurobehavioral Cognitive Status Examination (NCSE), and demonstrate impaired self-awareness.	NR
Rath et al. 2003(61)	Patients were selected based on higher level of functioning, rather than severity of brain injury. Patients had to have the ability to sustain attention for an hour-long session, take organized notes, give and receive feedback, state cognitive strengths and weaknesses, and relate to others with appropriate social skills. Patients also had to be between 20 and 65 years of age.	Patients excluded if their medical records indicated psychosis, active substance abuse, or other neurological impairment.
Levine et al. 2000(63)	Patients included in the study were 3 to 4 years post-injury and represented a full-range of TBI severity from mild to severe.	Patients excluded if they had a serious medical illness, psychiatric illness, or substance abuse.
Neistadt 1991(68)	Patients had to 1) be aged 18 to 55 years; 2) have a condition diagnosed diffuse brain injury secondary to traumatic head injury; 3) be at least 6-months postinjury; 4) receiving treatment in long-term rehabilitation program; 5) have functional use of both arms; 6) have at least an eighth grade education; 7) be functional communicators; 8) show no signs of unilateral neglect on line bisection test; 9) have a pretest scaled score of 10 or lower on the WAIS-R Block Design subtest; and demonstrate room for improvement in their constructional and meal preparation skills	NR

NR Not reported.
WAIS Wechsler adult intelligence scale.

Table 27. Patient Characteristics of Studies Addressing Executive Function Deficits

Study	Group	n	Mean Age (SD)	Gender (% Male)	Race (% White)	Education (Mean Years, SD)	% Prior Substance Abuse	Admission Glasgow Coma Score (Mean, SD)	Length of Coma (Days, SD)	Length of Post-trauma Amnesia (Mean Days, SD)	Time Post Injury (Mean Months, SD)
Cheng and Man 2006(22)	AIP	11	54.9 (13)	63.6	NR	63.6 high school 18.2% some college	NR	12.6	NR	NR	1.2
	OT	10	58.1 (15.6)	60	NR	70% high school 0% some college	NR	10	NR	NR	1.5
Rath et al. 2003(61)[1]	Problem solving treatment	27	43.6 (11.2)	50	NR	15.7 (2.4)	NR	NR	NR	NR	48.3 (58.4)
	Standard care	19									
Levine et al. 2000(63)	GMT	15	29.0 (13.0)	33	NR	12.6 (2.5)	NR	10.7 (4.2)	NR	17.9 (14.7)	44 (7.5)
	MST	15	30.8 (13.0)	60	NR	13.0 (2.3)	NR	10.8 (4..2)	NR	14.6 (11.0)	46 (9.6)
Neistadt 1991(68)	Functional	23	33.2 (9.1)	100	NR	11.2 (1.8)	NR	NR	NR	NR	94.8
	Remedial	22									

[1] Patients' characteristics not reported separately per treatment group. Authors indicated that the mean verbal I. Q. score was 105.3 (13.7)

AIP Awareness intervention program.
GMT Goal management training.
MST Motor skills training.
NR Not reported.
OT Occupational therapy.
SC Standard care.

Table 28. Treatment Characteristics of Studies Addressing Executive Function Deficits

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Cheng and Man 2006(22)	Inpatient Awareness Intervention Program (AIP)	11	Provider not reported. Inpatient rehabilitation center in China	Patients received individual training on awareness of cognitive and other deficits, exercises of application of this knowledge, and practice in self-monitoring, problem solving, and goal setting.	NR	2 sessions a day, 5 days a week lasting 20 to 30 minutes long.	4 weeks A total of 20 hours	Post-test only (1 week following treatment)	11
	Occupational therapy	10	Occupational therapist Inpatient rehabilitation center in China	Patients received group training in activities of daily living, motor function, orientation and memory, and a pre-discharge arrangements group.	NR	2 to 3 sessions, 5 days a week lasting 20 to 30 minutes.	4 weeks A total of 20 hours	Post-test only (1 week following treatment)	10
Rath et al. 2003(61)[1]	Problem solving treatment	32	Therapists trained to deliver treatment	The 24 sessions of treatment were divided into two separate components, each lasting 12 weeks. The first component focused on problem orientation, which involved accurately recognizing problematic situations, applying problem-solving skills, and teaching self-efficacy. The second component focused on teaching and practicing specific problem-solving strategies.	NR	One 2 hour session per week for a total of 24 sessions.	24 weeks	6 months	31
	Standard care	28	Therapists trained to deliver treatment	Patients received group cognitive remediation that focused on five skill areas: awareness of strengths and deficits, attention, note taking, giving and receiving feedback, and social skills. Intervention was delivered using various group exercises. Patients also received group psychosocial therapy devoted to psychological and social issues.	NR	2 to 3 hour weekly sessions for a total of 24 sessions.	24 weeks	6 months	13

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Levine et al. 2000(63)	GMT	15	Research assistant trained in delivering the treatment	The overall purpose of GMT is to help patients stay on task. GMT was delivered in five stages. The first stage involved orienting and alerting the patient to the task at hand. The second and third stage involved goal setting and dividing goals into manageable subgoals. The final two stages involved retention of subgoals and monitoring progress.	NR	One, 1-hour session	1 hour	Post-treatment only	15
	MST	15	Research assistant trained in delivering the treatment	The MST procedural processes were unrelated to goal management. Training in this group involved reading and tracing mirror-reversed text and designs. Patients in this group received instruction and encouragement similar to that provided to patients in the GMT group.	NR	One, 1-hour session	1 hour	Post-treatment only	15
Neistadt 1991(68)*	Functional	23	Master's level occupational therapists Inpatient rehabilitation center in the United States	Patients in this group received training in the preparation of snacks and hot beverages that gradually increased in level of complexity (e.g., making a sandwich to making fruit salad).	NR	Patients received three 30-minute individual sessions for 6 weeks.	6 weeks A total of 9 hours	Post-treatment only	23
	Remedial	22	Master's level occupational therapists Inpatient rehabilitation center in the United States	Patients in this group received training in parquetry block design that gradually increased.	NR	Patients received three 30-minute individual sessions for 6 weeks.	6 weeks A total of 9 hours	Post-treatment only	22

NR Not reported.
GMT Goal management training.
MST Motor skills training.

KEY QUESTION 6: Multi-Modal CRT

Table 29. Patient Eligibility Criteria of Studies Addressing Executive Function Deficits

Study	Inclusion Criteria	Exclusion Criteria
Vanderploeg et al. 2008(56)	Patients had to 1) have moderate to severe TBI within six months prior to treatment (as evidenced by GCS score of 12 or less, or coma of 12 hours or more, PTA of 24 hours or more); 2) have a RLAS cognitive level of 5 to 7 at time of randomization; 3) be 18 years or older; 4) be an active duty military member or veteran; and 5) have an anticipated length of needed acute TBI rehabilitation of 30 or more days.	Patients were excluded if they had a prior history of TBI rehabilitation and prior history of moderate to severe TBI or other severe neuropsychological or psychiatric condition.
Ruff and Niemann 1990(70) & Ruff et al. 1989(71)*	Patients had to 1) have been injured between 1 and 7 years prior to treatment; 2) have medical documentation suggesting a severe head injury; 3) have sufficient receptive and expressive language ability to engage in treatment; 4) have at least one functional hand; 5) have at least 25% intact vision; 6) be between 16 and 65 years of age; be sufficiently motivated to complete 12 weeks of treatment; and 7) have no premorbid history of a psychiatric disability.	NR

* Same patient population in both studies, but each study reports on separate outcomes.

CRT Cognitive rehabilitation therapy.
GCS Glasgow Coma Scale.
PTA Posttraumatic Amnesia.
NR Not reported.
RLAS Rancho Los Amigos Score.

Table 30. Patient Characteristics of Studies on Multi-Modal CRT Programs

Study	Group	n	Mean Age (SD)	Gender (% Male)	Race (% White)	Education (Mean Years, SD)	% Prior Substance Abuse	Admission Glasgow Coma Score (Mean, SD)	Length of Coma (Days, SD)	Length of Post-trauma Amnesia (Mean Days, SD)	Time Post Injury (Mean Months, SD)
Vanderploeg et al. 2008(56)	Didactic CRT	184	33.2 (13.5)	92	68	63% at least high school graduate	NR	6.8 (3.5)	33% >1 to 7 days	42% between 7 to 30 days	1.63 (0.95)
	Functional CRT	182	31.7 (12.9)	94	69	54% at least high school graduate	NR	6.7 (3.7)	27% >1 to 7 days	37% between 7 to 30 days	1.7 (0.99)
Ruff and Niemann 1990(70) & Ruff et al. 1989(71)*	CRT	20	29.9 (9.9)	70	NR	13.3 (1.4)	NR	NR	32.1 (31.4)	NR	38.1 (23.9)
	Control	20	31.7 (9.2)	65	NR	13.0 (2.0)	NR	NR	48.8 (26.4)	NR	52.4 (19.5)

* Same patient population in both studies, but each study reports on separate outcomes.

CRT Cognitive rehabilitation therapy.
NR Not reported.

Table 31. Screening Measures of Studies on Multi-Modal CRT Programs

Study	Group	n	GOAT (Mean/SD)	DRS (Mean/SD)	RLSE (Mean/SD)
Ruff and Niemann 1990(70) & Ruff et al. 1989(71)*	CRT	20	89.4 (10.9)	130 (10.0)	79.3 (9.2)
	Control	20	84.9 (10.6)	127.0 (10.9)	77.6 (10.9)

Note: No between-group differences were observed on any of the tests.

* Same patient population in both studies, but each study reports on separate outcomes.

CRT Cognitive rehabilitation therapy.
DRS Dementia rating scale.
GOAT Galveston orientation and amnesia test.
RLSE Ruff language screening examination.

Table 32. Treatment Characteristics of Studies Addressing Multi-Modal CRT

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Vanderploeg et al. 2008(56)	Didactic CRT	184	Multidisciplinary team Four Veterans Administration acute inpatient TBI rehabilitation programs	The didactic protocol implemented treatment approaches to target 4 cognitive domains of impairment: attention, memory, executive function, and pragmatic communication skills. Patients participated in progressively more difficult paper and pencil or computerized tasks in 1 to 1 therapy sessions.	Occupational and physical therapy plus psychological support services	1.5 to 2.5 hours daily of protocol-specific treatment plus 2 to 2.5 hours daily of occupational and physical therapy	The duration of treatment ranged from 20 to 60 days depending on the needs of the individual.	1 year	180
	Functional CRT	182	Multidisciplinary team Four Veterans Administration acute inpatient TBI rehabilitation programs	The functional protocol used real-life performance situations and common tasks to remediate or compensate for brain injury deficits. Interventions occurred in group settings and natural environments, and focused on learning by doing.	Occupational and physical therapy plus psychological support services	1.5 to 2.5 hours daily of protocol-specific treatment plus 2 to 2.5 hours daily of occupational and physical therapy	The duration of treatment ranged from 20 to 60 days depending on the needs of the individual.	1 year	180

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Ruff and Niemann 1990(70) & Ruff et al. 1989(71)*	CRT	20	Multidisciplinary team Outpatient rehabilitation center in the United States	Cognitive remediation program was organized into four modules: attention, visuospatial abilities, learning and memory, and problem solving. Each module involved teaching patients task and strategies aimed at improving the associated cognitive deficit. Patients received group training.	Group psychotherapy (50 minutes/day)	The program ran for eight consecutive 4-day weeks, for 5 hours/day. Each module lasted 2 weeks. Group sessions within each treatment module lasted 50 minutes plus patient attended a wrap-up session at the end of the day. Overall, 20 treatment hours/week Total of 160 hours of treatment	8 weeks A total of 106.6 hours	Post-treatment only	20

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
	Control	20	Multidisciplinary team Outpatient rehabilitation center in the United States	Patients in this group received treatment that emphasized psychosocial adjustment, leisure, and activities of daily living.	Group psychotherapy (50 minutes/day)	The program ran for eight consecutive 4-day weeks, for 5 hours/day. Each day of treatment, patients attended four 50-min group sessions plus a wrap-up session at the end of the day. Overall, 20 treatment hours/week Total of 160 hours of treatment	8 weeks A total of 106.6 hours	Post-treatment only	20

***** Same patient population in both studies, but each study reports on separate outcomes.

CRT Cognitive rehabilitation therapy.
NR Not reported.

KEY QUESTION 7: Comprehensive CRT Programs

Table 33. Patient Eligibility Criteria of Studies Addressing Comprehensive Cognitive Rehabilitation

Study	Inclusion Criteria	Exclusion Criteria
Cicerone et al. 2008(54)	Included patients had to 1) have documentation of TBI within 24 hours of injury; 2) be at least three months post-injury; 3) be between 18 to 62 years of age; 4) have adequate language skills; 5) be judged to require at least four months of comprehensive treatment; 6) be clinically appropriate for either arm of treatment; 8) be capable of attending treatment three days per week; and 8) be capable of giving informed consent.	Patients were excluded if they had a prior history of TBI, premorbid learning disability, psychiatric disorder, substance abuse, or pain that would prevent compliance with treatment;
Tiersky et al. 2005(60)	Included patients had to 1) be fluent in the English language; 2) have no current or prior history of bipolar disorder, mania, or schizophrenia; 3) have no current history of substance abuse; 4) no concurrent neurological disease known to affect cognitive functioning; 5) no evidence of a behavioral disorder as the primary diagnosis; 6) be one to 20 years post injury; 7) have a Disability Rating Score of between 1 and 5 at study inclusion; 8) demonstrate cognitive deficits in the area of attention and memory and express emotional distress; 9) not be involved in other treatment; and 10) be on a stable dosage of any psychotropic drug.	NR
Salazar et al. 2000(64)	Included patients had to 1) have moderate to severe TBI (as indicated by GCS of 13 or less or PTA for at least 24 hours); be at least three months postinjury at time of study; 3) have a Rancho Los Amigos cognitive level of seven; 4) be an active duty military member, not pending medical separation; 5) be accompanied in the home setting by at least one responsible adult; 6) be able to ambulate independently; and 7) have no prior severe TBI.	Patients with mild TBI were excluded.

GCS Glasgow Coma Scale.
NR Not reported.
PTA Posttraumatic amnesia.

Table 34. Patient Characteristics of Studies on Comprehensive CRT Programs

Study	Group	n	Mean Age (SD)	Gender (% Male)	Race (% White)	Education (Mean Years, SD)	% Prior Substance Abuse	Admission Glasgow Coma Score (Mean, SD)	Duration of LOC (Minutes, SD)	Length of Coma (Days, SD)	Length of Post-trauma Amnesia (Mean Days, SD)	Time Post Injury (Mean Months, SD)	Disability Rating Score (Mean, SD)
Cicerone et al. 2008(54)	Comprehensive CRT	34	34.5 (12.4)	62	71	12.5 (1.2)	12	NR	NR	NR	NR	37.0 (58.2)	NR
	Standard Rehabilitation	34	38.7 (11.1)	74	79	13.2 (1.9)	29	NR	NR	NR	NR	49.6 (76.5)	NR
Tiersky et al. 2005(60)[1]	CRT plus CBT	11	47.5 (11.78)	54.5	91	46% have a Bachelor's degree	NR	NR	0 mins.: 27.3% 1 to 29 mins.: 73.0% >29 mins.: 0.0%	NR	NR	60.1 (65.5)	Median: 3.5
	No Treatment Control	9	46.0 (9.35)	33.3	89	67% have a Bachelor's degree	NR	NR	0 mins.: 55.6% 1 to 29 mins.: 33.3% >29 mins.: 11.1%	NR	NR	65.6 (49.1)	Median: 3.5
Salazar et al. 2000(64)	Inpatient Comprehensive CRT	67	25 (6.63)	93	69	41% had some or more college	40	9.4 (3.7)	>60 mins. = 53% >24 hours = 30%	NR	>7 days: 41%	1.3 (0.786)	NR
	Less Intense In-home Rehabilitation	53	26 (6.22)	96	70	44% had some or more college	34	9.5 (3.4)	>60 mins. = 76% >24 hours = 38%	NR	>7 days: 42%	1.3 (1.10)	NR

[1] Six patients discontinued the study from the control group causing the number of patients to be below 10 for this group. However, this study was included because greater than 10 patients were randomized to the treatment or control group.

CBT Cognitive behavioral therapy.
CRT Cognitive rehabilitation therapy.
LOC Loss of consciousness.

Table 35. Treatment Characteristics of Studies on Comprehensive CRT Programs

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Cicerone et al. 2008(54)	Comprehensive CRT	34	Various therapists, including occupational, physical, and speech therapist and neuropsychologist. Treatment took place in a postacute brain rehabilitation center.	Treatment emphasized the integration of interventions for cognitive deficits, emotional difficulties, interpersonal behaviors, and functional skills. Treatments were organized around specific themes delivered in phases both individually and within a group setting. The phases including 3 weeks of directly practicing strategies addressing problem areas.	Patients continued with any medical care or counseling they were receiving prior to the study	15 hours per week for three days a week	16 weeks	6 months	28
	Standard Rehabilitation	34	Various therapists, including occupational, physical, and speech therapist and neuropsychologist. Treatment took place in a postacute brain rehabilitation center.	Treatment consisted of individual therapies including physical, occupational, and speech. In addition, all patients received 1 hour/day of neuropsychological (NP) treatment that involved awareness of deficits and strategies to overcome deficits.	Patients continued with any medical care or counseling they were receiving prior to the study	15 hours per week for three days a week	16 weeks	6 months	30

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Tiersky et al. 2005(60)[1]	CRT plus CBT	11	Psychologist trained in TBI rehabilitation. Treatment was delivered in outpatient clinic	Treatment focused on improving neuropsychological functioning, emotional well-being, and functional status. Treatment involved cognitive remedial therapy focusing mostly on deficits of attention and memory, and CBT to increase effective coping, reduce stress, prevent relapse, and help cope with loss.	NR	5 hours of treatment per week over the course of 3 days/ week	11 weeks	Post Treatment	11
	No Treatment Control	9	---	Control patients did have minimal contact with the principal investigator 2 to 3 times per week via telephone. The contact did not involve providing any treatment.	NR	---	---	---	9

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Follow-up	N at Follow-up
Salazar et al. 2000(64)	Inpatient Comprehensive CRT	67	Various therapists, including a psychiatrist, neuropsychologist, occupational, physical, and speech therapist. Treatment took place in a U.S. military tertiary care hospital inpatient rehabilitation program.	The treatment involved interdisciplinary cognitive rehabilitation modeled after Prigatano's milieu-oriented approach and modified to fit a military environment. Treatment was delivered both individually and within a group setting. A typical day included physical fitness training, group and individual cognitive, speech, occupational, and coping skills therapy. Two to three hours per day were devoted to work therapy.	NR	7.5 hours/ day for five days a week	8 weeks	1 year	60
	Less Intense in Home Rehabilitation	53	Treatment provided by a psychiatric nurse within the patient's home. Most of the treatment took place over the telephone	Patients received TBI education and individual counseling from a psychiatric nurse	NR	Weekly 30 minute phone calls from nurse	8 weeks	1 year	47

[1]Six patients discontinued the study from the control group causing the number of patients to be below 10 for this group. However, this study was included because greater than 10 patients were randomized to the treatment or control group.

CBT Cognitive behavioral therapy.
CRT Cognitive rehabilitation therapy.
LOC Loss of consciousness.

Appendix F. Individual Study Results

KEY QUESTION 1: CRT for Attention Deficits

Table 36. Key Question 1: Neuropsychological Tests of Attention and Memory

Study	Test	Cognitive Function	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Fosotti et al. 2000(62)	Rey's 15-Word (Acquisition)	Memory	TPM (12)	0.12 (1.18)	0.68 (1.32)	0.138 (-0.670 to 0.947, p = 0.737)
			Control (10)	-0.08 (0.88)	0.32 (0.93)	
	Rey's 15-Word (Recall)	Memory	TPM (12)	0.11 (0.96)	0.83 (1.25)	0.252 (-0.559 to 1.062, p = 0.543)
			Control (10)	-0.02 (1.15)	0.41 (0.99)	
	Riverhead Memory Test	Memory	TPM (12)	-0.03 (1.01)	0.22 (0.83)	0.449 (-0.370 to 1.267, p = 0.283)
			Control (10)	0.04 (1.09)	-0.15 (0.70)	
	PASAT	Attention	TPM (12)	-0.07 (0.95)	0.75 (1.42)	0.108 (-0.700 to 0.916, p = 0.783)
			Control (10)	-0.16 (1.02)	0.53 (1.02)	
	Simple Reaction Time	Attention	TPM (12)	-0.04 (0.78)	0.11 (2.13)	-0.524 (-1.346 to 0.298, p = 0.212)
			Control (10)	0.25 (1.23)	-0.46 (1.00)	
	Choice Reaction Time	Attention	TPM (12)	0.04 (0.92)	-0.35 (1.12)	0.271 (-0.540 to 1.082, p = 0.513)
			Control (10)	0.14 (1.11)	-0.54 (0.91)	

Study	Test	Cognitive Function	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Novack et al. 1996(65)	Digit Span (total score)	Attention	Structured Attention Re-training (22)	9.5 (4.2)	12.7 (3.9)	-0.117 (-0.698 to 0.464, p = 0.693)
			Unstructured Control (22)	10.7 (4.6)	14.4 (4.0)	
	Trail Making (A)	Attention	Structured Attention Re-training (22)	NR	80.2 (28.2)	-0.016 (-0.597 to 0.564, p = 0.956)
			Unstructured Control (22)	NR	80.7 (31.5)	
	Trail Making (B)	Attention	Structured Attention Re-training (22)	NR	79.8 (25.7)	0.138 (-0.443 to 0.719, p = 0.641)
			Unstructured Control (22)	NR	76.0 (28.2)	
	Simple Reaction Time	Attention	Structured Attention Re-training (22)	1.4 (0.8)	0.6 (0.2)	0.415 (-0.172 to 1.001, p = 0.166)
			Unstructured Control (22)	1.2 (0.8)	0.7 (0.5)	
	Choice Reaction Time	Attention	Structured Attention Re-training (22)	2.2 (2.3)	0.7 (0.3)	0.212 (-0.370 to 0.794, p = 0.476)
			Unstructured Control (22)	1.8 (2.7)	0.8 (0.6)	
	Logical Memory (I)	Memory	Structured Attention Re-training (22)	NR	88.1 (17.3)	0.124 (-0.457 to 0.705, p = 0.676)
			Unstructured Control (22)	NR	85.8 (19.1)	
	Logical Memory (II)	Memory	Structured Attention Re-training (22)	NR	80.5 (19.0)	0.102 (-0.479 to 0.683, p = 0.731)
			Unstructured Control (22)	NR	78.4 (21.4)	
	Benton Sentence Test	Memory	Structured Attention Re-training (22)	NR	93.3 (16.7)	-0.096 (-0.677 to 0.484, p = 0.745)
			Unstructured Control (22)	NR	95.0 (17.9)	
Neimann et al. 1990(69)	Attention d2	Attention	Attention Re-training (13)	241.00 (77.0)	279.60 (90.0)	-0.069 (-0.814 to 0.676, p = 0.856)
			Memory Control (13)	279.50 (78.7)	312.2 (84.4)	
	PASAT	Attention	Attention Re-training (13)	25.70 (10.7)	31.6 (8.9)	-0.149 (-0.894 to 0.597, p = 0.696)
			Memory Control (13)	27.30 (10.0)	34.80 (11.6)	

Study	Test	Cognitive Function	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Neimann et al. 1990(69) (continued)	Divided Attention Test	Attention	Attention Re-training (13)	19.0 (9.7)	25.0 (9.3)	-0.207 (-0.953 to 0.540, p = 0.588)
			Memory Control (13)	21.30 (7.7)	25.50 (6.6)	
	Trail Making (B-only reported)	Attention	Attention Re-training (13)	0.97 (0.62)	1.42 (0.82)	0.514 (-0.244 to 1.271, p = 0.184)
			Memory Control (13)	1.14 (0.43)	1.26 (0.51)	
	Rey's Verbal Learning Total	Memory	Attention Re-training (13)	36.50 (10.8)	39.10 (10.0)	-0.213 (-0.960 to 0.533, p = 0.576)
			Memory Control (13)	38.10 (10.5)	43.20 (13.4)	
	Block Span Total	Memory	Attention Re-training (13)	22.20 (9.9)	27.60 (10.5)	0.389 (-0.363 to 1.141, p = 0.310)
			Memory Control (13)	23.60 (6.7)	25.40 (8.1)	
	Ruff 2 & 7 Test	Attention	Attention Re-training (13)	-2.07 (1.11)	-2.09 (1.12)	0.034 (-0.710 to 0.779, p = 0.928)
			Memory Control (13)	-1.36 (1.21)	-1.42 (1.03)	
	Logical Memory Total	Memory	Attention Re-training (13)	-1.01 (1.41)	-0.78 (1.29)	0.156 (-0.590 to 0.902, p = 0.682)
			Memory Control (13)	-1.33 (1.82)	-0.84 (1.86)	
	Ruff-Light Trail Learning Test	Attention	Attention Re-training (13)	-1.72 (2.49)	-1.99 (2.23)	0.172 (-0.574 to 0.918, p = 0.651)
			Memory Control (13)	-2.23 (2.15)	-2.14 (3.15)	

Note: None of the studies reported follow-up data for neuropsychological tests further than post-treatment.

Note: On all tests except those measuring time or number of errors, higher scores indicate improved performance.

[a]All effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

NR Not reported.

Table 37. Key Question 1: Patient-Oriented Outcomes

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between-Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Novack et al. 1996(65)[b]	FIM (ADLs)	Structured Attention Training (12)	28.3 (15.9)	57.6 (16.6)	-0.448 (-1.230 to 0.335, p = 0.263)
		Unstructured Control (12)	32.6 (16.3)	61.8 (15.1)	
	FIM (cognition)	Structured Attention Training (12)	11.8 (1.3)	21.3 (7.3)	0.070 (-0.87 to 0.228, p = 0.378)
		Unstructured Control (12)	11.2 (5.4)	23.8 (7.4)	

Note: Higher scores indicate improved performance.

[a] All effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

[b] Data were only available for 24 out of 44 patients (12 in each treatment group)

FIM Functional Independence Measure.
NS Not significant.

KEY QUESTION 2: CRT for Communication Deficits

Table 38. Key Question 2: Communication and Patient-Rated Outcomes

Study	Outcome (Test)	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[1]
McDonald et al. 2008(55)	**Social Behavior (as measured using the Behaviorally Referenced Rating System of Intermediary Social Skills-Revised BRISS-R)[2]**				
	Use of reinforces (max 7)	Social Training (n = 10)	3.43 (0.64)	3.59 (0.61)	---
		Placebo (n = 11)	3.26 (0.61)	3.25 (0.73)	0.252 (-0.495 to 1.00, p = 0.508)
		Waitlist (n = 13)	3.47 (0.61)	3.41 (0.70)	0.331 (-0.418 to 1.081, p = 0.386)
	Partner involvement (max 7)	Social Training (n = 10)	3.05 (0.80)	3.74 (0.76)	---
		Placebo (n = 11)	2.83 (0.84)	3.01 (0.94)	0.588 (-0.173 to 1.350, p = 0.130)
		Waitlist (n = 11)	3.03 (0.96)	2.98 (0.89)	0.836 (0.058 to 1.615, p = 0.035)
	Self-centered behavior (max 7)	Social Training (n = 10)	3.08 (0.74)	3.75 (0.79)	---
		Placebo (n = 11)	2.79 (0.88)	2.94 (0.96)	0.628 (-0.136 to 1.392, p = 0.107)
		Waitlist (n = 11)	3.02 (0.91)	2.92 (0.94)	0.878 (0.096 to 1.660, p = 0.028)

Study	Outcome (Test)	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[1]
McDonald et al. 2008(55) (continued)	Use of humor (max 7)	Social Training (n = 10)	4.08 (0.47)	4.32 (0.39)	---
		Placebo (n = 11)	3.80 (0.76)	3.83 (0.84)	0.315 (-0.435 to 1.064, p = 0.410)
		Waitlist (n = 11)	3.72 (0.67)	3.96 (0.71)	0.000 (-0.744 to 0.744, p = 1.000)
	Self-disclosure (max 7)	Social Training (n = 10)	3.15(0.34)	3.32 (0.41)	---
		Placebo (n = 11)	3.21 (0.56)	3.32 (0.76)	0.105 (-0.640 to 0.850, p = 0.782)
		Waitlist (n = 11)	3.17 (0.52)	3.06 (0.56)	0.580 (-0.181 to 1.341, p = 0.135)
	Social manners (max 7)	Social Training (n = 10)	3.96 (0.45)	4.08 (0.37)	---
		Placebo (n =11)	3.88 (0.31)	3.94 (0.40)	0.149 (-0.597 to 0.894, p = 0.696)
		Waitlist (n = 11)	3.93 (0.32)	4.12 (0.92)	0.105 (-0.640 to 0.850, p = 0.782)

Study	Outcome (Test)	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[1]
McDonald et al. 2008(55) (continued)	**Social Perception (as measured using The Awareness of Social Inference Test-TASIT)[2]**				
	Emotion evaluation (max 28)	Social Training (n = 13)	20.2 (4.4)	21.7 (3.3)	---
		Placebo (n = 13)	17.3 (4.1)	15.6 (5.3)	0.703 (-0.066 to 1.471, p = 0.073)
		Waitlist (n = 13)	18.5 (5.6)	19.1 (4.8)	0.187 (-0.559 to 0.934, p = 0.623)
	Social reference (max 60)	Social Training (n = 13)	48.1 (9.9)	45.1 (10.4)	---
		Placebo (n = 13)	42.4 (9.2)	41.7 (12.1)	0.156 (-0.590 to 0.902, p = 0.682)
		Waitlist (n = 13)	43.4 (9.1)	39.5 (7.9)	0.093 (-0.652 to 0.838, p = 0.807)
	Social inference (max 64)	Social Training (n = 13)	47.3 (8.3)	49.2 (6.8)	---
		Placebo (n = 13)	43.9 (9.4)	43.6 (7.2)	0.263 (-0.484 to 1.011, p = 0.491)
		Waitlist (n = 13)	43.4 (9.1)	40.6 (7.2)	0.569 (-0.191 to 1.330, p = 0.142)

Study	Outcome (Test)	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[1]
McDonald et al. 2008(55) (continued)	**Depression Anxiety Stress Scales (DASS)[3]**				
	Depression (max 21)	Social Training (n = 13)	11.3 (12.7)	10.6 (11.9)	---
		Placebo (n = 11)	13.5 (10.9)	11.9 (10.9)	0.075 (-0.670 to 0.820, p = 0.844)
		Waitlist (n = 12)	14.6 (12.2)	14.5 (13.5)	0.046 (-0.699 to 0.791, p = 0.903)
	Anxiety (max 21)	Social Training (n = 13)	7.2 (8.8)	5.2 (5.7)	---
		Placebo (n = 11)	9.4 (8.2)	6.6 (7.7)	0.099 (-0.646 to 0.844, p = 0.795)
		Waitlist (n = 12)	8.8 (9.1)	7.7 (9.1)	0.103 (-0.642 to 0.848, p = 0.786)
	Stress (max 21)	Social Training (n = 13)	14.2 (11.9)	10.5 (9.7)	---
		Placebo (n = 11)	17.5 (10.1)	12.9 (9.6)	0.084 (-0.661 to 0.828, p = 0.826)
		Waitlist (n = 12)	12.6 (9.1)	10.7 (10.6)	0.167 (-0.579 to 0.912), p = 0.662

Study	Outcome (Test)	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[1]
McDonald et al. 2008(55) (continued)	**Sydney Psychosocial Reintegration Scale (SPRS)[2]**				
	SPRS (max 72)	Social Training (n = 13)	41.2 (15.6)	46.8 (13.4)	---
		Placebo (n = 11)	32.7 (12.1)	35.1 (10.1)	0.238 (-0.510 to 0.985, p = 0.533)
		Waitlist (n = 12)	37.8 (14.9)	44.4 (16.9)	0.063 (-0.681 to 0.808, p = 0.868)
Dahlberg et al. 2007(58)	**Profile of Functional Impairment in Communication (PFIC)[3]**				
	Logical content	Social training (25)	0.78 (0.99)	0.58 (0.66)	0.262 (-0.318 to 0.843, p = 0.375)
		Waitlist (20)	0.75 (0.87)	0.78 (0.82)	
	General participation	Social training (25)	2.78 (1.02)	1.86 (1.11)	0.976 (0.364 to 1.588, p = 0.002)
		Waitlist (20)	2.50 (1.06)	2.68 (1.23)	
	Quantity	Social training (25)	1.64 (0.74)	1.06 (0.67)	0.727 (0.130 to 1.324, p = 0.017)
		Waitlist (20)	1.38 (0.76)	1.35 (0.81)	
	Quality	Social training (25)	0.54 (0.71)	0.36 (0.55)	0.294 (-0.287 to 0.875, p = 0.321)
		Waitlist (20)	0.73 (0.88)	0.78 (0.92)	
	Internal relation	Social training (25)	1.70 (0.84)	1.00 (0.69)	0.823 (0.221 to 1.425), p = 0.007
		Waitlist (20)	1.58 (1.05)	1.63 (1.00)	
	External relation	Social training (25)	2.26 (0.96)	1.46 (1.11)	0.943 (0.333 to 1.552, p = 0.002)
		Waitlist (20)	1.60 (1.02)	1.80 (1.06)	

Study	Outcome (Test)	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[1]
Dahlberg et al. 2007(58) (continued)	Clarity of expression	Social training (25)	1.68 (0.86)	1.12 (0.71)	0.684 (0.090 to 1.279, p = 0.024)
		Waitlist (20)	1.53 (1.03)	1.58 (0.89)	
	Social style	Social training (25)	1.78 (0.87)	1.00 (0.82)	1.039 (0.423 to 1.655, p = 0.044)
		Waitlist (20)	1.40 (0.97)	1.58 (0.99)	
	Subject matter	Social training (25)	1.30 (0.87)	0.84 (0.92)	0.608 (0.017 to 1.199, p = 0.044)
		Waitlist (20)	1.20 (0.92)	1.30 (0.91)	
	Aesthetics	Social training (25)	1.90 (1.03)	1.36 (1.03)	0.628 (0.036 to 1.220, p = 0.038)
		Waitlist (20)	1.58 (1.00)	1.68 (0.92)	
	Community Integration Questionnaire (CIQ)[2]				
	Social integration	Social training (25)	7.96 (2.11)	7.72 (2.23)	-0.090 (-0.668 to 0.488, p = 0.700)
		Waitlist (20)	8.62 (2.26)	8.58 (2.12)	
	Productivity	Social training (25)	4.08 (1.66)	3.88 (1.62)	0.234 (-0.346 to 0.814, p = 0.429)
		Waitlist (20)	4.31 (1.26)	3.73 (1.71)	
	Craig Handicap Assessment and Reporting Technique-Short Form (CHART-SF)[2]				
	Occupation	Social training (25)	61.56 (34.45)	53.84 (32.81)	-0.046 (-0.624 to 0.532, p = 0.876)
		Waitlist (20)	70.58 (34.02)	64.46 (35.48)	
	Social integration	Social training (25)	71.60 (26.68)	72.16 (21.74)	-0.059 (-0.636 to 0.519, p = 0.842)
		Waitlist (20)	87.42 (19.29)	86.65 (18.67)	

Study	Outcome (Test)	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[1]
Dahlberg et al. 2007(58) (continued)	**Satisfaction with Life Scale (SWLS)[2]**				
		Social training (25)	18.46 (8.86)	20.81 (9.32)	0.120 (-0.458 to 0.699, p = 0.683)
		Waitlist (20)	22.62 (7.52)	23.96 (6.39)	

Note: Not presented in the table are the results of ratings provided by relatives or significant others. These results are not reported because they were considered secondary outcomes in both of the studies. All outcomes reported in the table were either measured by trained observers or self-reported.

Note: Individual effect size estimates calculated for McDonald et al. are comparing the skills training group to the placebo group or the waitlist control group.

[1] All effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

[2] Higher scores indicate improvement.

[3] Lower scores indicate improvement.

KEY QUESTION 3: CRT for Memory Deficits

Table 39. Key Question 3: Neuropsychological Tests of Memory

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	p-Value[a]	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI)[b]	p-Value	Follow-up Mean (SD)
Milders et al., 1995(66) & Berg et al., 1991(67)[c,d]	Memory Sum Score (composite of Rey's 15 Word Test, Face-Naming, and Shopping list)	Memory Training	-0.355	0.437	p <0.05	NC	---	0.274
		Control	-0.704	-0.243	NS			0.256
		No Treatment	-0.389	-0.015	NS			0.101

[a] Calculated by study authors, unless specified otherwise.

[b] All effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

[c] Data abstracted from Figure 1 (page 28) presented in Milders et al.(66) The figure did not provide sufficient information to calculate a standard deviation, and we, therefore, did not calculate any individual study effect sizes.

[d] The authors indicated that there were statistically significant differences in mean memory summary scores between the strategy group and the pseudotraining group and no-treatment control (favoring the strategy group) at post-treatment. No statistically significant differences were observed at the at the four-year follow-up.

NC Not calculated.
NS Not significant.
NR Not reported.

Table 40. Key Question 3: Patient Ratings of Memory and Employment Status (Milders et al. 1995)

Group	Functioning at Pre-Injury Status (%)	Functioning below Pre-Injury Status (%)	Not in Paid Employment (%)	Improved Since Previous Evaluation (%)	Deteriorated Since Previous Evaluation (%)	No Change Since Previous Evaluation (%)
Employment Status						
Memory Training (n = 15)	40	40	20	53.3	13.3	33.3
Control (n = 8)	50	37.5	12.5	37.5	0	62.5
No-Treatment (n = 3)	37.5	25	37.5	12.5	12.5	75.0
Memory Status						
Memory Training (n = 15)	---	---	---	60	NR	NR
Control (n = 8)	---	---	---	50	NR	NR
No-Treatment (n = 8)	---	---	---	50	NR	NR

NR Not reported.

Table 41. Key Question 3: Individual Study Results of Bourgeois et al.

Study	Outcome	Treatment Group (n)	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	One-month Follow-up Mean (SD)	Pre to Post-Treatment Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)	Pre to Follow-up Effect Size Estimate Hedges' g (95% CI, p-Value)
Bourgeois et al. 2007(57)	Goals mastered (correct response to prompt question)	SR (n = 22)	---	2.50 (0.79)	2.47 (0.9)	0.815 (0.158 to 1.471, p = 0.01	1.23 (0.543 to 1.920, p <0.001)
		Placebo control (16)	----	1.67 (1.23)	1.25 (1.06)		
	Generalization (use of therapy techniques in other settings)	SR (n = 22)	---	0.5 (0.89)	1.39 (1.2)	0.845 (0.187 to 1.504, p = 0.01)	0.783 (0.128 to 1.437, p = 0.02)
		Placebo control (16)	---	0.33 (0.65)	1.07 (1.21)		
	Frequency of reported memory problems	SR (n = 22)	24.78 (28.2)	16.85 (16.1)	16.64 (18.5)	0.066 (-0.564 to 0.697, p = 0.836)	0.150 (-0.482 to 0.781, p = 0.642)
		Placebo control (16)	18.63 (11.25)	12.09 (13.97)	13.63 (13.0)		
	CDS	SR (n = 22)	1.8 (0.70)	1.5 (0.78)	1.30 (0.78)	0.171 (-0.461 to 0.803, p = 0.596)	0.029 (-0.601 to 0.660, p = 0.927)
		Placebo control (16)	2.28 (0.58)	1.86 (0.62)	1.80 (0.48)		
	CIQ	SR (n = 22)	14.62 (5.15)	15.44 (4.26)	15.56 (5.15)	0.097 (-0.534 to 0.727, p = 0.764)	0.086 (-0.545 to 0.716, p = 0.790)
		Placebo control (16)	16.36 (4.76)	16.71 (4.77)	16.83 (6.28)		

CDC Cognitive Difficulties Scale.
CIQ Community Integration Questionnaire.
SR Spaced Retrieval.

Table 42. Key Question 3: Individual Study Results of Dou et al.

Study	Test	Treatment Comparison (n)	Pre-Post F Statistic (p-Value)	Hedges' g (95% CI, p-Value)
Dou et al. 2006(59)	RBMT (total score)	TAMR (n = 11) vs. CG (n = 13)	11.75 (p <0.01)	1.362 (0.496 to 2.227, p = 0.002)
		CAMR (n = 13) vs. CG (n = 13)	11.85 (p <0.01)	1.302 (0.478 to 2.126, p = 0.002)
	NCSE (total score)	TAMR (n = 11) vs. CG (n = 13)	4.76 (p = 0.015)	0.863 (0.050 to 1.676, p = 0.037)
		CAMR (n = 13) vs. CG (n = 13)	5.17 (p = 0.02)	0.863 (0.083 to 1.644, p = 0.030)

CAMR Computer assisted memory rehabilitation.
CG No-treatment control group.
NCSE Neurobehavioral Cognitive Status Examination.
RBMT Rivermead Behavioral Memory Test-Cantonese Version.
SR Spaced Retrieval.
TAMR Therapist assisted memory rehabilitation.

KEY QUESTION 5: CRT for Executive Function Deficits

Table 43. Key Question 5: Neuropsychological Tests of Executive Function

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[b]
Levine et al. 2003(63)	Stroop Interference Procedure	MST vs. GMT	NR NR	Independent t-test[a] t = 2.94, p <0.5	NC
	Trails Making B	MST vs. GMT	NR NR	Independent t-test[a] t = 1.97, p <0.6	NC
Neistadt 1991(68)	WAIS-R Block Design	Functional (23)	5.23 (2.76)	5.64 (3.20)	0.120 (-0.455 to 0.694, p = 0.683)
		Control (22)	5.44 (2.17)	6.17 (2.15)	

Note: On all tests except those measuring time or number of errors, higher mean scores indicate improved performance.

[a] Calculated by study authors. The scores favor the control group (MST). In other words, the MST group performed better on timed tests.

[b] All effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

GMT Goal Management Training.
MST Motor Skills Training.
NC Not calculated.
NR Not reported.
WAIS-R Wechsler Adult Intelligence Scale-Revised.

Table 44. Key Question 5: Patient Oriented Outcomes

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Cheng & Mann 2006(22)[a]	SDAI	AIP (11)	5.5 (2.4)	0.7 (1)	1.297 (0.386 to 2.208, p = 0.005)
		Control (10)	5.1 (2.5)	3.6 (3)	
	FIM (Total)	AIP (11)	67 (30.1)	104.8 (16.7)	0.470 (-0.364 to 1.304, p = 0.270)
		Control (10)	75.3 (31.4)	100 (19.6)	
	FIM (Physical)	AIP (11)	44.5 (35.3)	74.6 (15.8)	0.322 (-0.506 to 1.150, p = 0.446)
		Control (10)	49.5 (27.4)	70.3 (18.1)	
	FIM (Cognitive)	AIP (11)	22.6 (8.6)	29.8 (5.9)	0.495 (-0.341 to 1.331, p = 0.246)
		Control (10)	25.8 (5.4)	29.7 (2.3)	
	LADL	AIP (11)	4.4 (6.6)	14.3 (8.8)	0.569 (-0.271 to 1.409, p = 0.184)
		Control (10)	4.6 (6.8)	9.6 (9.7)	

Note: Higher scores on the FIM indicate improved functioning. Higher scores on the SDAI indicate more problematic behavior.

[a] All the effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

FIM Functional independence measure.(81)
LADL Lawton adult daily living skills.(99)
SDAI Self-awareness of deficits interview.(23)

Table 45. Key 5: Cognitive and Patient-Oriented Outcomes for Rath et al.

Study	Test	Treatment Group (n)	Posttreatment Independent Paired T-test (p-Value)[a]	Posttreatment Within Group Effect Size Estimate Hedges' g (95% CI, p-Value)[b]
Cognitive Skills				
Rath et al. 2003(61)	Logical memory (immediate recall)	Problem solving (n = 32)	-2.74 (p = 0.01)	0.473 (0.115 to 0.830, p = 0.010)
		Standard care (n = 28)	-3.91 (p = 0.001)	0.718 (0.312 to 1.124, p = 0.001)
	Logical memory (delayed recall)	Problem solving (n = 32)	-2.48 (p = 0.01)	0.428 (0.074 to 0.782, p = 0.018)
		Standard care (n = 28)	-2.73 (p = 0.01)	0.501 (0.118 to 0.885, p = 0.010)
	Visual memory (immediate recall)	Problem solving (n = 32)	-3.93 (p <0.001)	0.678 (0.301 to 1.054, p <0.001)
		Standard care (n = 28)	NR	NC
	Visual memory (delayed recall)	Problem solving (n = 32)	-2.48 (p = 0.01)	0.428 (0.074 to 9.782, p = 0.018)
		Standard care (n = 28)	-2.67 (p = 0.01)	0.490 (0.108 to 0.873, p = 0.012)
	Watson-Glaser Critical Thinking	Problem solving (n = 32)	NR	NC
		Standard care (n = 28)	-2.26 (p <0.05)	0.415 (0.039 to 0.791, p = 0.031)

Study	Test	Treatment Group (n)	Posttreatment Independent Paired T-test (p-Value)[a]	Posttreatment Within Group Effect Size Estimate Hedges' g (95% CI, p-Value)[b]
Psychosocial Functioning				
Rath et al. 2003(61)	Symptom complaints (Problem Checklist, PCL)	Problem solving (n = 32)	NR	NC
		Standard care (n = 28)	3.08 (p <0.05)	0.566 (0.176 to 0.955, p = 0.004)
	Self-esteem (Rosenberg Self-Esteem Scale, RSES)	Problem solving (n = 32)	1.99 (p <0.05)	0.343 (-0.005 to 0.692, p = 0.053)
		Standard care (n = 28)	1.46 (p <0.08)	0.268 (-0.099 to 0.635, p = 0.152)
Problem Solving				
Rath et al. 2003(61)	Wisconsin Card Sorting Test (WCST)	Problem solving (n = 32)	-2.16 (p <0.05)	0.373 (0.022 to 0.723, p = 0.037)
		Standard care (n = 28)	NR	NC
	Problem Solving Inventory (PSI)	Problem solving (n = 32)	3.33 (p = 0.005)	0.574 (0.208 to 0.940, p = 0.002)
		Standard care (n = 28)	NR	NC
	Problem Solving Questionnaire (PSQ)	Problem solving (n = 32)	Clear thinking subscale: -2.74 (p = 0.01) Self-regulation subscale: -2.65 (p <0.01)	0.473 (0.115 to 0.830, p = 0.012) 0.457 (0.101 to 0.813, p = 0.012)
		Standard care (n = 28)	NR	NC
	Problem Solving Role Play Test (PSRPT)	Problem solving (n = 32)	-2.96 (p = 0.005)	0.510 (0.150 to 0.871, p = 0.006)
		Standard care (n = 28)	NR	NC

[a] Calculated by the authors of the study. The authors only report significant pre to posttreatment independent t-test results for each study group, and do not report any between group results for any of the outcomes at posttreatment.

[b] All within group effect sizes calculated by ECRI Institute using the t-values and sample sizes provided in the study and converting the final value to a Hedges' g estimate. A positive value indicates a better posttreatment outcome. Between group effect size estimates could not be calculated with the data provided in the study.

NC Not calculated.
NR Not reported.

KEY QUESTION 6: Multi-Modal CRT

Table 46. Key Question 6: Neuropsychological Tests of Multi-Modal CRT

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Measures of Attention Skills					
Ruff et al. 1989(71)	Digit Span	Attention Training (20)	6.37 (1.36)	6.85 (1.14)	0.244 (-0.366 to 0.854, p = 0.434)
		Control (20)	6.24 (1.24)	6.42 (1.02)	
	Digit Symbol	Attention Training (20)	4.6 (1.61)	5.7 (2.20)	0.418 (-0.196 to 1.033, p = 0.182)
		Control (20)	5.0 (2.35)	5.1 (2.89)	
	Digits Total	Attention Training (20)	77.5 (18.8)	94.2 (24.8)	0.305 (-0.306 to 0.916, p = 0.328)
		Control (20)	85.6 (35.6)	92.7 (39.1)	
	Seashore Rhythm Test	Attention Training (20)	24.6 (3.37)	24.4 (4.65)	0.122 (-0.486 to 0.730, p = 0.695)
		Control (20)	23.7 (5.24)	24.1 (5.60)	
	Ruff 2 & 7	Attention Training (20)	79.0 (20.7)	94.1 (23.7)	0.400 (-0.214 to 1.013, p = 0.202)
		Control (20)	84.4 (28.8)	88.7 (31.2)	
	Block Span	Memory Training (20)	5.50 (0.69)	5.85 (0.83)	0.053 (-0.555 to 0.660, p = 0.865)
		Control (20)	5.44 (1.09)	5.74 (1.05)	
	Letter Span	Memory Training (20)	5.47 (0.92)	5.90 (1.37)	0.494 (-0.123 to 1.111, p = 0.117)
		Control (20)	5.50 (0.76)	5.42 (0.77)	

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Measures of Memory					
Ruff et al. 1989(71)	Logical Memory (Wechsler Short Stories – Immediate Recall)	Memory Training (20)	29.9 (12.2)	34.4 (14.7)	0.064 (-0.544 to 0.671, p = 0.837)
		Control (20)	25.5 (12.0)	30.9 (15.4)	
	Logical Memory (Wechsler Short Stories – Delayed Recall)	Memory Training (20)	21.6 (12.4)	28.0 (15.)	0.072 (-0.536 to 0.680, p = 0.816)
		Control (20)	19.1 (10.2)	26.5 (15.0)	
	Rey's Visual Memory (3 min-present)	Memory Training (20)	9.0 (3.94)	11.5 (4.37)	0.023 (-0.584 to 0.631, p = 0.940)
		Control (20)	7.2 (3.66)	9.6 (4.60)	
	Rey's Visual Memory (3 min placement)	Memory Training (20)	1.6 (0.80)	1.4 (0.94)	0.797 (0.165 to 1.429, p = 0.014)
		Control (20)	1.8 (1.35)	2.7 (1.91)	
	Rey's Visual Memory (60 min-present)	Memory Training (20)	8.9 (4.10)	11.3 (4.46)	0.223 (-0.387 to 0.832, p = 0.474)
		Control (20)	6.7 (4.38)	10.1 (4.62)	
	Rey's Visual Memory (60 min placement)	Memory Training (20)	1.6 (0.98)	1.5 (1.01)	0.592 (-0.029 to 1.213, p = 0.062)
		Control (20)	2.0 (1.20)	2.7 (1.80)	
	Bushke Long-Term Memory	Memory Training (20)	82.9 (20.4)	92.5 (19.3)	0.255 (-0.355 to 0.865, p = 0.413)
		Control (20)	83.7 (79.9)	79.9 (28.1)	
	Bushke Total	Memory Training (20)	32.1 (27.9)	43.6 (33.3)	0.235 (-0.374 to 0.845, p = 0.449)
		Control (20)	38.8 (36.0)	42.1 (38.1)	
	Trails Total Errors	Memory Training (20)	52.6 (29.0)	47.4 (44.4)	0.004 (-0.604 to 0.611, p = 0.991)
		Control (20)	61.6 (37.2)	56.3 (38.7)	

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Measures of Visuospatial Skill					
Ruff et al. 1989(71)	Benton Facial	Visuospatial Training (20)	20.4 (3.72)	20.9 (3.57)	0.191 (-0.418 to 0.800, p = 0.539)
		Control (20)	19.5 (3.28)	19.3 (3.76)	
	Picture Completion	Visuospatial Training (20)	8.4 (3.36)	9.7 (3.51)	0.183 (-0.426 to 0.792, p = 0.539)
		Control (20)	7.7 (2.59)	8.4 (3.24)	
	Rey Complex Figure (Construction Present)	Visuospatial Training (20)	16.9 (2.8)	16.8 (3.59)	0.755 (0.125 to 1.384, p = 0.019)
		Control (20)	14.1 (4.80)	16.9 (1.75)	
	Rey Complex Figure (Construction Placement)	Visuospatial Training (20)	0.7 (0.71)	0.8 (9.3)	0.091 (-0.517 to 0.699, p = 0.769)
		Control (20)	1.3 (0.90)	2.0 (1.95)	
	Block Design	Visuospatial Training (20)	8.7 (2.25)	9.3 (2.08)	0.042 (-0.566 to 0.649, p = 0.893)
		Control (20)	7.6 (2.37)	8.3 (2.67)	
Measures of Problem Solving Skills					
Ruff et al. 1989(71)	Wisconsin Card Sorting (completed categories)	Problem Solving Training (20)	5.03 (1.04)	5.60 (1.05)	0.143 (-0.465 to 0.751, p = 0.645)
		Control (20)	4.42 (1.65)	4.79 (1.62)	
	Wisconsin Card Sorting (perseverations)	Problem Solving Training (20)	2.45 (3.07)	2.35 (3.03)	0.097 (-0.511 to 0.705, p = 0.755)
		Control (20)	5.18 (7.34)	4.53 (7.18)	
	Figural Fluency (mean number of designs)	Problem Solving Training (20)	10.3 (2.86)	13.4 (4.16)	0.416 (-0.198 to 1.030, p = 0.185)
		Control (20)	11.9 (4.55)	13.1 (5.59)	
	Figural Fluency (sum of perseverations)	Problem Solving Training (20)	13.2 (16.7)	11.5 (11.6)	0.048 (-0.559 to 0.656, p = 0.876)
		Control (20)	22.1 (30.8)	21.5 (23.7)	

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Measures of Global Intelligence					
Ruff et al. 1989(71)	Verbal IQ	CRT (20)	92.6 (12.0)	96.2 (12.7)	0.281 (-0.329 to 0.892, p = 0.367)
		Control (20)	92.4 (11.1)	92.6 (11.5)	
	Performance IQ	CRT (20)	84.1 (13.5)	89.8 (14.2)	0.151 (-0.457 to 0.760, p = 0.626)
		Control (20)	82.2 (11.5)	85.8 (14.6)	
	Full-Scale IQ	CRT (20)	87.8 (12.2)	92.9 (13.3)	0.175 (-0.434 to 0.784, p = 0.573)
		Control (20)	86.8 (9.55)	89.8 (11.5)	

Note: On all tests except those measuring time or number of errors, higher scores indicate improved performance.

[a] All effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

[b] Pre to post significance levels calculated by ECRI Institute using data reported by authors in Table 4 of Appendix B on page 35 of original article.(71)

NR Not reported.
NS Not significant.

Table 47. Key Question 6: Psychosocial Measures

Study	Test	Treatment Group (n)	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Vanderploeg et al. 2008(56)	FIM Motor Score	Didactic CRT (n = 171)	60.1 (24.8)	82.7 (14.1)	-0.005 (-0.219 to 0.209, p = 0.966)
		Functional CRT (n = 163)	57.8 (24.9)	80.5 (14.7)	
	FIM Cognitive Score	Didactic CRT (n = 171)	19.1 (8.0)	27.3 (6.2)	0.142 (-0.073 to 0.356, p = 0.198)
		Functional CRT (n = 163)	18.4 (7.4)	25.6 (6.0)	
	DRS	Didactic CRT (n = 171)	NR	7.6 (4.8)	0.118 (-0.107 to 0.344, p = 0.303)
		Functional CRT (n = 150)	NR	8.2 (5.3)	
Ruff & Niemann 1990(70)	Katz (Social Obstreperousness)	CRT (n = 12)	58.8 (12.5)	62.8 (12.8)	0.179 (-0.595 to 0.953, p = 0.651)
		Control (n = 12)	67.9 (14.9)	68.9 (21.5)	
	Katz (Acute Psychoticism)	CRT (n = 12)	15.8 (2.4)	16.0 (2.3)	0.276 (-0.500 to 1.053, p = 0.486)
		Control (n = 12)	18.3 (4.5)	20.3 (9.9)	
	Katz (Withdrawn Depression)	CRT (n = 12)	17.9 (4.7)	17.7 (5.0)	0.103 (-0.670 to 0.876, p = 0.793)
		Control (n = 12)	19.4 (4.9)	18.7 (3.9)	

Note: Higher scores on Katz indicate more problematic behavior.

[a] All the effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

CRT Cognitive rehabilitation therapy.
DRS Disability Rating Scale.
FIM Functional independence measure.(81)
Katz Katz adjustment scale.(151)

Table 48. Key Question 6: Binary Outcomes of Multi-Modal CRT

Study	Outcome	Treatment Group (n)	One-year Follow-up Number of patients (%)	Post-treatment Between Group Effect Size Estimate Odds Ratio (95% CI, p-Value)[a]
Vander ploeg et al. 2008(56)	Working or in school	Didactic CRT (n = 164)	65 (38.9)	1.165 (0.745 to 1.820, p = 0.503)
		Functional CRT (n = 164)	58 (34.4)	
	Living Independently	Didactic CRT (n = 167)	93 (56.3)	0.784 (0.506 to 1.215, p = 0.276)
		Functional CRT (n = 164)	101 (62.0)	
	Satisfied with life	Didactic CRT (n = 167)	80 (62.0)	0.942 (0.612 to 1.450, p = 0.787)
		Functional CRT (n = 164)	81 (65.3)	

[a] Effect sizes represent the odds ratio, values greater than one favor the experimental group, and values less than one favor the control group.

Note: All outcomes measured at 1 year posttreatment.

CRT Cognitive rehabilitation therapy.

KEY QUESTION 7: Comprehensive CRT Programs

Table 49. Key Question 7: Patient-Oriented Test Outcomes of Comprehensive CRT Programs

Study	Test	Treatment Group (n)	Pretreatment Mean (SD)	Posttreatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]	Follow-up Mean (SD)[a]	Pre-follow-up Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[b]
Cicerone et al. 2008(54)	CIQ (total score)	Comprehensive CRT (34)	11.2 (3.4)	12.9 (3.4)	0.542 (0.064 to 1.021, p = 0.026)	13.2 (4.3)	0.291 (-0.181 to 0.764, p = 0.227)
		Standard Care (34)	12.1 (4.0)	11.7 (4.4)		12.9 (4.4)	
	PQOL (total score)	Comprehensive CRT (34)	59.0 (21.7)	66.8 (17.5)	0.364 (-0.110 to 0.838, p = 0.132)	66.1 (20.8)	0.448 (-0.028 to 0.924, p = 0.065)
		Standard Care (34)	61.2 (16.5)	62.2 (17.2)		59.6 (17.2)	
	SEsx (total score)	Comprehensive CRT (34)	84.3 (28.9)	94.1 (29.2)	0.261 (-0.211 to 0.733, p = 0.278)	92.4 (22.7)	0.314 (-0.159 to 0.787, p = 0.193)
		Standard Care (34)	82.6 (27.9)	84.8 (28.9)		81.9 (30.0)	
Tiersky et al. 2005(60)	Global Symptom Inventory (SCL-90R)	CRT plus CBT (11)	1.16 (0.724)	0.86 (0.41)	0.529 (-0.331 to 1.388, p = 0.228)	NR	NR
		Waitlist Control (9)	1.62 (0.75)	1.74 (1.00)			
	Depression Inventory (SCL-90R)	CRT plus CBT (11)	1.50 (0.83)	1.12 (0.45)	0.455 (-0.400 to 1.317, p = 0.297)	NR	NR
		Waitlist Control (9)	2.07 (0.94)	2.11 (1.14)			
	Anxiety Inventory (SCL-90R)	CRT plus CBT (11)	0.921 (0.85)	1.39 (0.70)	0.413 (-0.441 to 1.266, p = 0.343)	NR	NR
		Waitlist Control (9)	0.72 (0.42)	1.53 (1.03)			
	CRI	CRT plus CBT (11)	10.75 (3.17)	13.06 (2.57)	1.047 (0.143 to 1.951, p = 0.023)	NR	NR
		Waitlist Control (9)	13.25 (2.66)	12.58 (2.21)			

Study	Test	Treatment Group (n)	Pretreatment Mean (SD)	Posttreatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]	Follow-up Mean (SD)[a]	Pre-follow-up Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[b]
Salazar et al. 2000(64)[c]	Katz (belligerence)	Inpatient Comprehensive CRT (32)	NR	NR	NR	17.1 (4.8)	0.356 (-0.149 to 0.860, p = 0.167)
		In-home rehabilitation (28)				19.8 (9.7)	
	Katz (social irresponsibility)	Inpatient Comprehensive CRT (32)	NR	NR	NR	29.3 (6.1)	0.016 (-0.484 to 0.517, p = 0.949)
		In-home rehabilitation (28)				29.4 (6.1)	
	Katz (antisocial behavior)	Inpatient Comprehensive CRT (32)	NR	NR	NR	9.5 (3.2)	0.304 (-0.200 to 0.807, p = 0.237)
		In-home rehabilitation (28)				11.1 (6.8)	
	Katz (social withdraw)	Inpatient Comprehensive CRT (32)	NR	NR	NR	10.8 (2.9)	0.222 (-0.281 to 0.724, p = 0.387)
		In-home rehabilitation (28)				11.6 (4.2)	
	Katz (apathy)	Inpatient Comprehensive CRT (32)	NR	NR	NR	6.9 (3.0)	0.345 (-0.159 to 0.850, p = 0.180)
		In-home rehabilitation (28)				8.2 (4.4)	

[a] One-year follow-up

[b] All the effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

[c] Effect size estimates calculated using follow-up scores only

CBT	Cognitive behavioral therapy.
CIQ	Community Integration Questionnaire, higher scores indicate a higher level of community integration in terms of home and social integration and productive activity.
CRI	Coping Response Inventory.
CRT	Cognitive rehabilitation therapy.
NR	Not reported.
PQOL	Perceived Quality of Life, higher scores indicate higher global satisfaction with quality of life along 10 areas of functioning. Scores range 10 to 100.(54)
SCL-90R (GSI)	Symptom Checklist-90 Revised (Global Severity Index), lower scores indicate improvement in overall symptoms, such as depression and anxiety.
SEsx	Perceived Self Efficacy, higher scores indicate higher confidence.(54)

Table 50. Key Question 7: Neuropsychological Test Outcomes of Comprehensive CRT Programs

Study	Test	Treatment Group (n)	Pretreatment Mean (SD)	Posttreatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Cicerone et al. 2008(54)	Attention and Processing (A)	Comprehensive CRT (34)	32.2 (12.9)	33.5 (12.7)	0.054 (-0.416 to 0.524, p = 0.823)
		Standard Care (34)	34.9 (13.2)	36.9 (12.8)	
	Attention and Processing (B)	Comprehensive CRT (34)	33.0 (14.1)	36.4 (10.7)	0.000 (-0.470 to 0.470, p = 1.00)
		Standard Care (34)	33.3 (11.4)	36.7 (13.7)	
	California Verbal Learning Test	Comprehensive CRT (34)	42.1 (15.1)	46.4 (15.6)	0.090 (-0.380 to 0.560, p = 0.708)
		Standard Care (34)	38.6 (11.7)	44.2 (14.3)	
	Rey Complex Figure	Comprehensive CRT (34)	35.8 (15.1)	38.3 (15.5)	0.061 (-0.409 to 0.531, p = 0.799)
		Standard Care (34)	32.5 (12.7)	35.9 (14.6)	
	Total Neuropsychological Score (total of above tests)	Comprehensive CRT (34)	36.6 (8.5)	39.5 (9.1)	0.076 (-0.394 to 0.546, p = 0.750)
		Standard Care (34)	35.9 (9.0)	39.5 (9.6)	
Tiersky et al. 2005(60)	Paced Auditory Attention Task	CRT plus CBT (11)	116.07 (33.07)	135.55 (30.71)	0.455 (-0.400 to 1.311, p = 0.297)
		Waitlist Control (9)	112.50 (51.02)	110.88 (60.28)	
	Attention Questionnaire	CRT plus CBT (11)	31.30 (9.88)	19.42 (11.56)	0.638 (-0.229 to 1.505, p = 0.149)
		Waitlist Control (9)	34.56 (6.05)	29.29 (9.94)	
Salazar et al. 2000(64)[b]	Buschke Selective Reminding Test	Inpatient Comprehensive CRT (32)	53 (34)	67 (34)	0.056 (-0.414 to 0.526, p = 0.817)
		In-home rehabilitation (28)	47 (33)	63 (40)	
	Trahan Continuous Visual Memory Test	Inpatient Comprehensive CRT (32)	34 (6)	38 (3)	0.206 (-0.265 to 0.677, p = 0.391)
		In-home rehabilitation (28)	36 (5)	39 (3)	
	Pace Auditory Attention Task	Inpatient Comprehensive CRT (32)	117 (33)	147 (42)	0.144 (-0.357 to 0.646, p = 0.572)
		In-home rehabilitation (28)	109 (32)	145 (50)	

Study	Test	Treatment Group (n)	Pretreatment Mean (SD)	Posttreatment Mean (SD)	Pre-Post Between Group Effect Size Estimate Hedges' g (95% CI, p-Value)[a]
Salazar et al. 2000(64)[b] (continued)	Wisconsin Card Sorting	Inpatient Comprehensive CRT (32)	12 (10)	16 (16)	0.183 (-0.319 to 0.685, p = 0.475)
		In-home rehabilitation (28)	7 (5)	9 (9)	

[a] All the effect sizes calculated using Hedges' g. A positive value indicates a better outcome for the primary CRT group.

[b] All tests administered at pretreatment and one year posttreatment. The table only reports test scores for which the mean and standard deviation were provided in the study.

Table 51. Key Question 7: Patient-Oriented Binary Outcomes of Comprehensive CRT Programs

Study	Outcome	Treatment Group (n)	Pretreatment Number of Patients (%)	Posttreatment Number of Patients (%)	Post-treatment Between Group Effect Size Estimate Odds Ratio (95% CI, p-Value)[a]	Follow-up Number of Patients (%)	Follow-up Between Group Effect Size Estimate Odds Ratio (95% CI, p-V alue)[a]
Cicerone et al. 2008(54)[1]	Engaged in employment	Comprehensive CRT (34)	3 (9)	16 (47)	3.429 (1.176 to 9.994, p = 0.024)	20 (59)	2.041 (0.777 to 5.361, p = 0.148)
		Standard Care (34)	4 (12)	7 (21)		14(41)	
	Unemployed	Comprehensive CRT (34)	31 (91)	18 (53)	0.292 (0.100 to 0.850, p = 0.024)	14 (41)	0.490 (0.187 to 1.287, p = 0.148)
		Standard Care (34)	30 (88)	27 (79)		20 (59)	
Salazar et al. 2000(64)[2,3]	Return to work	Inpatient Comprehensive CRT (67)	NR	NR	NR	60 (90)	0.514 (0.126 to 2.093, p = 0.353)
		In-home rehabilitation (53)				50 (94)	
	Fitness for duty	Inpatient Comprehensive CRT (67)	NR	NR	NR	49 (73)	1.400 (0.639 to 3.067, p = 0.400)
		In-home rehabilitation (53)				35 (66)	

[1] In the Cicerone study, employment was defined as engaging in supported, transitional (e.g., education, job coaching), or competitive community-based employment. Unemployment was defined as being unemployed or participating in a sheltered employment program.

[2] In the Salazar study, work was defined as either full-time (≥35 hours/week) or part-time (<35 hours/week) gainful military or civilian employment. Of those employed in the study, 91% of the inpatient group and 93% of the home group were working full-time.

[3] In the Salazar study, "fitness for duty included all patients who were still on active military duty or had received a normal discharge from the service, but excluded those who had a medical discharge [or one pending]."

Appendix G. Meta-Analytic Results

Figure 9. Key Question 1: Meta-Analytic Results of Intermediate Measures of Attention

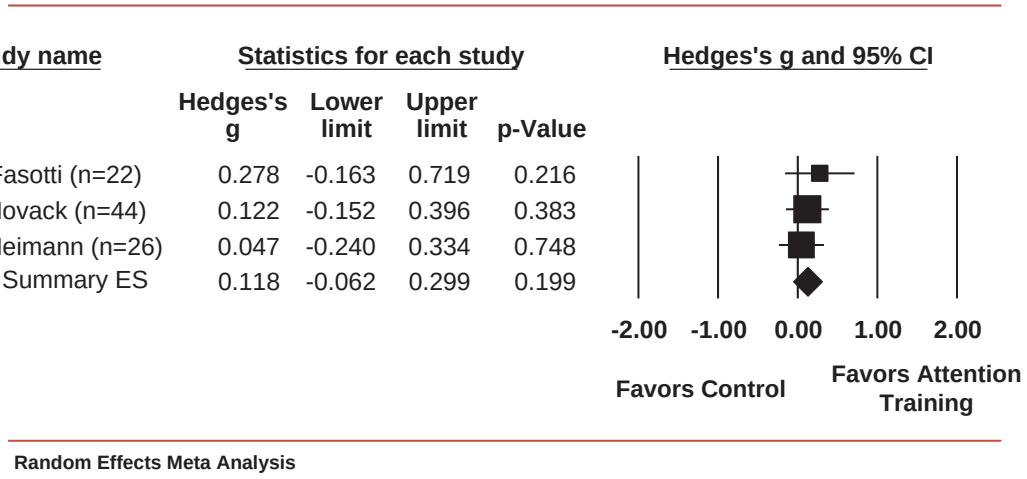


Figure 10. Key Question 1: Meta-Analytic Results of Intermediate Measures of Memory

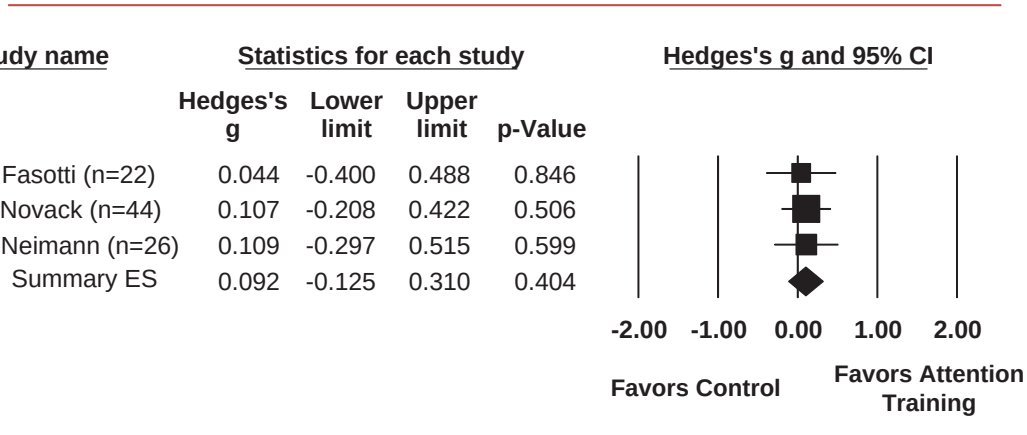
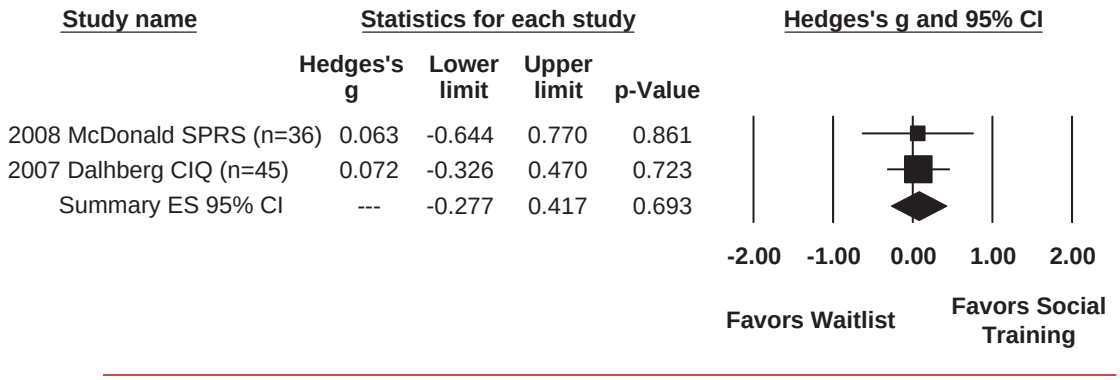
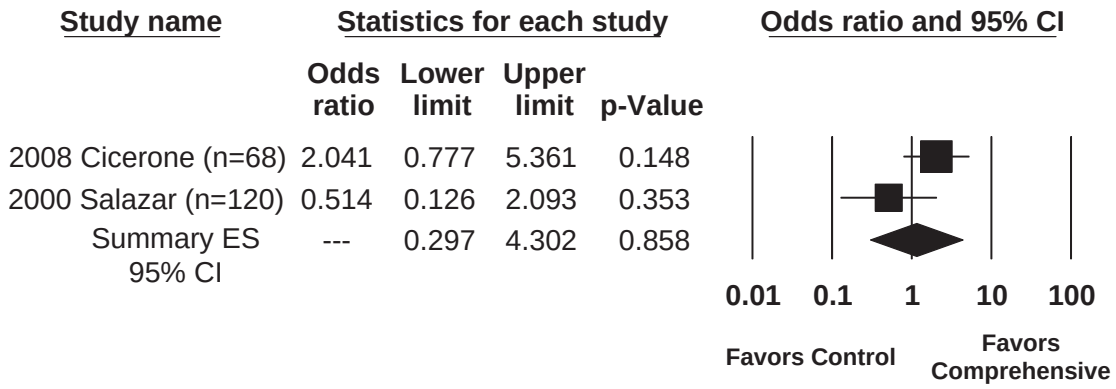


Figure 11. Key Question 2: Meta-Analytic Results of Measures of Community Integration



Random Effects Meta-Analysis

Figure 12. Key Question 7: Meta-Analytic Results for Return to Work



Random effects Meta Analysis

Appendix H. Information on Previous Systematic Reviews and Ongoing Clinical Trials on CRT

Table 52. Characteristics of Other Systematic Reviews

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Rohling et al. 2009(114) *Effectiveness of Cognitive Rehabilitation Following Acquired Brain Injury: A Meta-Analytic Re-Examination of Cicerone et al.'s (2000, 2005) Systematic Review*	This study used the same studies identified and reviewed by Cicerone et al. 2000(33) and 2005(152)	Same as Cicerone, 2005 plus the following additional exclusion criteria: case reports or studies with less than 4 patients and studies with insufficient data to calculate an effect size estimate	119 (72 single group studies and 47 treatment and control group studies. Total number of treated patients = 2,014 and nontreatment (or control) patients = 870.	Adults with acquired brain injury—included patients with etiologies of stroke and TBI.	Outcomes related to (scores on related tests or other types of outcomes) attention/ executive function, visuospatial, language, memory, and comprehension.	American Academy of Neurology (AAN) criteria for classes of evidence (I to IV), with Class I evidence from RCTs and Class IV from non-controlled studies.[a] All studies were pooled in meta-analysis regardless of study design.	Quantitative—preformed a meta-analysis. The authors pooled all studies, regardless of design, into a random effects meta-analysis to come up with an overall effect size. To account for "retest effects" in single group studies, the authors' subtracted the effect size estimate (0.41) calculated for the control group in the two group studies from the estimate calculated in the single group studies	The results of the meta-analysis showed a small overall treatment effect size of 0.30 attributable to CRT. Treatment effects were moderated by cognitive deficit treated (e.g., attention, memory, etc), time postinjury, type of brain injury (stroke or TBI), and age. In conclusion, the authors' indicated that the results of their analysis "revealed sufficient evidence for the effectiveness of attention training after [TBI] and of language and visuospatial training for aphasia and neglect syndrome after stroke."

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Snell et al. 2009(153) *A Systematic Review of Psychological Treatments for Mild Traumatic Brain Injury: An Update of the Evidence* This report serves to update two previous reviews: Borg et al. 2004(154) & Comper et al. 2005(155)	Searched MEDLINE, EMBASE, CINAHL, PsycINFO, AMED, and Cochrane database	Studies were included if the participants were aged 16 or older, the participants had mild TBI, the intervention was intended to treat mild TBI, and the study employed a control group	The evidence base for CRT consisted of three studies, two of which were RCTs, with a total of 122 patients	Adults with mild TBI	Cognitive functioning, emotional adjustment, and functional status	The authors assessed internal validity using the following criteria: random allocation, concealment of allocation, use of blind assessors, blinding of treating therapists, loss to follow-up, and intent-to-treat analysis. Only one of the three studies attempted to conceal allocation, used blind outcome assessors, had less than 10% of patients lost to follow-up, and used an intent to treat analysis	Narrative	According to the authors, only one of the three studies found a small treatment effect in favor of CRT using the Community Integration Questionnaire (CIQ). Overall, the authors conclude that the evidence for CRT for treating mild TBI remains inconclusive.
Blue Cross Blue Shield Technology Evaluation Center, 2009(115) *Cognitive Rehabilitation for Traumatic Brain Injury in Adults*	Searched MEDLINE and used studies that met inclusion criteria from two previous reviews: Gordon (2006) and Cicerone (2005)	Studies were included if they had more than 8 patients/treatment arm, the sample was predominately patients with TBI, patients underwent a distinct and definable CRT program, randomized control trial, measured health outcomes, and described patients and treatment process with adequate detail	12 RCTs and 1 non-randomized controlled trial (the authors of this review thought the non-RCT study was important of include)	Adults with cognitive deficits resulting from TBI (no other etiologies considered) who required CRT treatment	Health outcomes, cognitive functioning (did not assess results of neuropsychological tests), and quality of life measures	NR	Narrative	According to the authors, patients in most of the RCT studies did not show an improvement in health outcomes after treatment with CRT. The one non-RCT study included in the review did show an improvement, but the study had serious limitations, such as differences in types of patients enrolled in the two study groups and no long-term follow-up.

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Ehlhardt et al. 2008(156) *Evidence-based Practice Guidelines for Instructing Individuals with Neurogenic Memory Impairments: What Have we Learned in the Past 20 Years?*	Searched Academic Search Premier, Education Research Complete, ERIC, MEDLINE, Psychology and Behavioral Sciences Collection, and PsycINFO from 1986 to 2006	Studies were included if participants had acquired memory impairments as primary cognitive deficit due to various etiologies, including TBI; evaluated the use of instruction or training to learning or re-learning, and provided original data.	Overall 51 studies made up the evidence base. Of those, 38 assessed treatment of patients with acquired brain injury due to TBI or stroke. The authors did not specify the number of studies that specifically assessed TBI.	Adults and children (8 to 11 years) with acquired brain injury. Overall, 451 patients received treatment for memory impairment, 42 control patients had cognitive deficits, and 163 control patients were non-disabled	Memory deficits	American Academy of Neurology (AAN) criteria for classes of evidence (I to IV), with Class I evidence from RCTs and Class IV from non-controlled studies.	Narrative	Overall, the authors concluded that "the majority of the studies reported positive outcomes in favor of systematic instruction" to treat memory impairment following brain injury. However, they also state that "issues related to [study] design and execution of [treatment] lack clarity and require further study."
Kennedy et al. 2008(157) *Intervention for Executive Functions after Traumatic Brain Injury: A Systematic Review, Meta-analysis, and Clinical Recommendations*	Searched MEDLINE, CINAHL, and ERIC for studies published through 2004	Studies were excluded if they were not published in English, were single case reports or used a single-subject design.	The evidence base consisted of 15 controlled trials that focused on interventions designed to treat executive function deficits. Overall, the studies enrolled a total of 268 patients.	Patients ranged from mild to severe TBI	Improvement of impairment as measured by neuropsychological tests and tasks	American Academy of Neurology (AAN) criteria for classes of evidence (I to IV), with Class I evidence from RCTs and Class IV from non-controlled studies.	Quantitative—preformed a meta-analysis.	Meta-analysis was performed on a subset of five group studies that used step-by-step metacognitive instruction (MSI) to treat patients with executive function deficits. Based on the results of their analyses, the authors concluded that there was sufficient evidence to recommend that MSI be used with young to middle-aged adults with TBI to help improve everyday functional problems.

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Geusgens et al. 2007(158) *Occurance and Measurement of Transfer in Cognitive Rehabilitation: A Critical Review*	Searched CINAHL, MEDLINE, and PsychINFO for literature published between 1983 and 2005	Studies were included if they were interventional studies evaluating cognitive strategy training to improve cognitive deficits. Participants had to be adults with a clinical diagnosis of acquired brain injury. Studies had to report on the outcome of interest and be in English.	41 studies of which14 included patients with TBI	Adult patients with acquired brain injury including TBI and stroke. The mean age of patients with TBI was under 40 years and time post injury ranged from 14 days to 25 years.	Transfer outcomes, such as scales or self-report of performance of daily tasks	NR	Narrative	Overall, the authors concluded that transfer effects of cognitive strategy training to improve cognitive deficits have been measured in few studies. Among studies that to measure transfer effects, the outcome measures used fall into one of three categories: non-trained items, daily tasks and daily life. Most studies reported positive results with regard to the occurance of transfer of training effects. However, the author indicates that most studies have serious methodological limitations, such as small sample size and lack of control group.

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Rees et al. 2007(159)	Searched CINAHL, MEDLINE, and PsychINFO for literature published between 1980 and 2006	No specific inclusion/exclusion criteria reported Review included all study designs and studies that compared treated group with healthy controls	8 studies with a total of 223 patients were used to assess CRT for attention deficits; 27 studies with a total of 430 patients were used to assess CRT for memory deficits; and 17 studies with a total of 684 patients were used to assess CRT for executive functioning.	Adults with moderate to severe acquired brain injury	Attention, concentration & information processing speed, learning and memory, and executive function	Used the PEDro and Downs and Black methods of assessing methodology of randomized and non-randomized studies	Narrative	According to the authors: 1) moderate evidence suggests that structured training methods (e.g., drill and practice techniques) are not effective for improving attention; 2) moderate evidence suggests that dual task training is an effective intervention for attention; 3) strong evidence suggests that external and internal aids are effective for memory impaired patients for day-to-day memory problems and improving recall; 4) limited evidence suggests that memory-retraining is not an effective method of treatment; there is limited evidence to suggest that group intervention and general CRT is effective for treating deficits of executive function; and moderate evidence to suggest that goal management training improves paper and pencil everyday tasks.

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Gordon et al. 2006(160) *Traumatic Brain Injury Rehabilitation: State of the Science*	Searched MEDLINE, CINAHL, and PsychINFO for studies published from January 1998 to 2004	Studies were excluded if they had less than 20 patients per treatment arm, 75% or less adult patients, and fewer than 75% patients with TBI.	This review examined overall rehabilitation of TBI. Thirteen studies made up the evidence base for CRT—6 RCTs, 4 CTs, and 3 non-controlled trials. Overall number of patients not reported in review.	Patients ranged from mild to severe TBI	Outcomes ranged from neuropsychological tests to community integration	American Academy of Neurology (AAN) criteria for classes of evidence (I to IV), with Class I evidence from RCTs and Class IV from non-controlled studies.	Narrative	According to the authors, three small Class I studies provide weak evidence that training in the use of compensatory strategies seems to be effective for the remediation of attention deficits and mild memory problems. The authors point out that the three studies were limited by small sample sizes and lack of representative samples, which seriously weakened the strength of the findings of these studies.

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Cicerone et al. 2005(161)[b] *Cognitive Rehabilitation for Traumatic Brain Injury and Stroke: Updated Review of the Literature form 1998 through 2002 with Recommendations for Clinical Practice* This review serves to update a previous review on the same topic by Cicerone et al. 2000(33)	Searched Pubmed and Infotrieve for studies from 1998 to 2002	Studies were excluded if they did not address an intervention or provide an adequate description of an intervention, included children, were not peer reviewed, described a pharmacological intervention, or were non-English.	Overall, 87 articles were examined. Of those, 17 were randomized controlled trials of CRT for TBI and stroke. The evidence base for TBI consisted primarily of 7 RCTs enrolling a total of 291 patients with mild to moderate TBI.	Patients with mild to severe brain damage as a result of TBI or stroke.	Outcomes ranged from neuropsychological tests to community integration	American Academy of Neurology (AAN) criteria for classes of evidence (I to IV), with Class I evidence from RCTs and Class IV from non-controlled studies.	Narrative	Overall, the authors concluded that CRT is beneficial for patients with TBI based on the positive results reported in 6 of the 7 comparative studies evaluated in the review. Specifically, the authors indicated that the evidence supports the use of strategy training for memory impairment, attention deficits, and functional communication deficits.

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Park & Ingles 2001(162) *Effectiveness of Attention Rehabilitation After Acquired Brain Injury: Meta-Analysis*	Searched MEDLINE and PsychINFO for studies from 1966 to 1997	To be included studies had to evaluate the effectiveness of interventions specific to attention disorders following brain damage. Studies also had to have at least one quantitative outcome measure for which an effect size could be computed.	30 studies (n = 359)	Patients with acquired brain damage of which 57% of included studies had only patients with TBI.	Measures of cognitive function (including test of attention, learning, memory, and other skills)	Study quality not assessed	Meta-analysis Effect size calculated using Hedges' g	According to the authors, the results of their analyses indicated that performance significantly improved on two specific-skill measures—driving-related tasks and attention behavior (95% confidence intervals were 0.28 to 2.02 and 0.08 to 1.94, respectively). These results were sustained when controlling for study design (controlled versus non-controlled trials). For all of the other outcomes, the effect size estimates were only statistically significant in the non-controlled trials. According to the authors, such results suggest that improved performance on the other outcomes was mainly attributable to the effects of practice, rather than to any attention-specific intervention. The authors point out that the presence of substantial practice effects is methodologically important because it underscores the necessity of controlling for these effects when designing studies to evaluate CRT. The possibility of practice effects also highlights the difficulties of drawing conclusions about the effectiveness of CRT from studies without an adequate control group.

Citation	Search Strategy	Key Inclusion/ Exclusion Criteria	Evidence Base	Participant Characteristics	Outcomes Assessed	Method of Assessing Study Quality	Type of Review	Results and/or Authors' Conclusions
Carney et al. 1999(34)[c] *Effect of cognitive rehabilitation on outcomes for persons with traumatic brain injury: a systematic review*	Searched MEDLINE, HealthSTAR, CINAHL, PsychINFO, and Cochrane Library for studies published from 1976 to 1997.	Studies were excluded if not TBI, included children, focused on pharmacological interventions, were case reports, included drug/alcohol abuse as primary outcome, or were non-English language.	11 RCTs (n = 319)	Patients with moderate to severe TBI	Health outcomes (i.e., quality of life), employment, and intermediate outcomes (neuro-psychological tests)	**Class I**: randomized controlled trials in which raters were blinded and study reported follow-up data; **Class II:** randomized controlled trials that contained design flaws preventing a specification of Class I, or multicenter or population-based longitudinal (cohort) studies, or controlled trials that were not randomized, or case control studies, or case series with adequate description of the patient population, interventions, and outcomes measured; **Class III**: uncontrolled case series.	Narrative	According to the authors, one small randomized controlled trial (Class I) and one observational study (Class III) provide evidence of the direct effects of compensatory cognitive devices (notebooks, wristwatch alarms, programmed reminder devices) on the reduction of everyday memory failures for people with TBI. A second randomized controlled trial (Class II) provides evidence that compensatory cognitive rehabilitation reduces anxiety and improves self-concept and interpersonal relationships for people with TBI. Further, two small randomized controlled trials (Class I) provide limited evidence that practice and computer-aided cognitive rehabilitation improve performance on laboratory-based measures of immediate recall. No studies evaluated the link between such cognitive tests and health outcomes, and the associations between performance on cognitive tests and employment in the literature were inconsistent. Overall, the authors concluded that no strong evidence exists for or against the effectiveness of CRT.

[a] The AAN uses the following definitions for the level of classification of evidence: Class I: Prospective randomized, controlled clinical trial with masked outcome assessment; Class II: Prospective matched group cohort study with masked outcome assessment; Class III: Case controlled trials (e.g., natural history controls or patients served as own controls); Class IV: Uncontrolled trials, case series, case reports, and expert opinion.

[b] This review serves to update a previous review published by the same authors.(33)The overall conclusions in updated review are based on studies in both the previous and updated review. Thus, the previous review is not presented in the table.

[c] This is part of a larger evidence report published by the Agency of Healthcare Research and Quality (AHRQ) that provided a qualitative review of overall rehabilitation for TBI of which the efficacy of CRT was addressed in one question.(25)

APT Attention process training.
CT Controlled trial.
NR Not reported.
RCT Randomized controlled trial.

Table 53. Ongoing Clinical Trials

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Design	Purpose	Start Date	Expected Completion Date	Estimated Enrollment
NCT00627237	Mount Sinai School of Medicine and Centers for Disease Control and Prevention	Open label, placebo controlled RCT	The purpose of this study is to determine the efficacy of an intensive short term CRT program aimed towards improving executive functioning in individuals with TBI.	2008	2012	200
NCT00166348	Mayo Clinic	Open-label RCT	The purpose of this study is to determine whether there is benefit from providing CRT in a group setting.	2003	NR	20
NCT00714571	Department of Veterans Affairs and Emory University	Single blind RCT with active control group	This project intends to assess the efficacy of CRT in patients with TBI and other brain injuries that cause memory deficits, such as dementia. This study will also use neuroimaging (functional magnetic resonance imaging - fMRI) to assess changes in brain activity CRT.	2008	2013	60
NCT00927576	Department of Veterans Affairs	Open-label RCT	To evaluate the possibility to improve memory and attention in patients who have suffered TBI through the use of at-home computer training.	2009	2012	100
NCT00704067	Department of Defense	Single blind RCT with active control group	To investigate CRT “augmentation of supported employment to improve cognitive performance and work outcomes,” which are expected to result in improved quality of life and community integration for veterans with mild to moderate TBI.	2008	2011	64
NCT00715494	Vanderbilt University	Single blind RCT	The purpose of this study is to test the feasibility of a 12-week in-home (through face-to-face visits and tele-visits) intervention provided at the time of discharge from the hospital that incorporates cognitive, physical, and functional rehabilitation.	2008	2009	130

Clinicaltrials.gov Identifier or Other Identifier	Sponsor	Design	Purpose	Start Date	Expected Completion Date	Estimated Enrollment
NCT00676182	Department of Veterans Affairs	Open label, single group study	The purpose of this program is to meet the "rehabilitation needs of combat wounded veterans with mild to moderate [TBI] via telerehabilitation and determine the effect of this modality of care on patients' physical health and function and community participation."	2008	2010	60
NCT00233129	Mount Sinai School of Medicine	Single blind RCT with active control group	This study compares a standard day treatment program for individuals with TBI with the "Executive Plus" program. The latter "emphasizes training of attention, emotional self-regulation and problem solving."	2005	2009	200
ISRCTN92582254	Department of Health in the United Kingdom	Single blind RCT with active and placebo control group	The purpose of this study is to compare the effectiveness of two types of ceurocognitive rehabilitation for memory deficits for patients with acquired brain damage.	2005	2008	180

Appendix I. Names and Curricula Vitae of Those Involved in the Preparation of This Report

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