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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. 16

July 31, 2007

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.

July 31, 2007

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. 16
     Task Order No. 16
     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 Schoelles, M.D., S.M.
                         Medical Director

Enclosure

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

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Summary of Findings

Traumatic brain injury (TBI) is an acute injury to the brain caused by an external mechanical force. Immediately following a TBI, patients usually experience diminished or altered state of consciousness. 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 1.5 million Americans sustain a TBI. 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. While the risk of having TBI is substantial among all age groups, this risk is highest among adolescents, young adults, 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.

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 can be distinguished from traditional rehabilitation and psychotherapy by its primary focus—alleviation of acquired neurocognitive impairment and disability. Although CRT may incorporate interventions directed at the patient's emotional and psychosocial functioning when these issues relate directly to the acquired neurocognitive dysfunction, they are not the treatment's sole focus.

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

7) For persons with TBI, what are the reported harms/adverse events associated with CRT?

8) For persons with TBI, what is the consensus of experts regarding the efficacy and safety of CRT?

We based the answers to the first seven 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

Strength of Evidence Rating	Interpretation
Qualitative Conclusion (Direction of Effect)	
Strong Evidence	Evidence supporting the qualitative conclusion is convincing, making it highly unlikely that new evidence will lead to a change in this conclusion.
Moderate Evidence	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.
Weak Evidence	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.
Inconclusive	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 eight 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. The overall evidence base for this report consisted of seven studies, published in nine separate publications, enrolling a total of 237 patients. The overall quality of the studies included in the evidence base for this report was low to 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 (e.g., occupational therapy)?*

  > **For adults with moderate to severe TBI, it is unclear whether CRT for attention deficits is more effective than a sham treatment control condition for improving intermediate outcomes of attention or memory (i.e., scores on neuropsychological tests) due to inconclusive findings.**

  > **For adults with moderate to severe TBI, no conclusions could be drawn as to whether CRT for attention deficits is more effective than a sham treatment control condition for improving patient-oriented outcomes (e.g., functional status) due to an insufficient quantity of evidence.**

Three studies enrolling a total of 92 patients 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 (median score 7.2, range 7.1 to 7.2). 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 three separate meta-analyses: two for tests of attention and one for tests of memory. The estimated random-effects summary statistic for each of the three 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 (e.g., occupational therapy)?*

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

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 (e.g., occupational therapy)?*

> ➢ **For adults with moderate to severe TBI, no conclusions could be drawn as to whether CRT for memory deficits is more effective than no treatment or a sham treatment control for improving intermediate outcomes of memory due to an insufficient quantity of evidence.**

One study enrolling a total of 39 patients addressed this question. The results of this study were reported in two separate publications—Berg et al., (1991) reported outcomes at post-treatment and Milders et al. (1995) reported outcomes at four years followup.(1,2) Patients in this study were randomized to receive either memory strategy training (n = 17), a sham control condition (n = 11), or no treatment (n = 11). Several neuropsychological tests were to measure the effects of CRT on patients' memory skills. The quality assessment score was moderate for post-treatment (short-term outcomes) and low for long-term outcomes (6.4 to 6.8, respectively). The primary reason for the moderate quality of the study at post-treatment was lack of blinding of both the patients and outcome assessors. The quality score was lower for long-term outcomes because of substantial attrition at this time point.

Since only one study of moderate to low quality (depending on the length of followup) addressed Key Question 3, we drew no conclusion as to whether CRT for memory deficits is more effective than no treatment group or a sham treatment control condition.

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 (e.g., occupational therapy)?*

> ➢ **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 (e.g., occupational therapy)?*

> ➢ **For adults with moderate to severe TBI, no conclusions could be drawn as to whether CRT for disorders of executive function are more effective than standard care or a sham treatment control for improving executive function due to an insufficient quantity of evidence.**

Two studies enrolling 66 patients addressed this question. Cheng & Man (2006) randomized 21 patients with moderate TBI to receive either a new program developed by the authors to address impaired self-awareness called Awareness Intervention Program (AIP, n = 11) or to standard care (n = 10). In the second study, Neistadt (1991) randomized 45 adult males with moderate to severe TBI to receive either functional skills training in meal preparation (n = 23), or remedial training involving practice on a block assembly task (n = 22). Cheng and Mann measured the efficacy of AIP on deficits of self-awareness using the following patient-oriented measures: the Functional Independence Measure (FIM), the Lawton's Instrumental Activities of Daily Living Scale (IADL, Chinese version), and the Self-Awareness of Deficits Interview (SADI). The other study used neuropsychological tests to measure the effects of CRT. The

quality assessment score for the Cheng & Man study was 7.0 (moderate quality). The primary reason for the moderate quality of this study was that the authors reported that outcome assessors were blinded to the grouping of the patients, but did not report whether or not the patients themselves were blinded to treatment. The Neistadt study received a quality score of 6.6 (low quality). The reasons for the low quality of this study were differences among the patients in the study groups, lack of blinding of the outcome assessors, and not reporting whether patients were blinded to treatment.

Since both the treatment characteristics and reported outcomes differed considerably between the two studies, we did not attempt to combine the results of the studies. Further, the small size and moderate quality of each study precluded us from drawing any evidence-based conclusions regarding the efficacy of CRT for deficits of executive function. Results from the Cheng & Man study suggest that CRT directed toward deficits of self-awareness may have some benefit over traditional occupational therapy for patients experiencing problems of awareness. However, more studies assessing the efficacy of AIP are needed before any conclusions can be reached about the true benefit of this program.

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 (e.g., occupational therapy)?*

> ➢ **For adults with moderate to severe TBI, no conclusions could be drawn as to whether CRT used to treat multiple cognitive deficits is more effective in improving intermediate measures of cognitive functioning or patient-oriented outcomes than an alternative treatment focused on general activities due to an insufficient quantity of evidence.**

For this question, we considered studies in which CRT was intended to treat multiple cognitive deficits. One study reported in two separate publications that met our inclusion criteria addressed this question.(3,4) The two publications, Ruff and Niemann (1990) and Ruff et al., (1989), reported on different outcomes. In this study, 40 adults with severe TBI were randomized to receive either a cognitive remediation program (n = 20) 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 (n = 20). The quality assessment score for both publications was 6.9, indicating the study was of moderate quality for each outcome of interest. The primary reasons for the moderate quality ratings were lack of comparability of patients in the study groups and lack of blinding.

Since only one small study of moderate quality addressed Key Question 6, we drew no conclusions regarding the efficacy of multi-modal CRT (treatment addressing multiple cognitive deficits) for either intermediate or patient-oriented outcomes. However, individual study results indicated significant between-group differences in favor of the CRT group on the following neuropsychological tests: Rey's Visual Memory test and the Wisconsin Card Sorting test.

__Key Question 7__: 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 8__: 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

A sufficient number of studies addressed Key Question 1 for us to conduct quantitative analyses. All studies addressing this question compared CRT directed toward deficits of attention to a sham control condition. In all, we performed three separate random-effects meta-analyses—two of which included neuropsychological tests that measured attention skills and one that included tests of memory. However, the findings of our analyses of the effects of CRT directed toward remediating attention deficits were inconclusive, and no evidence-based conclusions could be drawn. The inconclusiveness of the results of our meta-analyses is most likely due to the small size of the evidence base (ie., the evidence base may be too small to have sufficient statistical power to identify a clinically significant effect). However, if our conclusions indicated a positive effect for attention-focused CRT, we could, at best, make only a general conclusion about its efficacy. This is because of the considerable differences that exist between the included studies, such as differences in patients' brain injury chronicity, treatment characteristics, and outcomes assessed. More studies with larger sample sizes would be needed to determine if treatment effects differed along patient or treatment characteristics (e.g., chronicity of injury, treatment tasks, duration of treatment) or outcomes assessed (intermediate versus patient-oriented).

Another possible reason for the lack of conclusiveness is that the sham control condition used in the studies had some kind of effect on the target problem (attention deficits). Individual study results indicated that both the treatment and control group demonstrated similar pre- to post-treatment performance on all the neuropsychological tests in all the 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.

For Key Question 2 through 6, the evidence base was of insufficient quality (median quality ranged from low to moderate) and quantity (less than three studies) to draw any evidence-based conclusions.

Preface

Organization of This Report

There are six major sections in this report: 1) *Overview*, 2) *Key Questions and Outcomes Assessed*, 3) *Methods*, 4) *Synthesis of Results*, 5) *Economic and Regulatory Issues*, 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.

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 synthesis 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.

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.

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 moderate to severe traumatic brain injury (TBI). The use of CRT to treat any other disorder, such as stroke or mild brain injury, is outside the scope of this report, as are any other methods of treating TBI. Further, this report does not consider intensive brain injury rehabilitation programs in which CRT may be delivered as part of a more comprehensive treatment approach that includes other rehabilitation services such as occupational therapy,

physical therapy, speech therapy, psychotherapy, and vocational therapy. However, we do consider studies in which CRT was used to address multiple cognitive deficits.

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)

Traumatic brain injury (TBI) is an acute injury to the brain caused by an external mechanical force. Immediately following a TBI, patients usually experience a diminished or altered state of consciousness. 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 1.5 million Americans sustain a TBI. 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.(5) While the risk of having TBI is substantial among all age groups, this risk is highest among adolescents, young adults, and persons older than 75 years. 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)

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.(6) 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.(7)

Underlying Mechanism of TBI

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.(8) 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. (8)

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.(8) 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.(9)

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.(10)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).(9) 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.(10)

Diagnosis

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).(11,12) 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.(13)

➢ PTA is defined as the length of time from the point of injury until the individual has a continuous memory for ongoing events.(14) 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).(15) 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. Evaluting 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.(12) 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.(12)

Course and Stages of Recovery

The course of recovery from moderate to severe 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.(8) In general, according to Bond, recovery from TBI occurs in three stages.(16) 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.(8) 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.(17)

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.(18) 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.(19)

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.(11,20,21) 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.(8) 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.(8)

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.(18) 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.(8)

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.(8) 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.(8) 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.(8) 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 results 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.

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.(8,27,28) Establishing a patient's preinjury background is necessary in order to properly interpret other examination data. For instance, it is important to be able to distinguish a low score on a neuropsychological test that is as good as the patient has ever done from a similarly low score when it represents a significant loss in premorbid performance level.(28) 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.(8,27)

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).(28) 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.(29) Further, tests may need to be modified to accommodate severely brain injured individuals or special patient populations, such as the elderly.(28)

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 reveal whether cognitive problems are exacerbated by depression, anxiety, or fatigue. Therefore, behavioral and functional assessments should be admininstered 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 can be distinguished from traditional rehabilitation and psychotherapy by its primary focus—alleviation of acquired neurocognitive impairment and disability.(33) Although CRT may incorporate interventions directed at the patient's emotional and psychosocial functioning when these issues relate directly to the acquired neurocognitive dysfunction, they are not the treatment's sole focus.

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).(8) 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.(8) 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 2 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.(8) 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.(27) 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 it is inappropriate to contrast these two approaches, 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.(27)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.

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.(17) 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 in-patient 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 out-patient 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 followup 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 website 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 in-patient or out-patient bases, 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 counselling, 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 website 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 16 private third party payers for coverage policies of CRT. Four of the 16 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 11 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 10 of Appendix B.

Key Questions and Outcomes Assessed

For this report, we addressed the following eight 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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

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 (e.g., occupational therapy)?

7) For persons with TBI, what are the reported harms/adverse events associated with cognitive rehabilitation?

8) 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 moderate to severe 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

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 B 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 B.

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:

➤ *All patients in a study must have cognitive deficits resulting from moderate to severe TBI, or, if not, results for them must have been reported separately.*
This report does not consider cognitive deficits resulting from a brain injury other than moderate to severe TBI. For instance, this report does not consider deficits resulting from stroke, mild TBI, or some other neurological condition (e.g., Alzheimer's disease).

➤ *Eighty-five percent (85%) of patients in a study were between the ages of 18 and 65 years of age, or, if not, results for them must have been reported separately.*
Patients younger than 18 were excluded from this report because differences in cognitive development between children, adolescents, and adults may impact the effects of rehabilitation.(25) Likewise, older adults were excluded from this report to minimize the

effects of age-related degenerative changes that may confound the cognitive sequelae of TBI.

➢ *For Key Question 1-7, 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 moderate to severe head trauma, especially within the first three to six months following the injury.(7) 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 it is likely that different arms of the study will 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.

➢ *Only outcomes within a study that had a score of 5.0 or greater on ECRI Institute's quality assessment scale (Appendix C) were included for data analysis.* Outcomes with scores of 4.9 or less are likely to be biased and cannot be considered as reliable sources of information. Because each outcome in a study is given a quality score, some outcomes within a study may fall below 5.0 and be excluded, while other outcomes may score better than 5.0 and be included. A study may be "included" in the report because it met the other inclusion criteria, and yet have all of its data excluded from analysis due to poor quality.

➢ *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 329 potentially relevant articles. The majority of these 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. Seven studies, published in nine different publications, met the inclusion criteria and addressed at least one Key Question. The studies, which are listed in Table 2, enrolled a total of 237 patients. Three studies addressed Key Question 1, zero studies addressed Key Question 2, one study addressed Key Question 3, zero studies addressed Key Question 4, two addressed Key Question 5, one study addressed Key Question 6, and zero studies addressed Key Question 7. The CRT program used in the study that addressed Key Question 6 was designed to target the following deficits: attention, memory, visuospatial integration, and executive function. The program consisted of four, two-week treatment modules, with each module focusing on a different cognitive deficit (e.g., attention, visuospatial, memory, and executive function). We did not consider this study to have addressed Key Questions 1 through 5, because the authors of the study measured outcomes prior to treatment and after all four modules were completed. They did not report outcomes after the completion of each module. Therefore, it is not possible to determine the independent effect of each module on the associated deficit the module was intended to address.

A total of 23 studies were excluded from consideration. The majority of these studies (k = 14) were excluded because they included patients with mixed etiology of TBI and did not report outcomes separately for patients with moderate to severe TBI. Table 9 in Appendix B lists the reasons for exclusion of all excluded studies.

Figure 2. Study Attrition Diagram

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                    ▼
              ◇ Publications ◇ ────────────▶ ┌──────────────────────────────────┐
                  reviewed                   │ 23  studies excluded [a]          │
                    │                        │                                   │
                    │                        │   14 Mixed etiology or severity   │
                    │                        │   1 Outcome  did not differ       │
                    │                        │   from training measure           │
                    │                        │   6 Less than 10 patients per     │
                    │                        │   treatment arm                   │
                    │                        │   1 Experimental group            │
                    │                        │   received multiple treatments,   │
                    ▼                        │   in addition  to  CRT.           │
┌─────────────────────────────────────┐     │   1 Did not use standardized       │
│ 7 studies published in nine different │     │   instrument to measure            │
│            publications               │     │   outcome of interest              │
└─────────────────────────────────────┘     └──────────────────────────────────┘
                    │
                    ▼
              ◇ Study quality ◇ ───────────▶ ┌──────────────────────────┐
                assessment [b]               │   0 Study excluded [a]     │
                    │                        └──────────────────────────┘
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┌─────────────────────────────────────┐
│   7 studies assessed in this report [c] │
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[a]   Table 9.   Excluded Randomized Controlled Trials
[b]   See Determining the Quality of Individual Studies in Appendix C on page 79
[c]   Table 2.   Key Questions Addressed by Included Studies

Table 2. Key Questions Addressed by Included Studies

Reference	Treatment	N Patients	Key Questions Addressed				
			Q1 Attention	Q3 Memory	Q5 Executive Function	Q6 Multi-modal
Cheng and Man 2006(22)	Awareness Intervention Program (AIP)	11			✓	
	Occupational Therapy	10				
Fasotti et al. 2000(54)	Time Pressure Management (TPM)	12	✓			
	Control	10				
Novack et al. 1996(55)	Structured Attention Training	22	✓			
	Control	22				
Milders et al. 1995(2) & Berg et al. 1991(1)	Cognitive Memory Strategies	17		✓		
	Control	11				
	No Treatment	11				
Neistadt, M. 1991(56)	Functional Constructional Training	23			✓	
	Remedial Control	22				
Neimann et al. 1990(57)	Attention Training	13	✓			
	Memory Control	13				
Ruff and Niemann 1990(3) & Ruff et al. 1989(4)	Structured Cognitive Rehabilitation	20				✓
	Control	20				
		237	3	1	2	1

Note: Milders et al. 1995(2) reports four year follow-up data for the same patient population in Berg et al. 1991. (1) Ruff and Niemann 1990(3) and Ruff et al. 1989(4) 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.

Note: Key Questions 2, 4, and 7 are not presented in the table because none of the included studies addressed these questions.

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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).(58) ECRI Institute's system employs 10 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 10 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 tools were 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 2.5. 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 3 below.

Table 3. Study Quality Categories

	Overall quality of evidence base		
	Low	**Moderate**	**High**
Median overall quality score of the evidence base	5.0 to <6.7	6.8 to <8.5	8.5 or higher

Data Synthesis

Whenever relevant data from three or more studies were available and could be combined, we summarized the results using meta-analysis. Meta-analysis allows the pooling of data from different studies to obtain an average estimate of the treatment effect. One of the advantages of an integrated analysis is that it will have more statistical power to detect a treatment effect than an analysis based on a single study. Meta-analysis also provides a means for formally identifying and exploring important differences among the results of different studies (heterogeneity).

The set of analytic techniques used in this report include random-effects meta-analysis and heterogeneity testing using the I^2 statistic. We used Hedges'g to calculate individual study effect size estimates and for all meta-analyses.[2] When performing a meta-analysis, we first tested the available data to determine whether the study results included in the meta-analysis differed from one another using the I^2 statistic (an $I^2 \geq 50\%$ indicates moderate inconsistency).(60,61) If the study results did not differ in this manner (i.e., the data were not very heterogeneous), we then pooled the study results in a random-effects meta-analysis to obtain a summary estimate.(61) If the study results did differ (i.e., the data were heterogeneous), then no single estimate can summarize the results. In such instances, a random-effects meta-analysis was performed for the purpose of reaching a qualitative conclusion about the direction of the effect.

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.(62) 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. The statistical approaches we used are described in more detail in Appendix C. 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 $g = \left(\dfrac{M_1 - M_2}{s} \right) * \left(1 - \dfrac{3}{(4*(N-2))-1} \right)$ where M_1 is the mean for one group, M_2 is the mean 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.(59)

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 (e.g., occupational therapy)?

> ➤ **For adults with moderate to severe TBI, it is unclear whether CRT for attention deficits is more effective than a sham treatment control condition for improving intermediate outcomes of attention or memory (i.e., scores on neuropsychological tests) due to inconclusive findings.**

> ➤ **For adults with moderate to severe TBI, no conclusions could be drawn as to whether CRT for attention deficits is more effective than a sham treatment control condition for improving patient-oriented outcomes (e.g., functional status) due to an insufficient quantity of evidence.**

Three studies enrolling a total of 92 patients addressed this question.(54,55,57) Each study assessed the effects of CRT to remediate deficits of attention, 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). The specific neuropsychological tests used in each of the studies are presented below in Table 4. 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.(55) This study used the Functional Independence Measure (FIM) to examine patients' functional recovery.(63) 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 score for the studies that addressed Key Question 1 was moderate (median score 7.2, range 7.1 to 7.2). Table 12 in Appendix D presents the quality assessment score for each study. Out of the three studies, only one study reported that the outcome assessor was blinded to treatment.(54) The other two studies did not report whether or not the assessor was blinded. And in all of the studies, the patients were either not blinded to treatment(54) or the authors of the study did not report that they were blinded.(55,57)

Table 4. Neuropsychological Tests Reported in Studies Addressing Key Question 1

Test and Associated Cognitive Function	Fasotti et al. 2000(54)	Novack et al. 1996(55)	Neimann et al. 1990(57)
Attention			
Attention Test d2(28) — Selective and sustained attention			✓
Digit Span(64) — Selective and immediate attention		✓	
Divided Attention(28) — Visual and auditory divided attention			✓
Paced Auditory Serial Addition Test (PASAT)(28) — Auditory selective and sustained attention; information processing	✓		✓
Ruff 2 & 7(65) — Selective and sustained attention			✓
Ruff-Light Trail Learning Test(65) — Selective and sustained attention			✓
Seashore Rhythm Test(28) — Selective and sustained attention			
Single/Choice Reaction Time(28) — Speed of information processing	✓	✓	
Trail Making Test(28) — Selective and sustain attention		✓	✓
Memory			
Benton Sentence Repetition Test(28) — Learning and recall of visual information		✓	
Buschke Selective Reminding Test(66) — Learning and recall of visual material			
Block Span Learning Test(28) — Learning and recall of visual material			✓
Rey's Auditory Verbal Learning Test (AVLT)(28) — Learning and recall of verbal material	✓		✓

Test and Associated Cognitive Function		Study		
		Fasotti et al. 2000(54)	Novack et al. 1996(55)	Neimann et al. 1990(57)
Rey's Visual Memory (RVT)(28)	Learning and recall of visual material			
Rivermead Behavioral Memory Test(67)	Everyday memory problems (e.g., remember an appointment)	✓		
Wechsler Memory Scale(64,68)	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 severe TBI.[3] Table 14 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).(55) 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.(54,57) 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.(55,57) 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.(54) 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

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[3] 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.

videotapes of situations they are likely to encounter in everyday life. Patients in the treatment 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. According to Hart (2007), a sham treatment control in the cognitive rehabilitation literature "is a control method that provides a treatment theoretically irrelevant to the target problem."(48) The sham treatment, sometimes referred to as an attention control, is meant to control for expectancy effects and the effects of common factors associated with professional contact and stimulation. 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.(54,55) In the Neimann (1990) study, patients in the control group received training on memory tasks instead of tasks specific to attention.(57) 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 15 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. However, according to Hart, there are several drawbacks to using a sham control. 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 and Meta-Analytic Results of Neuropsychological Tests

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 4).[4] Table 23 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 post-treatment.

All three studies reported post-treatment 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 post-treatment evaluation. Since the neuropsychological tests differed across the studies, we could only pool data for selected tests. In determining which tests to include in a meta-analysis, we first looked to see which tests were used in more than one study. We then considered which tests measured the same construct(s) (e.g., sustained and/or selected attention, long-term memory recall, or speed of

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[4] Since attention and memory are closely related, we present the results of these tests in Table 23, as they may be of value to readers. We also pool the results of selected memory tests in a random-effects meta-analysis to see if treatment directed toward attention has any carry-over effect on memory skills.

information processing). Tests that were used in more than one study were selected first, followed by tests that measured the same cognitive construct. In all, we performed three separate meta-analyses—two of which included neuropsychological tests that measured attention skills and one that included tests of memory.

Table 5. Meta-Analyses Models

Neuropsychological Tests of Attention	
Model 1	Paced Auditory Serial Addition (PASAT)(54) and ***Trail Making Test-B***(55,57)
Model 2	Choice Reaction Time(8,54) and Paced Auditory Serial Addition (PASAT)(57)
Neuropsychological Tests of Memory	
Model 3	Rey's Verbal Learning Test (RVLT)(54) and ***Logical Memory (WAIS)***(54,57)

Note: Tests are categorized based on the cognitive domain the authors of the studies indicated they intended to measure. References for all the tests presented in this table are provided in Table 4.

Note: Bolded and italicized text indicates tests that were used in more than one study

ECRI Institute's Conclusions

Heterogeneity testing indicated that the studies included in each meta-analysis were quantitatively consistent (I^2 was 0 for all three meta-analyses). However, the estimated random-effects summary statistic for each of the three 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 each meta-analysis are presented in Figure 7 through Figure 9 in Appendix G.

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, if our conclusions indicated a positive effect for attention-focused CRT, we could, at best, make only a general conclusion about its efficacy. This is because of the considerable differences that exist between the included studies, such as differences in patients' brain injury chronicity, treatment characteristics, and outcomes assessed. More studies with larger sample sizes would be needed to determine if treatment effects differed along patient or treatment characteristics or outcomes assessed.

Another possible reason for the lack of conclusiveness is that the sham control condition used in the three studies had some kind of effect on the target problem (attention deficits). 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.

Individual Study Results of Patient-Oriented Outcomes

Only one of the three studies that addressed Key Question 1 reported on a patient-oriented outcome—functional independence. Novack et al. (1996) randomized 44 adults with severe TBI to receive either 20, 30-minute sessions of focused attention remediation (n = 22) or 20, 30-minute sessions of an unstructured intervention (n = 22).(55) Patients in this study were in the acute phase of recovery (time since injury less than three months). Further details about the characteristics of the patients and the treatment conditions are presented in Table 14 and Table 15 of Appendix E. The quality assessment score for this study was moderate (quality score = 7.2). The primary reason for the moderate quality of this study was that the authors did not report whether or not the patients or outcome assessors were blinded to the treatment condition.

As previously mentioned, this study used the Functional Independence Measure (FIM) to examine patients' functional recovery.(63) The FIM primarily concentrates on measuring motor and self-care skills involved in activities of daily living (ADLs). Data for the FIM were only available for 24 of the 44 patients enrolled in the study (12 patients from each treatment group). Individual study results for this outcome are reported in Table 24 of Appendix F. According to the results reported by the authors of the study, there were no statistically significant pre to post-treatment differences on scores of the FIM for either treatment group. There were also no statistically significant between-group differences in scores at post-treatment.

ECRI Institute's Conclusions

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 (e.g., occupational therapy)?

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

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 (e.g., occupational therapy)?

> ➤ **For adults with moderate to severe TBI, no conclusion could be drawn as to whether CRT for memory deficits is more effective than no treatment or a sham treatment control condition for improving memory skills due to an insufficient quantity of evidence.**

A single study enrolling a total of 39 patients addressed this question. The study findings were reported in two separate publications, each presenting results at different follow-up times.(1,2) Berg et al. (1991) reported outcomes at post-treatment and Milders et al. (1995) reported

outcomes at four years followup.(1,2) Patients in this study were randomized to receive either memory strategy training (n = 17), a control condition (n = 11), or no treatment (n = 11).

The results of our assessment of the quality of the two publications that addressed Key Question 3 can be found in Table 12 of Appendix D. Although this is basically a single study reported in two articles, the quality of each publication had to be rated separately because the results from each were recorded at different times. The Berg et al. article received a quality score of 6.8, which indicates that the short-term part of the study was of moderate quality.(1) The primary reason for the moderate quality rating was lack of blinding of both the patients and outcome assessors. The authors reported that patients in both the memory training and control group were informed of the experimental nature of the interventions they were receiving. The Milders et al. article received a quality score of 6.4, which indicates that the study was of low quality.(2) The primary reasons for the lower quality rating of the longer-term part of the study were high attrition combined with lack of blinding. Overall, 21% of the patients dropped out from post-treatment to the four-year followup (two patients dropped out of the memory training, three in the control group, and three in the no-treatment group).

Patient Baseline Characteristics of Included Studies

Overall, the average age of the patients in each of the treatment conditions was similar. The average age of the patients in the memory training group was 36 years old (range 10 to 58 years), 33 years old (range 18 to 57 years) in the control condition, and 35 years old (range 20 to 60) in the no-treatment group. The average years of education indicated that most patients in each of the treatment conditions had at least a high school education. Likewise, the average length of post trauma amnesia (PTA) was similar across the treatment groups (30 days for the memory group, 35 days for the control group, and 37 days in the no-treatment group). Finally, all the patients were in the later stages of recovery. Chronicity of the patients' brain injury at the time CRT was initiated ranged from 63.6 months to 81.6 months. Table 16 of Appendix E presents further information about the baseline characteristics of the patients.

Treatment Characteristics of Included Studies

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 expected to improve overall memory function. Internal memory aids included mnemonic strategies, such as associative imagery, and external aids included the use of memory notebooks or diaries. 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. In both groups, patients received a total of 18 hours of training. Further information about the characteristics of the treatment and control condition of the studies are presented in Table 17 of Appendix E.

Individual Study Results of Neuropsychological Tests

The following neuropsychological tests were used to measure the effects of CRT on patients' memory skills: Rey's 15-word Verbal Memory Test, Face Naming, and Shopping List. These tests are described in detail in Lezak (1983).(28) Instead of reporting separate results for each neuropsychological test, Berg et al. and Milders et al. combined test scores to create an average composite score for each evaluation point (pretreatment, postreatment, and four-year followup). Individual study results are presented in Table 25 of Appendix F.

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.[5] 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 (p <0.05).(2) No between-group differences were observed in the four-year follow-up study. According to the authors of the follow-up study, posthoc analysis revealed that "75% of patients in the control group improved relative to the post-treatment evaluation, compared to only 20% in the memory group and 37.5% in the no treatment group."(2)

Individual Study Results of Patient-Oriented Outcomes

The authors of the four year follow-up study reported on patient employment status and patient-rated change in memory and work performance.(2) Patients were asked about whether or not they had participated in paid employment since their last evaluation at post-treatment. Twenty percent (20%) 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 26 of Appendix F.

ECRI Institute's Conclusions

Since only one study of moderate to low quality (depending on the length of the followup) addressed Key Question 3, we drew no conclusion as to whether CRT for memory deficits is more effective than no treatment or a sham treatment control.

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 (e.g., occupational therapy)?

> ➢ **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 moderate to severe TBI, no conclusions could be drawn as to whether CRT for disorders of executive function are more effective than standard care or a sham treatment control for improving executive function due to an insufficient quantity of evidence.**

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[5] The authors of both studies did not report data in a manner that allowed us to calculate an individual study effect size for the composite scores at post-treatment or four-year follow-up.

Two studies enrolling 66 patients addressed this question.(22,56) Cheng and Man (2006) randomized 21 patients with moderate TBI to receive either a new program developed by the authors to address impaired self-awareness called Awareness Intervention Program (AIP, n = 11) or to standard care (n = 10). In the second study, Neistadt (1991) randomized 45 adult males with moderate to severe TBI to receive either functional skills training in meal preparation (n = 23), or remedial training involving practice on a block assembly task (n = 22).(56)

The results of our assessment of the quality of the two studies that addressed Key Question 5 can be found in Table 12 of Appendix D. The median quality assessment score for both studies was moderate (6.8). The Cheng and Man study received a quality score of 7.0, which indicates that the study was of moderate quality. The primary reason for the moderate quality of this study was that the authors reported that outcome assessors were blinded to the grouping of the patients, but did not report whether or not the patients themselves were blinded to treatment. The Neistadt study received a quality score of 6.6, which indicates that the study was of low quality. The primary reasons for the low quality of this study were differences among the patients in the study groups (the authors reported that the treatment group was significantly younger than the control group), lack of blinding of the outcome assessors, and not reporting whether patients were blinded to treatment.

Patient Characteristics of Included Studies

The patients in the studies differed in terms of age and chronicity of brain injury. Patients in the Cheng and Man study were older than patients in the Neistadt study. The average age of patients in the Cheng and Man study was 56.5 years, and in the Neistadt study the average age was 33.2 years. 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 second study, the average length of time post injury for all patients enrolled in the study was 94.8 months. Patients in both studies were similar in terms of years of education. In both studies, the majority of patients had at least a high school education. Table 18 of Appendix E presents further information about the characteristics of the patients enrolled in these studies.

Treatment Characteristics of Included Studies

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. Further information about both the treatment and control conditions of this study is presented in Table 19 of Appendix E.

In the Neistadt study, patients in functional skills group were given training in the preparation of snacks and hot beverages.(56) 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. Further information about both the treatment and control conditions of this study are presented in Table 19 of Appendix E.

Outcomes and Individual Study Results of Included Studies

Table 27 and Table 28 in Appendix F presents the individual study results for the outcomes reported on in these studies. Neither of the studies that addressed Key Question 5 reported on similar outcomes. Cheng and Mann measured the efficacy of AIP on deficits of self-awareness using the following patient-oriented measures: the Functional Independence Measure (FIM), the Lawton's Instrumental Activities of Daily Living Scale (IADL, Chinese version), and the Self-Awareness of Deficits Interview (SADI). The FIM examines patients' functional recovery, and focuses primarily on measuring motor and self-care skills involved in activities of daily living (ADLs).(63) The IADL also measures patients' performance on ADLs.(69) The SADI is a standardized interviewer-scored structured interview that assesses patients' self-awareness in three areas: self-awareness of deficits, self-awareness of functional implications of deficits, and inability to set realistic goals.(23)

In this 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 than the standard care group on post-treatment scores of the SADI ($p = 0.001$).

The Neistadt study used the Block Design subtest of the Wechsler Adult Intelligence Scale (WAIS) to measure the effect of CRT on deficits of executive function.[6] A detailed description of this subtest can be found in Lezak (1983).(28) In general, the test is intended to measure various components of executive functioning, such as purposive behavior, self-regulation, and performance.

Individual study results indicated that patients in the functional skills group demonstrated significant pre- to post-treatment improvement in scores on the WAIS Block Design task ($p = 0.0183$). No statistically significant pre- to post-treatment differences were observed among

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[6] Neistadt also 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. We did consider data from the WAIS Block Design Test. We recognize that this test is similar to the practice condition given to the control group. However, each test uses different blocks and requires different responses.

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

Since both the treatment characteristics and reported outcomes differed considerably between the two studies, we did not attempt to combine the results of the studies. Further, the small size and moderate quality of each study precluded us from drawing any evidence-based conclusions regarding the efficacy of CRT for 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 (e.g., occupational therapy)?

> ➢ **For adults with moderate to severe TBI, no conclusions could be drawn as to whether CRT used to treat multiple cognitive deficits is more effective in improving intermediate measures of cognitive functioning or patient-oriented outcomes than an alternative treatment focused on general activities due to an insufficient quantity of evidence.**

For this question, we considered studies in which CRT was intended to treat multiple cognitive deficits. One study described in two separate publications that met our inclusion criteria addressed this question.(3,4) The two publications, Ruff and Niemann (1990) and Ruff et al. (1989), reported on different outcomes. In this study, 40 adults with severe TBI were randomized to receive either a cognitive remediation program (n = 20) 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 (n = 20).

Although this was one study, we performed a separate quality assessment for each publication because of the different outcomes reported in each. The results of our quality assessment can be found in Table 12 of Appendix D. The median quality assessment score for both publications was 6.9, indicating that both were of moderate quality. The primary reasons for the moderate quality ratings were lack of comparability of patients in the study groups and lack of blinding. 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). Further, while the patients were blinded to treatment, the therapists and outcome assessors were not blinded. The authors reported that they used a single-blind, randomized experimental design.

Patient Characteristics of the Included Studies

Patients in both the CRT and control group were similar in age and in number of years of education. The average age of patients in the CRT group was 29.9 (SD ±9.9), and in the control group the average age was 31.7 (SD ±9.2). The average years of education in both groups

indicated that the majority of patients had some postsecondary education experience. The average amount of education for both groups was around 13 years. As previously mentioned, patients in the CRT group spent fewer days in a coma and fewer months between injury and treatment than patients in the control condition. The average number of days in a coma for the CRT group was 32.1 (SD ±21.4), and for the control group the average was 48.8 (SD ±26.4). The average length of post-injury time for patients in the CRT group was 38.1 (SD ±23.9) months, and 52.4 (SD ±19.5) months for patients in the control condition. Table 20 of Appendix E presents further information about the characteristics of the patients enrolled in these studies.

Treatment Characteristics of Included Studies

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. 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. Detailed information about the nature of the treatment given in each module of the CRT program is presented below, along with further information about the activities provided to the control group. Additional information about the treatment setting and providers can be found in Table 22 of Appendix E.

Attention Module

In this module, patients used specially developed computer programs that promoted focused, selective, alternating, and sustained attention using auditory and visual modalities. Patients were taught and practiced various attention-training strategies to assist them in selecting and focusing on relevant stimuli and to increase speed of information processing. Methods of visual search and scanning were emphasized, and because each patient received immediate feedback and a compilation of response variables, patients were able to monitor their own speed and accuracy. Improvements in performance were promoted by having each patient challenge their own best performance.

Visuospatial Module

The visuospatial module considered aspects of spatial relationships involving localization of specific stimuli in space relative to the patient's own position (i.e., personal space), as well as localization of two or more stimuli in space relative to each other (i.e., extrapersonal space). A computer program was developed to test and train audiospatial and visuospatial integration using a 5 X 5 array of lights and loudspeakers. In the first stage of training, patients were asked to identify the position of individual tones or lights among the larger array, using their own bodies as a central point of reference. In the second stage, patients were asked to identify a pattern of tones or lights in correct sequence, using the preceding stimulus as a point of reference. In addition, spatial integration was monitored by using commercial software and

remedial material that emphasized spatial relationships, size estimation, and figure-ground discrimination.

Memory Module

In this module, memory for verbal and visual information was retrained using strategies and techniques that aided the process of memory storage and retrieval. Emphasis was placed on assisting the patients to utilize cues and strategies that fit their own style and relative strengths and weaknesses. Training included development of internal mnemonic aids (e.g., imagery, chunking, and associations) and external aids (e.g., notebooks, schedules, and calendars). Computer programs were specifically designed to provide verbal and visual stimuli to which mnemonic methods could be applied.

Problem Solving Module

In the problem solving module, patients were taught the following four step process for problem solving: 1) label the problem, 2) brainstorm alternative plans, 3) choose and implement on plan, and 4) evaluate the outcome. This procedure was taught using the mnemonic "LACE" (Label, Alternative, Choose, and Evaluate). Once subjects learned the steps, they were presented with hypothetical situations (e.g., prepare a meal, throw a party), and were asked to apply the problem solving steps. This module also included commercial software designed to promote sequential logic and strategic thinking, allowing patients to directly apply the process they learned.

Control Treatment

Patients in the control condition received treatment that emphasized psychosocial adjustment, leisure, and activities of daily living. Each daily session focused on one of the six following areas: computer and video games (e.g., chess, poker); coping and relaxation training; health; discussion of issues related to family relations, employment, etc; independent living; and art.

Outcomes and Individual Study Results of Included Studies

Ruff et al. (1989) 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.(4) The individual tests included in the battery and the associated areas of cognitive functioning the tests are designed to measure are presented below in Table 6. See Lezak for a complete description of each tests included in the battery.(28) 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. Ruff and Niemann (1990) measured the effect of the CRT program on a patient-oriented outcome—psychosocial functioning.(3) Psychosocial functioning was measured using the Katz Adjustment Scale (KAS). The KAS is a widely used instrument designed to measure psychological adjustment along the following areas: social aggressiveness, acute psychopathology, and depression.(70)

Table 6. Neuropsychological Tests and Associated Cognitive Function

Cognitive Function	Tests
Attention	Digit Span Forward, Digit Symbol, Digits Total, Block Span, Letter Span, Ruff 2 & 7 Selective Attention test, Seashore Rhythm test
Visuospatial	Benton Facial test, Picture Completion, Rey Complex Figure, Block Design
Memory	Wechsler Short Stories, Rey's Visual Memory, Bushke Long-Term Memory, Trails Learning
Problem Solving	Wisconsin Card Sorting, Figure Fluency
Global Intelligence	Wechsler Adult Intelligence Scale-Verbal IQ, Performance IQ, and Full Scale IQ

Individual study results for each neuropsychological test included in the Ruff et al. study are presented in Table 29 of Appendix F.(4) Below, we summarize the results of the neuropsychological tests according to the cognitive function they are designed to measure. We present the findings in this manner to help guide the reader. However, 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.

Attention

Patients in the CRT program demonstrated significant pre- to post-treatment improvement on the following tests: Digit Symbol ($p = 0.020$), Digits Total ($p = 0.003$), and Ruff 2 & 7 Selective Attention test ($p = 0.006$). No significant pre- to post-treatment differences were observed for the control condition. Further, no between-group differences were observed on any of the tests of attention at post-treatment.

Visuospatial

Significant pre- to post-treatment differences were observed for the control group on one of the tests measuring visuospatial skills. Patients in this group demonstrated significant improvement from pre- to post treatment on the Rey Complex Figure placement score ($p = 0.007$). 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

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 ($p = 0.009$ and 0.013, repectively). No other significant between-group differences were observed.

Problem Solving

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 (p = 0.002).

Overall Impact of Treatment on Cognitive Functioning

To measure the overall impact of treatment, Ruff et al. (1989) used the full Wechsler Adult Intelligence Scale (WAIS)(71), 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.[7](4) 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. Such findings, according to the authors of the study, 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.

Psychosocial Adjustment

Ruff and Niemann (1990)(3) reported on the psychosocial adjustment of a subgroup of patients (n = 24 overall, 12 in each group) included in the Ruff et al. (1989) study, using the Katz Adjustment Scale (KAS). As previously mentioned, the KAS instrument measures psychological adjustment along the following three areas: social aggressiveness, acute psychopathology, and depression. No significant pre- to post-treatment differences were observed for either the CRT or control group. Likewise, no between-group differences were observed on the KAS at post-treatment. Individual study results for the KAS are presented in Table 30 of Appendix F.

<u>*ECRI Institute's Conclusion*</u>

Since only one small study of moderate quality addressed Key Question 6, we drew no conclusions regarding the efficacy of multi-modal CRT (treatment addressing multiple cognitive deficits) for either intermediate or patient-oriented outcomes.

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[7] 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. 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 #8. 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)(72)

> European Federation of Neurological Society (EFNS, 2005)(73)

The NZGG published a comprehensive set of guidelines for the management of patients with TBI that included recommendations for diagnosising, 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)(74)

> The Society for Cognitive Rehabilitation (SCR, 2004)(30)

> The Academy of Neurologic Communication Disorders and Sciences (ANCDS, 2004)(75)

> National Academy of Neuropsychology (NAN, 2002)(76)

> British Society of Rehabilitation Medicine (BSRM, 1998)(77)

> The National Institute of Health (NIH, 1998)(75)

> 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 four previous systematic reviews that evaluated the efficacy of CRT. The reviews were all published between 1999 and 2006. In addition to CRT, the most recent review also included an evaluation of other forms of TBI rehabilitation, such as medical management and family interventions.(78) Table 7 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.

In general, ECRI Institute's review differed from the other previous reviews in terms of scope, study inclusion/exclusion criteria, assessment of the quality and strength of the evidence, and analytic methods employed. ECRI Institute's review was specific to CRT for the treatment of patients with moderate to severe TBI. Only one of the other reviews was specific to this patient population—Carney et al.(34) This review, which was published in 1999, focused on the use of restorative and compensatory strategies to enhance outcomes of persons with TBI. The review included non-randomized controlled trials and rated the quality and strength of the evidence using a class system in which randomized trials that blinded outcome assessors and reported follow-up data received the highest quality rating. Only three small studies received a high (Class I) quality rating. The authors of this review did not attempt to pool the results of these studies in a meta-analysis, and instead based their conclusions on a qualitative assessment of the study findings. However, because of the small size of the evidence base, the overall conclusion of this review was that no strong evidence exists for or against the use of CRT for patients with moderate to severe TBI. The remaining reviews included studies of mixed etiology, ranging from mild to severe TBI, stroke, and other neurological conditions. As a consequence, the findings of these reviews may not be generalizable to the more focused patient population addressed in the present review.

Table 7. 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
Gordon et al. 2006(78) *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)[a]	Qualitative	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(79)[b] *Cognitive Rehabilitation for Traumatic Brain Injury and Stroke: Updated Review of the Literature form 1998 through 2002 with Recommendations for Clinical Practice*	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)	Qualitative	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(80) *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.	Qualitative	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.

APT   Attention process training.
CT   Controlled trial.
RCT   Randomized controlled trial.

[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)

Conclusions and Discussion

This report examined the efficacy of cognitive rehabilitation therapy (CRT) in the treatment of adult patients with moderate to severe traumatic brain injury (TBI). The efficacy of CRT was addressed through six 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). 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 seven studies published in nine 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 in Table 8. The overall quality of the studies that made up the evidence base for this report was low to moderate. The primary reasons for the low to moderate quality of the studies were not blinding or not reporting that the patients or outcome assessors were blinded, lack of comparability between the study groups, and attrition.

A sufficient number of studies addressed Key Question 1, allowing us to conduct quantitative analyses. All studies addressing this question compared CRT directed toward deficits of attention to a sham control condition. In all, we performed three separate random-effects meta-analyses—two of which included neuropsychological tests that measured attention skills and one that included tests of memory. Heterogeneity testing indicated that the studies included in each meta-analysis were quantitatively consistent (I^2 was 0 for all three 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 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, if our conclusions indicated a positive effect for attention-focused CRT, we could, at best, make only a general conclusion about its efficacy. This is because of the considerable differences that exist between the included studies, such as differences in patients' brain injury chronicity, treatment characteristics, and outcomes assessed. More studies with larger sample sizes would be needed to determine if treatment effects differed along patient or treatment characteristics (e.g., chronicity of injury, treatment tasks, duration of treatment) or outcomes assessed (intermediate versus patient-oriented).

Another possible reason for the lack of conclusiveness is that the sham control condition used in the studies had some kind of effect on the target problem (attention deficits). Individual study results indicated that both the treatment and control group demonstrated similar pre- to post-

treatment performance on all the neuropsychological tests in the 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.

For Key Question 2 through 6, the evidence base was of insufficient quality (median quality, ranged from low to moderate) and quantity (less than three studies) to draw any evidence-based conclusions.

Table 8. Summary of Evidence-Base and Findings

Decision Point	Key Question 1: Attention Deficits	Key Question 2: Language and Communitaion Deficits	Key Question 3: Memory Deficits	Key Question 4: Visuospatial Deficits	Key Question 5: Executive Function Deficits	Key Question 6: Multi-Modal CRT
Number of included studies (number of patients)	3 (n = 92)	0	1 (n = 39)	0	2 (n = 66)	1 (n = 40)
Quality of evidence-base	Moderate	---	Low	---	Moderate	Moderate
Quantitative analysis allowed	Yes	---	No	---	No	No
Homogeneous meta-analysis (I^2 <50)	Yes	---	---	---	---	---
Potentially Informative	No	---	No	---	No	No
Conclusion	Inconclusive (Summary effect size estimate not statistically significant and 95% CI were too wide to rule out possible clinical significance)	No Conclusion Possible (Insufficient quantity of evidence)	No Conclusion Possible (Insufficient quantity of evidence)	No Conclusion Possible (Insufficient quantity of evidence)	No Conclusion Possible (Insufficient quantity of evidence)	No Conclusion Possible (Insufficient quantity of evidence)

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	1982 through April 5, 2007	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Inception through 2007, Issue 2	http://www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Inception through 2007, Issue 2	http://www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Inception through 2007, Issue 2	http://www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Inception through 2007, Issue 2	http://www.thecochranelibrary.com
ECRI Institute Library Catalog	Inception through May 4, 2007	ECRI Institute
Embase (Excerpta Medica)	1980 through April 5, 2007	OVID
Health Technology Assessment Database (HTA)	Inception through 2007, Issue 2	http://www.thecochranelibrary.com
Healthcare Standards	1975 through May 4, 2007	ECRI Institute
International Health Technology Assessment (IHTA)	Inception through September 7, 2006	ECRI Institute
MEDLINE	1966 through April 5, 2007	OVID
metaRegister of Controlled Trials (mRCT)	Searched May 7, 2007	http://www.controlled-trials.com/mrct/
PubMed (PREMEDLINE)	In Process[sb] Searched April 5, 2007	http://www.pubmed.gov
U.K. National Health Service Economic Evaluation Database (NHS EED)	Inception through 2007, Issue 2	http://www.thecochranelibrary.com
U.S. Centers for Medicare & Medicaid Services (CMS) Web site	Searched May 4, 2007	http://www.cms.gov
U.S. National Guideline Clearinghouse™ (NGC™)	Inception through April 19, 2007	http://www.ngc.gov

Reimbursement

The following Web sites were searched for reimbursement policies:

Aetna US Healthcare
(http://www.aetnaushc.com/cpb/cpb_alpha.html)

Blue Cross/Blue Shield of Alabama
(http://www.bcbsal.org/providers/policies/)

Blue Cross/Blue Shield of Massachusetts
(http://www.bcbsma.com/common/en_US/hresource/medcat.jsp)

Blue Cross/Blue Shield of North Carolina
(http://www.bcbsnc.com/services/medpolicy/)

Blue Cross/Blue Shield of Tennessee
(http://www.bcbst.com/providers/mpm.shtm)

Cigna
(http://www.cigna.com/health/provider/medical/procedural/coverage_positions/medical/index.
html)

CMS Coverage Issues Manuals
(http://new.cms.hhs.gov/Manuals/PBM/itemdetail.asp?filterType=none&filterByDID=-
99&sortByDID=1&sortOrder=ascending&itemID=CMS021321)

Health Partners
(http://www.healthpartners.com/policies/)

Humana
(https://providers.humana.com/ciinter/cihome.asp)

Medica
(http://provider.medica.com/C9/MedicalPolicies/default.aspx)

Regence Blue Cross/Blue Shield
(http://www.regence.com/trgmedpol/)

Wellmark Blue Cross/Blue Shield
(http://www.wellmark.com/e_business/provider/medical_policies/medical_policies.asp)

We also used the Google and Vivisimo internet search engines to locate reimbursement
information, using a combination of topic-specific keywords and the following search terms:
(reimburs* OR coverage OR "medical policy").

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.

Search Strategies

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, Medline, and PsycINFO. 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

adj   =   proximity operator (adjacency)

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

[tw]   =   Text word

<u>Topic-specific Search Terms</u>

Attention

exp attention/	concentration.de.
attention.de.	distract$
attention disturbance.de.	distractability.de.
attention$	distraction.de.
concentrate$	

Brain Injury

abi	post adj2 brain injur$
acquir$ adj2 brain injur$	tbi
exp acquired brain injury/	trauma$ adj2 brain injur$
exp brain injuries/	exp traumatic brain injury/
exp brain injury/	

Cognitive rehabilitation

Cognitive rehabilitation.de.	memory$ adj2 remediat$
Cognitive$ adj2 rehab$	memory$ adj2 train$
Cognitive$ adj2 remediat$	Memory training.de.
Cognitive$ adj2 train$	Neuropsych$ adj2 rehab$
Compensatory adj2 rehab$	Neuropsych$ adj2 remediat$
Compensatory adj2 remediat$	Neuropsych$ adj2 train$
Compensatory adj2 train$	Neuropsychological rehabilitation.de.
Cues.de.	Restorative adj2 rehab$
Learning strategies.de.	Restorative adj2 remediat$
memory$ adj2 rehab$	Restorative adj2 train$

Communication disorders

Apraxia$	exp communication disorders/
exp apraxias/	Dysprax$
Communication disorder$	Language disorder$

Executive Function

Awareness.de.

exp cognitive ability/

Cognitive adj2 function$

Executive adj2 function$

Intellectual adj2 function$

Metacognition.de.

exp metacognition/

Problem solving.de.

Memory

Forgetting.de.

exp memory/

Memory$.ti.

Memory disorders.de.

Recall learning.de.

exp retention/

Perception

exp perception/

Visuo-spatial

Visuospatial

exp visuospatial ability/

Rehabilitation

Rehab$

exp rehabilitation/

rehabilitation.fs.

Self-help devices

Assistive device$

Augmentative communication.de.

Keyboard$

Pager$

PDA$

Personal digital assistant$

exp self-help devices/

Typewriter$

Thought

Think$

exp thinking/

Thought$

exp thought disorder/

CINAHL/Embase/Medline/PsycINFO
English language, human

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/
2		((post or trauma$ or acquir$) adj2 brain injur$) or (tbi or abi).ti.)
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 (controlled vocabulary terms)	(cognitive rehabilitation or neuropsychological rehabilitation or memory training or learning strategies or cues).de.
6	Rehabilitation	Exp rehabilitation/ or rehab$.ti,ab,sh. or rh.fs.
7	Cognitive	((Cognitive$ or neuropsych$ or memory or compensatory or restorative) adj2 (remediat$ or rehab$ or train$))
8	Attention	(Exp attention/ or (attention or attention disturbance or distraction or concentration or distractibility).de. or (attention$ or distract$ or concentrat$).ti.)
9	Memory	(exp memory/ or exp retention or (Memory disorders or recall learning or forgetting).de. or memory$.ti.)
10	Communication disorders	(Exp communication disorders/ or exp communication disorder/ or exp apraxias/ or (apraxia$ or dyspraxia$ or language disorder$ or communication disorder$))
11	Thought	exp thought disorder/ or exp thinking/ or think$.ti. or thought$.ti.
12	Perception	Visuospatial or exp perception/ or exp visuospatial ability/ or visuo-spatial
13	Executive function	(exp metacognition/ or exp cognitive ability/ or (Problem solving or awareness or metacognition).de. or ((executive or cognitive or intellectual) adj2 function$).ti,ab.)
14	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$).ti,ab.
15	Combine sets (cognitive elements)	or/7-14
16	Combine sets (cognitive elements & rehabilitation)	6 and 15
17	Combine sets (cognitive rehab for TBI)	4 and (5 or 16)

Set Number	Concept	Search statement
18	Limit by study type	17 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$) and (dummy or blind or sham)) or latin square or ISRTCN) or randomized controlled trial.pt.
19	Limit by population	18 and (exp child/ or child$ or adolescent$ or teen$ or pediatr$ or paediatr$ or infan$ or juvenile)
20		19 and adult
21		20 not 19
22		18 not 21
23	Eliminate overlap	Remove duplicates

Table 9. Excluded Randomized Controlled Trials

Study	Primary Cognitive Deficit	Experimental Treatment	Reason for Exclusion
Dou et al. 2006(81)	Memory	Computer-assisted memory training	The authors indicated that patients had varying degrees of TBI severity, but did not indicate how many had moderate to severe TBI.
Man et al. 2006(82)	Executive functioning	Computer-assisted problem-solving training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI
Man et al. 2006(83)	Executive functioning	Computer-assisted problem-solving training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI
Hewitt et al. 2005(84)	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(85)	Executive functioning	Computer-assisted problem-solving training	Study had less than 10 subjects per treatment arm and included patients with mixed etiology without reporting outcomes separately for moderate to severe TBI.
Tam et al. 2003(86)	Memory	Computer-assisted memory training	Study had less than 10 subjects per treatment arm.
Rath et al. 2003(87)	Executive functioning	Group treatment of problem-solving deficits	Study included patients who experienced mixed TBI severity (mild to severe) without reporting outcomes separately for those with moderate to severe TBI.
Kaschel et al. 2002(88)	Memory	Imagery training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI

Study	Primary Cognitive Deficit	Experimental Treatment	Reason for Exclusion
Wilson et al. 2001(89)	Memory and executive functioning	Paging system	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI
Levine et al. 2000(90)	Executive functioning	Goal management training	Study included patients who experienced mixed TBI severity (mild to severe) without reporting outcomes separately for those with moderate to severe TBI.
Salazar et al. 2000(91)	Multiple deficits	Intensive inpatient cognitive behavioral program versus limited home intervention	Patients in the cognitive behavioral program received comprehensive treatment that included occupational therapy, speech language therapy, and psychotherapy in addition to group cognitive rehabilitation. This study does not provide evidence of CRTs effectiveness in isolation of other interventions.
Sohlberg et al. 2000(92)	Attention	Attention process training (ATP)	Study had less than 10 subjects per treatment arm and included patients with mixed etiology without reporting outcomes separately for moderate to severe TBI.
Watanabe et al. 1998(93)	Temporal orientation	Calenders in room	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI
Ownsworth and McFarland 1999(94)	Memory	Diary training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI
Kasten et al. 1998(95)	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 moderate to severe TBI

Study	Primary Cognitive Deficit	Experimental Treatment	Reason for Exclusion
Schmitter and Fahy 1995(96)	Memory	Notebook training	Study included less than 10 patients per treatment arm.
Thomas-Stonell et al. 1994(97)	Cognitive-communication	TEACHware™	Study included less than 10 patients per treatment arm and mostly adolescents.
Twum and Parente 1994(98)	Memory	Imagery versus verbal labelling to improve memory	Outcome measures did not differ from the training measures.
Ruff et al. 1992(99)	Attention and memory	THINKable™	Study included less than 10 patients per treatment arm.
Gray and Robertson 1992(100)	Attention	Computer-assisted attention retraining	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI
Ryan and Ruff 1988(101)	Memory	Various tasks designed to improve memory	Study included patients with mild to moderate TBI. While the study reported outcomes separately based on severity, there were less than 10 subjects per treatment arm with moderate TBI in each group.
Lincoln et al. 1985(102)	Visual processing	Visual perceptual training	Study included patients with brain damage due to mixed etiology without reporting outcomes separately for patients with moderate to severe TBI
Helffenstein and Wechsler 1982(103)	Cognitive-communication	Interpersonal process recall (IPR)	Study included less than 10 patients per treatment arm.

Appendix B. Coverage Policies

Table 10. Commercial Coverage Policies

Third Party Payer	Website	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.	05/02/06	0214

Third Party Payer	Website	Coverage Policy	Date of Last Review	Policy/ Bulletin Number
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.	12/2006	NR
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.	07/15/06	0124
WellChoice	http://www.wellchoicenj.com	Only covered in patients with significantly impaired cognitive function after TBI.	09/14/06	MED.00081

Third Party Payer	Website	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.	03/26/07	439
BlueCross/BlueShield of Minnesota	http://www.notes.bluecrossmn.com	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 North Carolina	http://www.bcbsnc.com	CRT not covered because it is thought to be investigational	08/2006	0TH8040
BlueCross/BlueShield of Tennessee	http://bcbst.com	CRT not covered because it is thought to be investigational	03/08/07	NR
Harvard Health Plan	http://www.harvardpilgrim.org	Does not have a specific coverage plan for CRT, and does not mention that it is covered under PT or OT.	NR	NR
Health Partners	http://www.healthpartners.com	Does not have a specific coverage plan for CRT, and does not mention that it is covered under PT or OT.	NR	NR
Humana	http://apps.humana.com	Does not have a specific coverage plan for CRT, but does cover speech and communication complications resulting from head injury.	04/26/07	NR
Independence BlueCross/BlueShield	http://medpolicy.ibx.com	Does not have a specific coverage plan for CRT, but does cover speech and communication complications resulting from head injury.	NR	10.06.01a

Third Party Payer	Website	Coverage Policy	Date of Last Review	Policy/ Bulletin Number
Premera BlueCross/BlueShield	https://www.premera.com	Does not have a specific coverage plan for CRT, and does not mention that it is covered under PT or OT.	NR	NR
Regence BlueCross/BlueShield	http://www.regence.com	CRT not covered because it is thought to be investigational.	08/08/06	20
Tufts Health Plan	http://www.tufts-health.com	CRT is not considered appropriate for short-term rehabilitation and is, therefore, not covered under physical therapy services.	NR	NR

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-five 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 employ stochastic randomization?

3. Were any methods other than randomization used to make the patients in the study's groups comparable?

4. Were patients assigned to groups based on factors other than patient or physician preference?

5. Were the characteristics of patients in the different study groups comparable at the time they were assigned to groups?

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. Was the comparison of interest prospectively planned?

8. Did ≥85% of the patients complete the study?

9. Was there a ≤15% difference in completion rates in the study's groups?

10. Were all of the study's groups concurrently treated?

11. Was compliance with treatment ≥85% in both of the study's groups?

12. Was there concealment of allocation?

Blinding

13. Were subjects blinded to the treatment they received?

14. Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?

15. Was the treating physician blinded to the groups to which the patients were assigned?

16. Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?

Measurement/Instrument

17. Was the outcome measure of interest objective and was it objectively measured?

18. Were the same laboratory tests, clinical findings, psychological instruments, etc., used to measure the outcomes in all of the study's groups?

19. Was the instrument used to measure the outcome standard?

20. Were the follow-up times in all of the study's relevant groups approximately equal?

Treatment

21. Was the same treatment given to all patients enrolled in the experimental group?

22. Was the same treatment given to all patients enrolled in the control group?

23. Were all of the study's groups treated at the same center?

Investigator Bias

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

25. Were the author's conclusions, as stated in the abstract or the article's discussion section, supported by the data presented in the article's results section?

Strength-of-Evidence System

To arrive at the strength-of-evidence categories, we applied the ECRI Institute Strength of Evidence system. This system involves 10 decision points. The methods we used to resolve these 10 decision points appear next.

Decision Point 1: Determining Quality of Individual Studies

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 2.5. Quality scores were converted to categories as shown in Table 11 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.

Decision Point 2: Determining Quality of Evidence Base

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.

To determine whether the evidence base was High, Moderate, or Low quality, we used the thresholds listed in Table 11. 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.

Table 11. Categorization of Quality

	Overall quality of evidence base		
	Low	**Moderate**	**High**
Median Overall quality score of the evidence base	5.0 to <6.7	6.8 to <8.5	8.5 or higher

Decision Point 3: Is There Sufficient Information to Perform a Quantitative Analysis?
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 (the only exception to this rule is if the evidence base has two high-quality studies that are potentially informative when combined in a meta-analysis). 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 8 to begin a qualitative analysis.

Decision Point 4: Are Data Quantitatively Consistent (Homogeneous)?
This decision point was used only if the answer to Decision Point 3 was Yes. Consistency refers to the extent to which the results of studies in an evidence base agree with each other.(104) The more consistent the evidence, the more precise a summary estimate of treatment effect derived from the evidence base. Quantitative consistency refers to consistency tested in a meta-analysis using the Higgins and Thompson's I^2 statistic.(60) We considered the evidence base to be quantitatively consistent when I^2 was ≤50%. If it was not homogeneous, we proceeded to Decision Points 6 and 7.

If the evidence base was quantitatively consistent (i.e., homogeneous), we combined the results in a random-effects meta-analysis (REMA). We then determined whether the summary effect size is informative or non-informative. The summary effect is considered informative if it meets any one of the following three criteria:

1) The summary effect is statistically significant.

2) If the minimum boundary of clinical significance is greater than 0, the 95% confidence intervals of the summary effect must exclude the possibility of a clinically significant effect. (In this report, clinical significance equals 0.2. So, the 95% confidence intervals surrounding the summary statistic should not overlap with -0.2 or +0.2 using Hedges' g).

3) If the summary effect is informative, we then test the stability of the findings in decision point 5.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?
Robustness was addressed by determining the stability of the summary estimate. A stable summary estimate indicates that the accumulated body of evidence is large enough to have accurately measured the "true" effect size. The stability of the summary estimates was tested using the following methods:

Test 1. Width of confidence intervals. If the 95% confidence interval around the meta-analytic effect size allow for an effect size that is greater than the summary effect size plus the minimal clinically significant effect size then the estimate is automatically considered not robust. Example: clinical significance in this report is defined as 0.2. The summary effect size is 0.4 (0.1 to 0.7). Clinical significance plus effect size is 0.6, which is exceeded by the confidence intervals; therefore the estimate is not robust. If the estimate passes this robustness test, proceed with the next test.

Test 2. Removal of one study. The summary estimate should not depend heavily on the inclusion of any particular study in the evidence base. To test this, we calculated the summary effect size plus/minus clinical significance. These two lines will represent the range of acceptable deviation from the summary effect size in the sensitivity analysis. Remove one study at a time (and only one study removed; for each new analysis, replace the previously removed study and remove a different study) from the meta-analysis and re-calculate the summary effect size without it. If the new effect size exceeds the bounds defined above, the estimate is not robust.

Test 3. Cumulative meta-analysis. Calculate the summary effect size plus/minus clinical significance. These two lines will represent the range of acceptable deviation from the summary effect size in the cumulative meta-analysis. Add studies into the meta-analysis sequentially in order of publication date, starting with the earliest study. If the new effect size exceeds the bounds defined above, the estimate is not robust. If any of the steps of the cumulative meta-analysis shows heterogeneity (I^2 greater than or equal to 50%), the estimate is not robust.

Decision Point 6: Exploration of Heterogeneity

If we observed heterogeneity, we next attempted (if there were five or more studies) to explain the heterogeneity using meta-regression. If there were fewer than five studies in this situation, we did not arrive at a quantitative estimate. A priori, we planned to use the following factors as predictor variables:

➢ CRT setting (inpatient/outpatient)

➢ Duration of CRT (measured in weeks)

➢ Time to intervention of CRT (measured in months)

➢ Intensity of CRT (measured in hours)

For meta-regression, we planned to perform random-effects meta-regression in Stata using the permutation test p-value, as described by Higgins and Thompson.(105) We decided that a meta-regression could be considered to have explained the heterogeneity if the covariate was statistically significant by the permutation test, and if the p-value for the remaining heterogeneity was greater than 0.1.

Decision Point 7: Is Meta-regression Model Stable?
The purpose of Decision Point 7 is to test the stability of any quantitative findings that may emanate from meta-regression analysis. We used the same robustness test as in Decision Point #5.

Decision Point 8: Are Qualitative Findings Robust?

The robustness of the qualitative findings is tested as described for Decision Point 5. We considered findings to be overturned only when the sensitivity test alters the conclusion (for example, a statistically significant finding becomes non-significant).

Decision Point 9: Are Data Qualitatively Consistent?
This Decision Point is used only when the evidence base for an outcome consists of two studies. For our purposes, the two studies were considered qualitatively consistent if they met either of the following two situations: 1) both studies showed a statistically significant effect in the same direction; or 2) neither study showed a statistically significant effect.

Decision Point 10: Is Magnitude of the Treatment Effect 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 very large effect with a narrow confidence interval, then new evidence is unlikely to overturn the qualitative conclusion. To resolve this decision point, we consulted 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 point estimate itself was 0.8 or greater, we considered the effect to be large. Otherwise, we considered it to be not large. For example, an estimate of 0.85 with an interval from +0.6 to +1.1 would be considered a large effect, whereas an estimate of 0.85 with an interval from +0.4 to +1.3 would not be considered a large effect. Another effect that would be considered large is an estimate of -0.85 with an interval from -1.1 to -0.6 (large in the negative direction). The use of 0.5 and 0.8 is based on Cohen,(62) who stated that an effect size of 0.5 was "moderate" and an effect size of 0.8 was "large". Thus, the decision rule required that the point estimate be large and also that it be statistically significantly larger than "moderate". The use of 0.5 and 0.8 applies to standardized mean difference or Hedges'g as the measure of effect size. For log odds ratio, Cohen's magnitude of effect size translates to the following: small = 0.4, moderate = 0.9, and large = 1.5. These correspond to approximate odds ratios of 1.5, 2.5, and 4.5, respectively.

Special Instructions: Meta-analysis of Two High Quality Trials

We perform a random-effects meta-analysis of two high-quality trials, as long as the studies do not have statistically significant effect sizes in opposite directions (qualitative inconsistency). The only other requirement is that both studies must have enough information to allow calculation of accurate effect sizes (no imputation is allowed when only two studies are available).

Other parts of the algorithm
Some parts of the algorithm are not formally called "Decision Points", and yet some decisions must be made in order to apply them. These are described next.

Sufficient Data for Meta-Regression?
We required a minimum of 5 studies before attempting meta-regression.

Mega-Trial?
We defined a mega-trial as any trial that reported data on 1,000 or more patients.

Meta-Analysis Possible?
For continuous outcomes, meta-analysis is possible when the pertinent studies either report effect sizes and standard errors, or there is sufficient reported information for both effect sizes and standard errors to be calculated. For dichotomous outcomes, meta-analysis is possible when the pertinent studies report the total number of patients in each group as well as the number of events in each group.

Abbreviations

FEMA – Fixed Effects Meta-Analysis
MR –Meta-regression
REMA – Random Effects Meta-Analysis

Figure 3. General Section of Strength-of-Evidence System

ENTER ALGORITHM

Decision Point 1
Acceptable Quality?

Yes

No

Decision Point 2
Quality of Evidence Base?

EXCLUDE STUDY

High Quality

Moderate Quality

Low Quality

Follow High Quality Arm

Follow Moderate Quality Arm

Follow Low Quality Arm
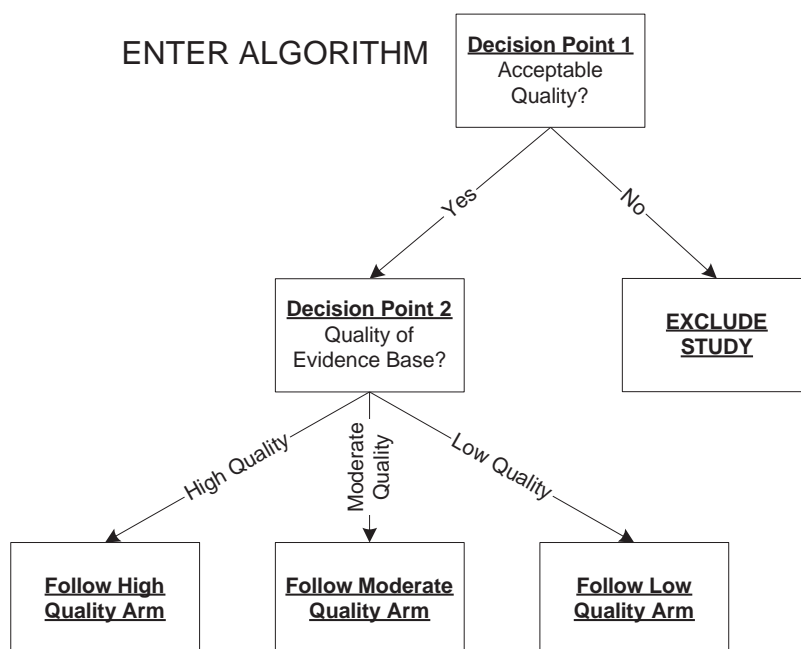
Figure 4. Highest Quality Pathway of Strength-of-Evidence System

Figure 5. Moderate Quality Pathway of Strength-of-Evidence System
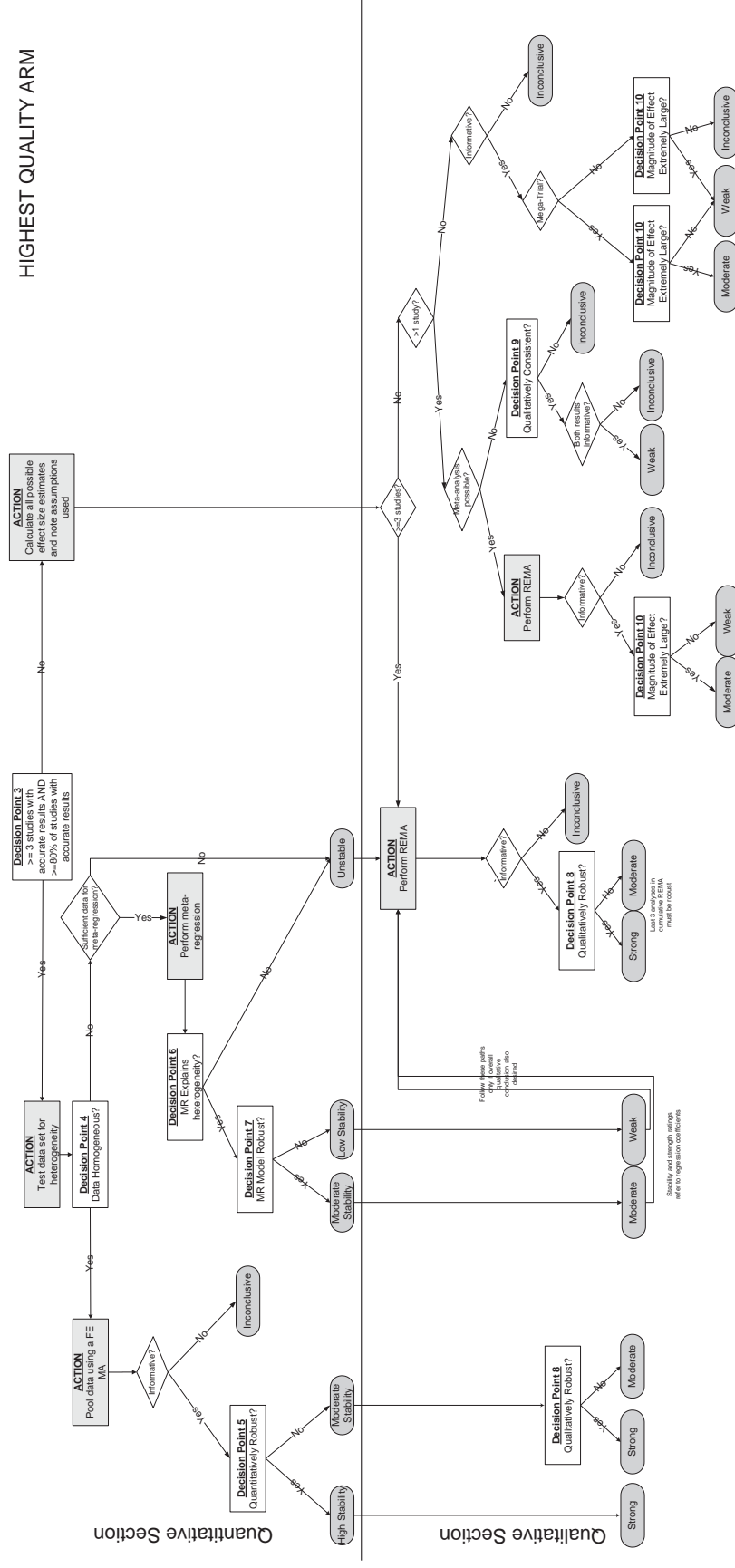
Figure 6. Lowest Quality Pathway of Strength-of-Evidence System
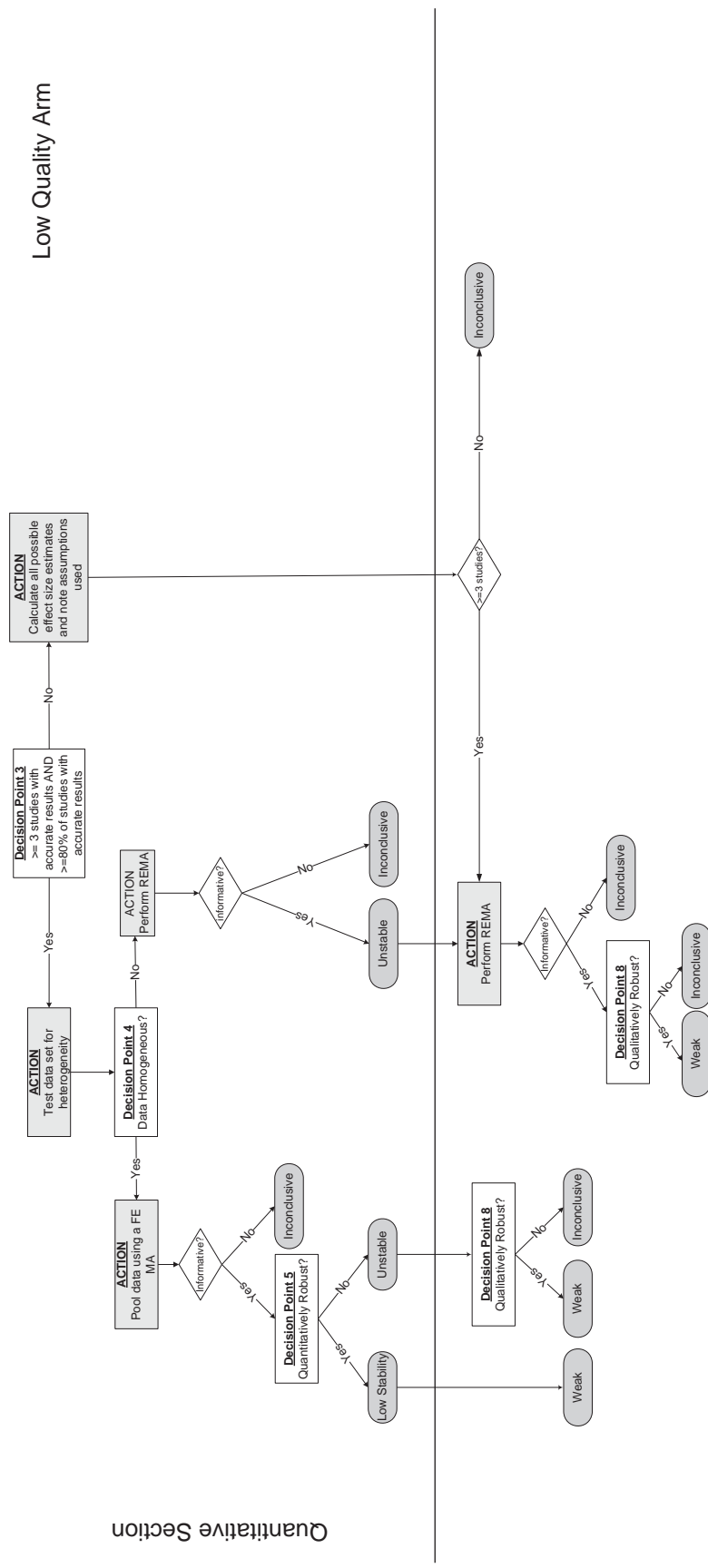
Appendix D. Quality Assessment Scores

Table 12. Quality Assessment of Included Studies by Outcome of Interest

Studies	Q1. Were pts randomly assigned to study groups?	Q2. Did the study employ stochastic randomization?	Q3. Were methods other than randomization used to make groups comparable?	Q4. Were pts assigned to groups based on factors other than pt or phy preference?	Q5. Were characteristics of pts in different groups comparable at assignment?	Q6. Did pts in different study groups have similar scores on all outcome measures at assignment?	Q7. Was comparison of interest prospectively planned?	Q8. Did ≥85% of the pts complete study?	Q9. Was there a ≤15% difference in completion rates in the study groups?	Q10. Were all of the study's groups concurrently treated?	Q11. Was compliance with treatment ≥85% in both groups?	Q12. Was there concealment of allocation?	Q13. Were subjects blinded?	Q14. Were tests performed to ensure blinding?	Q15. Was the treating phy blinded?	Q16. Were outcome assessors blinded?	Q17. Was the outcome objective and objectively measured?	Q18. Were the same instruments used to measure outcomes?	Q19. Was the instrument used to measure the outcome standard?	Q20. Were follow-up times of study groups equal?	Q21. Was the same tx given to exp group?	Q22. Was the same tx given to C group?	Q23. Were all study grps treated at the same center?	Q24. Was funding free of financial interest?	Q25. Were conclusions supported by data?	Overall Quality Score
Cognitive Outcomes (memory, attention, executive function, communication, visuospatial) As measured by Neuropsychological Tests																										
Fasotti et al. 2000(54)	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	7.2
Novack et al. 1996(55)	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	7.2
Milders et al. 1995(2)	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	NR	No	NR	No	NR	No	No	Yes	Yes	Yes	Yes	Yes	NR	Yes	6.4
Berg et al. 1991(1)	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	NR	Yes	6.8
Neistadt 1991(56)	Yes	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	6.6
Niemann et al. 1990(57)	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	No	NR	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	7.1
Ruff et al. 1989(4)	Yes	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NR	Yes	NR	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	6.9

Studies	Q1. Were pts randomly assigned to study groups?	Q2. Did the study employ stochastic randomization?	Q3. Were methods other than randomization used to make groups comparable?	Q4. Were pts assigned to groups based on factors other than pt or phy preference?	Q5. Were characteristics of pts in different groups comparable at assignment?	Q6. Did pts in different study groups have similar scores on all outcome measures at assignment?	Q7. Was comparison of interest prospectively planned?	Q8. Did ≥85% of the pts complete study?	Q9. Was there a ≤15% difference in completion rates in the study groups?	Q10. Were all of the study's groups concurrently treated?	Q11. Was compliance with treatment ≥85% in both groups?	Q12. Was there concealment of allocation?	Q13. Were subjects blinded?	Q14. Were tests performed to ensure blinding?	Q15. Was the treating phy blinded?	Q16. Were outcome assessors blinded?	Q17. Was the outcome objective and objectively measured?	Q18. Were the same instruments used to measure outcomes?	Q19. Was the instrument used to measure the outcome standard?	Q20. Were follow-up times of study groups equal?	Q21. Was the same tx given to exp group?	Q22. Was the same tx given to C group?	Q23. Were all study grps treated at the same center?	Q24. Was funding free of financial interest?	Q25. Were conclusions supported by data?	Overall Quality Score
Functional Independence																										
Novack et al. 1996(55)	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	No	NR	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	7.2
Cheng and Man 2006(22)	Yes	No	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	NR	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	7.0
Psychosocial/																										
Ruff and Niemann 1990(3)	Yes	NR	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	NR	Yes	NR	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	6.9
Self-Awareness																										
Cheng and Man 2006(22)	Yes	No	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	NR	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	7.0

Appendix E. Patient and Treatment Characteristic Tables

Table 13.   Patient Eligibility Criteria for Included Studies

Study	Inclusion criteria	Exclusion criteria
Cheng and 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
Fasotti et al. 2000(54)	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(55)	Patients had to have the ability to communicate in some fashion.	NR
Milders et al. 1995(2) & Berg et al. 1991(1)*	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 the age of 18 and 60 years.	NR
Neistadt 1991(56)	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
Niemann et al. 1990(57)	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

Study	Inclusion criteria	Exclusion criteria
Ruff and Niemann 1990(3) & Ruff et al. 1989(4)*	Patients had to 1) have been injured one to seven years prior to study randomization; 2) have medical documentation suggesting serious head injury; 3) have the expressive and receptive language ability necessary for interpersonal communication; have at least one functional hand and at least 25% or visual field intact; 4) be between the ages of 16 and 65 years; 5) be motivated and available to undergo 12 weeks of testing and treatment; and 6) have no premorbid neuropsychiatric disturbances.	NR

* Same patient population

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

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KEY QUESTION 1: CRT for Attention Deficits

Table 14. 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(54)	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(55)**	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(57)***	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.(57) 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)

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Table 15. 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 Followup	N at Followup
Fasotti et al. (2000)(54)	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

Study	Treatment Group	N	Provider and Setting	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Followup	N at Followup
	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
Novack et al. 1996(55)	Structured Attention Training	22	Master's degree level educator Study takes place in a rehabilitation center in the United States	Treatment was conceptionalized based on a hierarchy of attentional 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

Study	Treatment Group	N	Provider and Setting	Description of Cognitive Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Followup	N at Followup
	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 Followup	N at Followup
Niemann et al. 1990(57)	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 3: CRT for Memory Deficits

Table 16. 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(2) & Berg et al. 1991(1)*	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

* Same patient population. Milders et al.(2) 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.

NR   Not reported.

Table 17. 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 Followup	N at Followup
Milders et al. 1995(2) & Berg et al. 1991(1)*	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 Followup	N at Followup
	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

*Same patient population. Milders et al.(2) reports 4-year follow-up data.

NR   Not reported.

KEY QUESTION 5: CRT for Executive Function Deficits

Table 18. 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
Neistadt 1991(56)	Functional	23	33.2 (9.1)	100	NR	11.2 (1.8)	NR	NR	NR	NR	94.8
	Remedial	22									

AIP   Awareness intervention program.
NR   Not reported.
SC   Standard care.

Table 19. 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 Followup	N at Followup
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
	Standard Care	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

Study	Treatment Group	N	Provider and Setting	Description of Treatment	Ancillary Treatment	Number and Time of Sessions	Duration of Treatment	Length of Followup	N at Followup
Neistadt 1991 (56)*	Functional	23	Master's level occupational therapists In-patient 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 In-patient 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.

KEY QUESTION 6: Multi-Modal CRT

Table 20. 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)
Ruff and Niemann 1990(3) & Ruff et al. 1989(4)*	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 21. 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(3) & Ruff et al. 1989(4)*	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 22. 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 Followup	N at Followup
Ruff and Niemann, 1990(3) & Ruff et al., 1989(4)*	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 Followup	N at Followup
	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.

Appendix F. Individual Study Results

Table 23. Key Question 1: Neuropsychological Tests of Attention and Memory

Study	Test	Cognitive Function	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value[a]	Post-Post Between Group Effect Size Estimate Hedges g (95% CI)[b]	P-value
Fosotti et al. 2000(54)	Rey's 15-Word (Acquisition)	Memory	TPM (12)	0.12 (1.18)	0.68 (1.32)	0.007	0.298 (-0.514 to 1.110)	0.472
			Control (10)	-0.08 (0.88)	0.32 (0.93)	NS		
	Rey's 15-Word (Recall)	Memory	TPM (12)	0.11 (0.96)	0.83 (1.25)	0.002	0.354 (-0.460 to 1.168))	0.394
			Control (10)	-0.02 (1.15)	0.41 (0.99)	NS		
	Riverhead Memory Test	Memory	TPM (12)	-0.03 (1.01)	0.22 (0.83)	NS	0.460 (-0.359 to 1.271)	0.271
			Control (10)	0.04 (1.09)	-0.15 (0.70)	NS		
	PASAT	Attention	TPM (12)	-0.07 (0.95)	0.75 (1.42)	0.025	0.169 (-0.640 to 0.977)	0.683
			Control (10)	-0.16 (1.02)	0.53 (1.02)	0.026		
	Simple Reaction Time	Attention	TPM (12)	-0.04 (0.78)	0.11 (2.13)	NS	-0.320 (-0.493 to 1.132)	0.441
			Control (10)	0.25 (1.23)	-0.46 (1.00)	NS		
	Choice Reaction Time	Attention	TPM (12)	0.04 (0.92)	-0.35 (1.12)	NS	0.177 (-0.632 to -0.986)	0.668
			Control (10)	0.14 (1.11)	-0.54 (0.91)	0.01		

Study	Test	Cognitive Function	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value[a]	Post-Post Between Group Effect Size Estimate Hedges g (95% CI)[b]	P-value
Novack et al. 1996(55)	Digit Span (total score)	Attention	Structured Attention Re-training (22)	9.5 (4.2)	12.7 (3.9)	<0.05	-0.423 (-1.010 to 0.164)	0.158
			Unstructured Control (22)	10.7 (4.6)	14.4 (4.0)	<0.05		
	Trail Making (A)	Attention	Structured Attention Re-training (22)	NR	80.2 (28.2)	---	-0.016 (-0.597 to 0.564)	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)	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)	<0.05	0.258 (-0.325 to 0.841)	0.386
			Unstructured Control (22)	1.2 (0.8)	0.7 (0.5)	<0.05		
	Choice Reaction Time	Attention	Structured Attention Re-training (22)	2.2 (2.3)	0.7 (0.3)	<0.05	0.207 (-0.375 to 0.789)	0.486
			Unstructured Control (22)	1.8 (2.7)	0.8 (0.6)	<0.05		
	Logical Memory (I)	Memory	Structured Attention Re-training (22)	NR	88.1 (17.3)	---	0.124 (-0.457 to 0.705)	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)	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)	0.745
			Unstructured Control (22)	NR	95.0 (17.9)	---		

Study	Test	Cognitive Function	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value[a]	Post-Post Between Group Effect Size Estimate Hedges g (95% CI)[b]	P-value
Neimann et al. 1990(57)	Attention d2	Attention	Attention Re-training (13)	241.00 (77.0)	279.60 (90.0)	NS	-0.362 (-1.113 to 0.389)	0.345
			Memory Control (13)	279.50 (78.7)	312.2 (84.4)	NS		
	PASAT	Attention	Attention Re-training (13)	25.70 (10.7)	31.6 (8.9)	NS	-0.300 (-1.049 to 0.449)	0.433
			Memory Control (13)	27.30 (10.0)	34.80 (11.6)	NS		
	Divided Attention Test	Attention	Attention Re-training (13)	19.0 (9.7)	25.0 (9.3)	NS	-0.060 (-0.805 to 0.685)	0.874
			Memory Control (13)	21.30 (7.7)	25.50 (6.6)	NS		
	Trail Making (B-only reported)	Attention	Attention Re-training (13)	0.97 (0.62)	1.42 (0.82)	p <0.015	0.227 (-0.520 to 0.974)	0.552
			Memory Control (13)	1.14 (0.43)	1.26 (0.51)	p <0.015		
	Rey's Verbal Learning Total	Memory	Attention Re-training (13)	36.50 (10.8)	39.10 (10.0)	NS	-0.336 (-1.086 to 0.414)	0.380
			Memory Control (13)	38.10 (10.5)	43.20 (13.4)	NS		
	Block Span Total	Memory	Attention Re-training (13)	22.20 (9.9)	27.60 (10.5)	NS	0.227 (-0.520 to 0.974)	0.551
			Memory Control (13)	23.60 (6.7)	25.40 (8.1)	NS		
	Ruff 2 & 7 Test	Attention	Attention Re-training (13)	-2.07 (1.11)	-2.09 (1.12)	NS	0.603 (-0.159 to 1.365)	0.121
			Memory Control (13)	-1.36 (1.21)	-1.42 (1.03)	NS		

Study	Cognitive Function	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value[a]	Post-Post Between Group Effect Size Estimate Hedges g (95% CI)[b]	P-value
	Memory	Logical Memory Total	Attention Re-training (13)	-1.01 (1.41)	-0.78 (1.29)	NS	0.036 (-0.708 to 0.781)	0.924
			Memory Control (13)	-1.33 (1.82)	-0.84 (1.86)	NS		
	Attention	Ruff-Light Trail Learning Test	Attention Re-training (13)	-1.72 (2.49)	-1.99 (2.23)	NS	0.053 (-0.681 to 0.798)	0.889
			Memory Control (13)	-2.23 (2.15)	-2.14 (3.15)	NS		

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] 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.

NR   Not reported.
NS   Not significant.

Table 24. Key Question 1: Patient-Oriented Outcomes

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value[a]	Post-Post Between-Group Effect Size Estimate Hedges' g (95% CI)[b]	P-value
Novack et al. 1996(55)[c]	FIM (ADLs)	Structured Attention Training (12)	28.3 (15.9)	57.6 (16.6)	NS	-0.256 (-1.031 to 0.520)	0.519
		Unstructured Control (12)	32.6 (16.3)	61.8 (15.1)	NS		
	FIM (cognition)	Structured Attention Training (12)	11.8 (1.3)	21.3 (7.3)	NS	-0.328 (-1.107 to 0.450)	0.408
		Unstructured Control (12)	11.2 (5.4)	23.8 (7.4)	NS		

Note: Higher scores indicate improved performance.

[a] Calculated by study authors
[b] All effect sizes calculated using Hedges g. A positive value indicates a better outcome for the primary CRT group.
[c] Data were only available for 24 out of 44 patients (12 in each treatment group)

FIM   Functional Independence Measure
NS   Not significant

Table 25. Key Question 3: Neuropsychological Tests of Memory

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value[a]	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI)[b]	P-value	Follow-up mean (sd)
Milders et al., 1995(2) & Berg et al., 1991(1)[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 (pg. 229) presented in Milders et al.(2) 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 followup.

NS   Not significant.
NR   Not reported.

Table 26. Key Question 3: Patient Ratings of Memory and Employment Status (Milders et al. 1995)

	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

Table 27. Key Question 5: Neuropsychological Tests of Executive Function

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value[a]	Post-Post Between Group Effect Size Estimate Hedges g (95% CI)[b]	P-value
Neistadt. 1991(56)	WAIS-R Block Design	Functional (23)	5.23 (2.76)	5.64 (3.20)	0.0182	0.192 (-0.384 to 0.767)	0.514
		Control (22)	5.44 (2.17)	6.17 (2.15)	0.1311		

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

[a] Calculated by study authors, unless indicated otherwise.
[b] All effect sizes calculated using Hedges g. A positive value indicates a better outcome for the primary CRT group.
[c] Pre to post significance levels calculated by ECRI Institute Institute using data reported by authors in Table 4 of Appendix B on page 35 of original article.(4)

NR   Not reported.
NS   Not significant.
WAIS-R Wechsler Adult Intelligence Scale-Revised.

Table 28. Key Question 5: Patient Oriented Outcomes of CRT for Deficits of Executive Function

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value	Post-Post Between Group Effect Size Estimate Hedges g (95% CI)[b]	P-value
Cheng & Mann 2006(22)[a]	SDAI	AIP (11)	5.5 (2.4)	0.7 (1)	0.003	1.548 (0.602 to 2.495)	0.001
		Control (10)	5.1 (2.5)	3.6 (3)	0.011		
	FIM (Total)	AIP (11)	67 (30.1)	104.8 (16.7)	0.003	0.254 (-0.572 to 1.80)	0.546
		Control (10)	75.3 (31.4)	100 (19.6)	0.005		
	FIM (Physical)	AIP (11)	44.5 (35.3)	74.6 (15.8)	0.005	0.228 (-0.587 to 1.063)	0.572
		Control (10)	49.5 (27.4)	70.3 (18.1)	0.008		
	FIM (Cognitive)	AIP (11)	22.6 (8.6)	29.8 (5.9)	0.005	0.021 (-0.801 to 0.843)	0.960
		Control (10)	25.8 (5.4)	29.7 (2.3)	0.027		
	IADL	AIP (11)	4.4 (6.6)	14.3 (8.8)	0.003	0.488 (-0.347 to 1.324)	0.252
		Control (10)	4.6 (6.8)	9.6 (9.7)	0.012		

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

[a] P-values calculated by authors of study using Wilcoxon Signal Test (within group).
[b] All the effect sizes calculated using Hedges g. A positive value indicates a better outcome for the primary CRT group.

FIM   Functional independence measure.(63)
LADL   Lawton adult daily living skills.(69)
SDAI   Self-awareness of deficits interview.(23)

Table 29. Key Question 6: Neuropsychological Tests of Multi-Modal CRT

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI)[a]	P-value
		Measures of Attention Skills					
Ruff et al. 1989(4)	Digit Span	Attention Training (20)	6.37 (1.36)	6.85 (1.14)	0.101	0.390 (-0.224 to 1.003)	0.213
		Control (20)	6.24 (1.24)	6.42 (1.02)	0.485		
	Digit Symbol	Attention Training (20)	4.6 (1.61)	5.7 (2.20)	0.020	0.229 (-0.381 to 0.839)	0.462
		Control (20)	5.0 (2.35)	5.1 (2.89)	0.867		
	Digits Total	Attention Training (20)	77.5 (18.8)	94.2 (24.8)	0.003	0.045 (-0.381 to 0.652)	0.885
		Control (20)	85.6 (35.6)	92.7 (39.1)	0.401		
	Seashore Rhythm Test	Attention Training (20)	24.6 (3.37)	24.4 (4.65)	0.830	0.057 (-0.550 to 0.665)	0.854
		Control (20)	23.7 (5.24)	24.1 (5.60)	0.742		
	Ruff 2 & 7	Attention Training (20)	79.0 (20.7)	94.1 (23.7)	0.006	0.191 (-0.418 to 0.800)	0.539
		Control (20)	84.4 (28.8)	88.7 (31.2)	0.525		
	Block Span	Memory Training (20)	5.50 (0.69)	5.85 (0.83)	0.053	0.114 (-0.494 to 0.722)	0.713
		Control (20)	5.44 (1.09)	5.74 (1.05)	0.219		
	Letter Span	Memory Training (20)	5.47 (0.92)	5.90 (1.37)	0.123	0.423 (-0.191 to 1.038)	0.177
		Control (20)	5.50 (0.76)	5.42 (0.77)	0.641		

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI)[a]	P-value
			Measures of Memory				
Ruff et al. 1989(4)	Logical Memory (Wechsler Short Stories-Immediate Recall)	Memory Training (20)	29.9 (12.2)	34.4 (14.7)	0.150	0.228 (-0.382 to 0.837)	0.464
		Control (20)	25.5 (12.0)	30.9 (15.4)	0.096		
	Logical Memory (Wechsler Short Stories-Delayed Recall)	Memory Training (20)	21.6 (12.4)	28.0 (15.)	0.050	0.098 (-0.510 to 0.706)	0.752
		Control (20)	19.1 (10.2)	26.5 (15.0)	0.020		
	Rey's Visual Memory (3 min-present)	Memory Training (20)	9.0 (3.94)	11.5 (4.37)	0.014	0.415 (-0.199 to 1.029)	0.185
		Control (20)	7.2 (3.66)	9.6 (4.60)	0.018		
	Rey's Visual Memory (3 min placement)	Memory Training (20)	1.6 (0.80)	1.4 (0.94)	0.328	0.846 (-0.211 to 1.482)	0.009
		Control (20)	1.8 (1.35)	2.7 (1.91)	0.027		
	Rey's Visual Memory (60 min-present)	Memory Training (20)	8.9 (4.10)	11.3 (4.46)	0.020	0.342 (-0.270 to 0.955)	0.412
		Control (20)	6.7 (4.38)	10.1 (4.62)	0.003		
	Rey's Visual Memory (60 min placement)	Memory Training (20)	1.6 (0.98)	1.5 (1.01)	0.654	0.806 (-0.173 to 1.439)	0.013
		Control (20)	2.0 (1.20)	2.7 (1.80)	0.060		
	Bushke Long-Term Memory	Memory Training (20)	82.9 (20.4)	92.5 (19.3)	0.041	0.512 (-0.105 to 1.130)	0.104
		Control (20)	83.7 (79.9)	79.9 (28.1)	0.540		
	Bushke Total	Memory Training (20)	32.1 (27.9)	43.6 (33.3)	0.108	0.041 (-0.566 to 0.649)	0.895
		Control (20)	38.8 (36.0)	42.1 (38.1)	0.691		
	Trails Total Errors	Memory Training (20)	52.6 (29.0)	47.4 (44.4)	0.203	0.209 (-0.400 to 0.819)	0.500
		Control (20)	61.6 (37.2)	56.3 (38.7)	0.534		

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI)[a]	P-value
	Measures of Visuospatial Skill						
Ruff et al. 1989(4)	Benton Facial	Visuospatial Training (20)	20.4 (3.72)	20.9 (3.57)	0.542	0.428 (-0.187 to 1.042)	0.173
		Control (20)	19.5 (3.28)	19.3 (3.76)	0.801		
	Picture Completion	Visuospatial Training (20)	8.4 (3.36)	9.7 (3.51)	0.102	0.377 (-0.236 to 0.990)	0.228
		Control (20)	7.7 (2.59)	8.4 (3.24)	0.298		
	Rey Complex Figure (Construction Present)	Visuospatial Training (20)	16.9 (2.8)	16.8 (3.59)	0.891	-0.035 (-0.642 to 0.573)	0.911
		Control (20)	14.1 (4.80)	16.9 (1.75)	0.007		
	Rey Complex Figure (Construction Placement)	Visuospatial Training (20)	0.7 (0.71)	0.8 (9.3)	0.960	0.175 (-0.434 to 0.784)	0.573
		Control (20)	1.3 (0.90)	2.0 (1.95)	0.076		
	Block Design	Visuospatial Training (20)	8.7 (2.25)	9.3 (2.08)	0.225	0.269 (-0.004 to 0.543)	0.191
		Control (20)	7.6 (2.37)	8.3 (2.67)	0.225		
	Measures of Problem Solving Skills						
Ruff et al. 1989(4)	Wisconsin Card Sorting (completed categories)	Problem Solving Training (20)	5.03 (1.04)	5.60 (1.05)	0.023	1.009 (0.362 to 1.655)	0.002
		Control (20)	4.42 (1.65)	4.79 (1.62)	0.318		
	Wisconsin Card Sorting (perseverations)	Problem Solving Training (20)	2.45 (3.07)	2.35 (3.03)	0.883	0.494 (-0.123 to 1.11)	0.117
		Control (20)	5.18 (7.34)	4.53 (7.18)	0.690		
	Figural Fluency (mean number of designs)	Problem Solving Training (20)	10.3 (2.86)	13.4 (4.16)	0.001	0.060 (-0.548 to 0.667)	0.096
		Control (20)	11.9 (4.55)	13.1 (5.59)	0.304		
	Figural Fluency (sum of perseverations)	Problem Solving Training (20)	13.2 (16.7)	11.5 (11.6)	0.609	0.666 (-0.304 to 1.028)	0.847
		Control (20)	22.1 (30.8)	21.5 (23.7)	0.923		

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value	Post-Post Between Group Effect Size Estimate Hedges' g (95% CI)[a]	P-value
		Measures of Global Intelligence					
Ruff et al. 1989(4)	Verbal IQ	CRT (20)	92.6 (12.0)	96.2 (12.7)	0.202	0.291 (-0.320 to 0.902)	0.350
		Control (20)	92.4 (11.1)	92.6 (11.5)	0.937		
	Performance IQ	CRT (20)	84.1 (13.5)	89.8 (14.2)	0.077	0.272 (-0.338 to 0.883)	0.382
		Control (20)	82.2 (11.5)	85.8 (14.6)	0.235		
	Full-Scale IQ	CRT (20)	87.8 (12.2)	92.9 (13.3)	0.086	0.244 (-0.365 to 0.854)	0.432
		Control (20)	86.8 (9.55)	89.8 (11.5)	0.217		

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 Institute using data reported by authors in Table 4 of Appendix B on page 35 of original article.(4)

NR   Not reported.
NS   Not significant.

Table 30. Key Question 6: Patient Oriented Outcomes of Multi-Modal CRT

Study	Test	Treatment Group (n)	Pre-Treatment mean (sd)	Post-Treatment mean (sd)	P-value	Post-Post Between Group Effect Size Estimate Hedges g (95% CI)[a]	P-value
Ruff & Niemann 1990(3)	Katz (Social Obstreperousness)	CRT (12)	58.8 (12.5)	62.8 (12.8)	NS	0.333 (-0.445 to 1.111)	0.402
		Control (12)	67.9 (14.9)	68.9 (21.5)	NS		
	Katz (Acute Psychoticism)	CRT (12)	15.8 (2.4)	16.0 (2.3)	NS	0.578 (-0.212 to 1.367)	0.152
		Control (12)	18.3 (4.5)	20.3 (9.9)	NS		
	Katz (Withdrawn Depression)	CRT (12)	17.9 (4.7)	17.7 (5.0)	NS	0.215 (-0.560 to 0.9901)	0.586
		Control (12)	19.4 (4.9)	18.7 (3.9)	NS		

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.
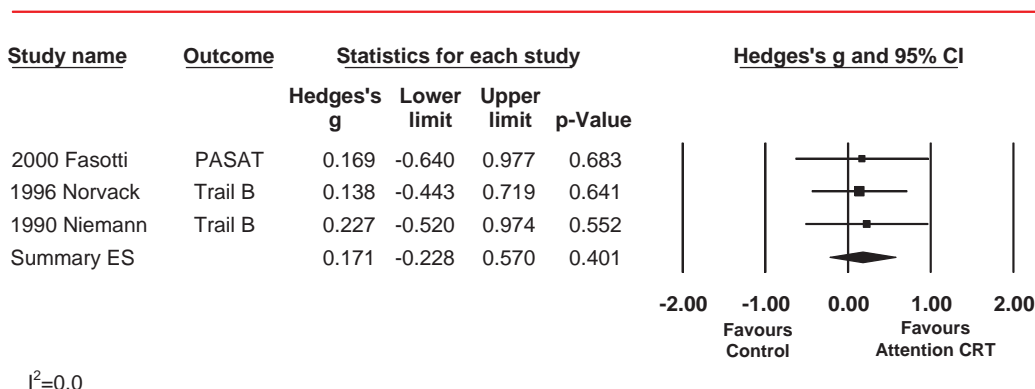
CRT   Cognitive rehabilitation therapy.
Katz   Katz adjustment scale(70)

Appendix G. Meta-Analytic Results

Figure 7. Key Question 1: Measures of Attention

Study name	Outcome	Statistics for each study				Hedges's g and 95% CI
		Hedges's g	Lower limit	Upper limit	p-Value	
2000 Fasotti	PASAT	0.169	-0.640	0.977	0.683	
1996 Norvack	Trail B	0.138	-0.443	0.719	0.641	
1990 Niemann	Trail B	0.227	-0.520	0.974	0.552	
Summary ES		0.171	-0.228	0.570	0.401	

$I^2 = 0.0$

Favours Control (-2.00, -1.00) — 0.00 — Favours Attention CRT (1.00, 2.00)

Note: A positive effect size estimate indicates a better outcome for the primary CRT group.

CRT   Cognitive rehabilitation therapy.

ES   Effect size.

Figure 8. Key Question 1: Measures of Attention

Study name	Outcome	Statistics for each study				Hedges's g and 95% CI
		Hedges's g	Lower limit	Upper limit	p-Value	
2000 Fasotti	Choice RT	-0.177	-0.986	0.632	0.668	
1996 Norvack	Choice RT	0.207	-0.375	0.789	0.486	
1990 Niemann	PASAT	-0.300	-1.049	0.449	0.433	
Summary ES		-0.031	-0.431	0.369	0.879	

$I^2 = 0.0$

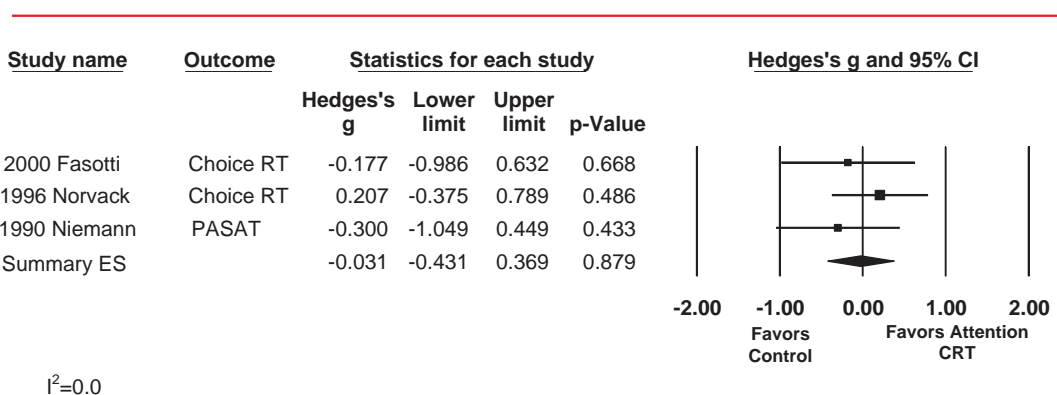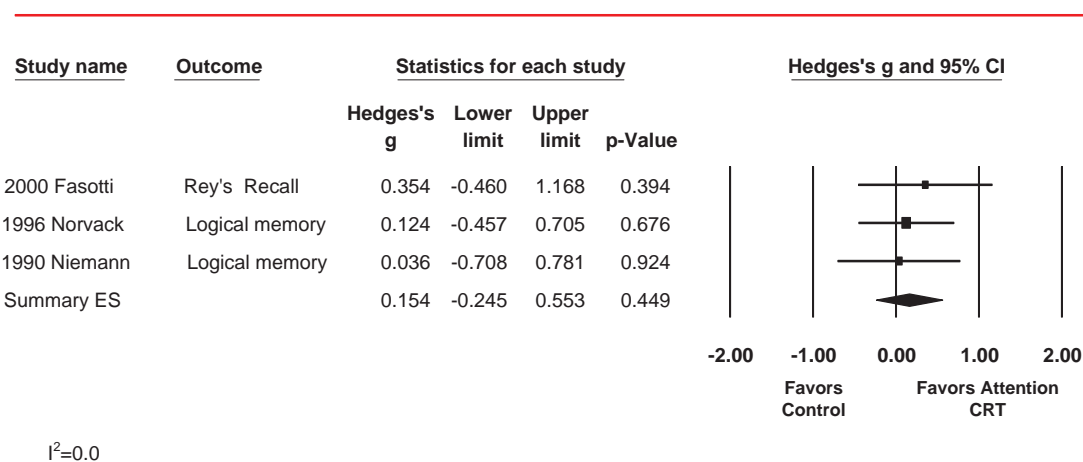Favors Control (-2.00, -1.00) — 0.00 — Favors Attention CRT (1.00, 2.00)

Note: A positive effect size estimate indicates a better outcome for the primary CRT group.

CRT   Cognitive rehabilitation therapy.

ES   Effect size.

Figure 9. Key Question 1: Measures of Memory

Study name	Outcome	Statistics for each study				Hedges's g and 95% CI
		Hedges's g	Lower limit	Upper limit	p-Value	
2000 Fasotti	Rey's Recall	0.354	-0.460	1.168	0.394	
1996 Norvack	Logical memory	0.124	-0.457	0.705	0.676	
1990 Niemann	Logical memory	0.036	-0.708	0.781	0.924	
Summary ES		0.154	-0.245	0.553	0.449	

-2.00   -1.00   0.00   1.00   2.00

Favors Control   **Favors Attention CRT**

I^2=0.0

Note: A positive effect size estimate indicates a better outcome for the primary CRT group.

CRT   Cognitive rehabilitation therapy.

ES   Effect size.

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

ECRI Institute Personnel

All ECRI Institute personnel involved in the preparation of this report may be contacted at:

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Karen Schoelles, M.D., S.M.
Medical Director

Karen Schoelles, M.D., S.M., EPC Medical Director, joined ECRI Institute in March 2005. Dr. Schoelles is responsible for assuring the clinical relevance of ECRI Institute's EPC projects and our Health Technology Assessment Group's work products. She also serves as our principal liaison with clinical reviewers.

Dr. Schoelles has over 20 years of clinical experience in internal medicine, with particular expertise in gerontology. Dr. Schoelles has a demonstrated track record of academic excellence and hands-on experience with evidence-based medicine, including systematic review methodology. A Clinical Instructor at Harvard Medical School for nine years, Dr. Schoelles has lectured extensively on geriatric assessment, preventive health measures in the elderly, and primary care of the older patient at Salem Hospital, Harvard Pilgrim Health Care, Brigham and Women's Hospital, Hebrew Rehabilitation Center for Aged (HRCA), Beth Israel Deaconess Medical Center (BIDMC), and Harvard Medical School Division on Aging. She participated in the development of a geriatric assessment tool for use by primary care physicians and developed a clinical program within which a model of geriatric care was developed and evaluated.

Dr. Schoelles has held professional and clinical positions at numerous hospitals and health care organizations in the Boston area. For seven years she was both the Associate Director of the Internal Medicine Residency Program and the Director of the Ambulatory Care Clinic at Salem Hospital. She subsequently entered private practice as a solo practitioner, caring for over 1,400 Medicare patients in their homes, in the office, in an acute care hospital, and in long-term care facilities. Dr. Schoelles later served as an Attending Physician at the Brigham and Women's Hospital and as a member of the Extended Care Facilities program for Harvard Pilgrim Health Care. She was a member of the BIDMC Division of Gerontology while she worked as Chief of Community Geriatrics Division at HRCA, with oversight of outpatient geriatric consultative and primary care clinics, the medical practice for a continuing care retirement community and a geriatric home visit program.

As Associate Medical Director at MetaWorks, Inc., Dr. Schoelles participated in systematic reviews and served as the principal investigator on numerous systematic review projects concerning topics such as bladder management following spinal cord injury, satisfaction with treatment among individuals with diabetes, and the efficacy and safety of certain

pharmaceuticals. In her current capacity as ECRI Institute EPC Medical Director, Dr. Schoelles is co-author of the evidence report The Role of Bone Growth Stimulating Devices and Orthobiologics in Healing Nonunion Fractures, a report requested by CMS for an October 2005 Medicare Coverage Advisory Committee (MCAC) meeting. Dr. Schoelles testified at the October 2005 MCAC, during which the Committee reviewed the scientific evidence on the effectiveness of various devices and orthobiologics used in treating nonunion fractures. In addition, Dr. Schoelles has overseen the development of the following evidence reports for ECRI Institute's EPC during her tenure: Cardiac Catheterization in Freestanding Clinics; Hip Replacement Surgery; and Non-Invasive Diagnostic Tests for Breast Abnormalities, a comparative effectiveness review mandated by Section 1013 of the Medicare Modernization Act.

Dr. Schoelles is certified in Internal Medicine by the American Board of Internal Medicine (ABIM) and in Home Care by the Institute for Clinical Evaluation of the ABIM. In 2005, Dr. Schoelles received a Master of Science in Health Policy and Management from the Harvard School of Public Health.

Stacey Uhl, M.S.S.
Lead Research Analyst

Ms. Uhl is responsible for writing and reviewing technology assessment reports for ECRI Institute's Health Technology Assessment Group. ECRI Institute provides research, design, development, review, analysis and education services to the VA/DoD Guideline Workgoup in support of their evidence-based Clinical Practice Guideline (CPG) development activities. Ms. Uhl worked as part of a team of ECRI Institute research analysts to provide the evidence-based research foundation for the VA/DoD CPG on Chronic Obstructive Pulmonary Disease, Bipolar Disorder, Depression, and Substance Abuse. She has also made significant contributions to a Comprehensive Evidence (Technology Assessment) Report on *Bulimia Nervosa: Efficacy of Available Treatment*. In addition, under ECRI Institute's Window of Medical Technology series, Ms. Uhl served as the primary research analyst on four reports: *Negative Pressure Wound Therapy for Chronic Wounds*, *Cochlear Implants for Individuals with Severe to Profound Hearing Loss, Inhaled Insulin for the Treatment of Type 1 Diabetes, and Eye Movement Desensitization and Reprocessing for the Treatment of Posttraumatic Stress Disorder.* She has also served as the primary analyst on two previous TRICARE reports titled *Hyperbaric Oxygen Therapy for the Treatment of Traumatic Brain Injury and Eye Movement Desensitization and Reprocessing for the Treatment of Posttraumatic Stress Disorder*.

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