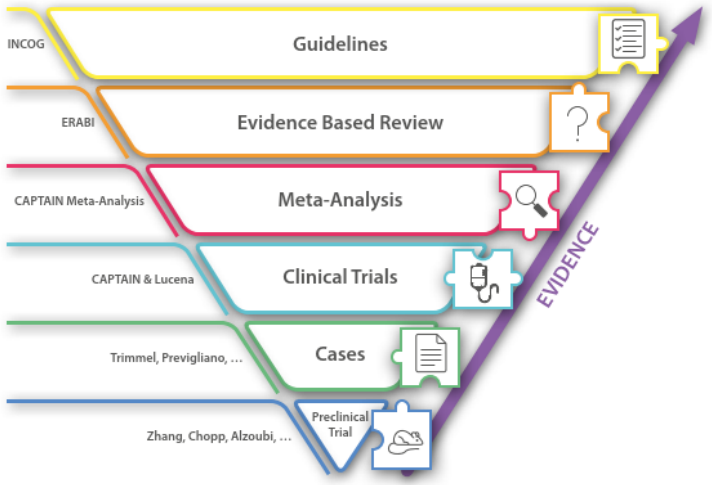

Meta-Analysis

Meta-Analysis

Brain Sci
. 2023 Mar 17;13(3):507. doi: 10.3390/brainsci13030507

Cerebrolysin in Patients with TBI: Systematic Review and Meta-Analysis

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Article notes
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Three studies were designed as blinded.

The intervention was administered to patients for 5–30 days, with a total study duration of up to 6 months.

In all studies, patients were given intravenously Cerebrolysin at a dosage of either 10 mL/day, 20 mL/day, 30 mL/day, or 50 mL/day IV.

Additionally, the treatment duration time was different in presented studies.

The time varied from 5 days (Chen et al.), 10 days (Muresanu et al., 2015), 20 days (Poon et al., Wong et al., Muresanu et al., 2020), and 20–30 days (Alvarez et al., 2003, Alvarez et al., 2008, Lucena et al., Khalil et al.).

The treatment administration varies from 24 h to >20 months.

Study Characteristics						Intervention	Comparator	Sample Characteristics			
Reference	**Country**	**Sponsorship**	**Blinding (Y/N)**	**Trial Duration (Days)**	**N Total Analyzed**	**Cerebrolysin Mean Dose/Day (mL); Duration**	**PBO or Other Intervention**	**Age (Mean)**	**N Male**	**% Male**	**Seizure (Y/N)**
Alvarez et al., 2008 [23]	Spain	industry	N	30 days	59	30 mL/day, 20 infusions over 4 weeks	NA	30.4	40	68	ND
Alvarez et al., 2003 [24]	Spain	industry	N	30 days	20	30 mL/day, 20 infusions over 4 weeks	Y	30.1	15	75	4
Chen et al., 2012 [25]	Taiwan	ND	Y	3 months	32	30 mL/day 5 days	PBO	44.8	21	66	0/32
Khalili et al., 2017 [20]	Iran	academia	N	6 months	129	10 mL/day 30 days	NA	33.3	109	85	Y
Lucena et al., 2022 [26]	Philippines	ND	N	28 days	87	30 mL/day Cerebrolysin for 14 days, 10 mL/day dosage for another 14 days	NA	34	73	84	ND
Poon et al., 2019 [27]	Hong Kong, Taiwan, Republic of Korea, Singapore, Philippines	industry	Y	30 days	40	50 mL of Cerebrolysin daily for 10 days, followed by two additional treatment cycles with 10 mL daily for 10 days	PBO	38.1	32	80	ND

Study Characteristics						Intervention	Comparator	Sample Characteristics			
Reference	**Country**	**Sponsorship**	**Blinding (Y/N)**	**Trial Duration (Days)**	**N Total Analyzed**	**Cerebrolysin Mean Dose/Day (mL); Duration**	**PBO or Other Intervention**	**Age (Mean)**	**N Male**	**% Male**	**Seizure (Y/N)**
Wong et al., 2005 [14]	China	ND	N	6 months	21	50 mL/day, 20 days	NA	64	13	62	ND
Ashgari et al., 2014 [21]	Iran	ND	N	1 month	53	10 mL/day, 10 days	NA	30	49	92	ND
Murescanu et al., 2015 [22]	Romania	ND	N	1 month	7693	20 mL/day, 10 days	NA	47	5415	70	ND
Murescanu et al., 2015a [22]	Romania	ND	N	1 month	6627	30 mL/day, 10 days	NA	47	5415	70	ND
Muresanu et al., 2020 [15]	Romania	ND	Y	3 months	139	50 mL/day for 10 days, two additional treatment cycles with 10 mL per day for 10 days)	PBO	47.4	123	88.5	ND

Treatment initiation time, initial GCS, TBI severity in Cerebrolysin and control groups

Reference	Treatment Initiation Time	Initial GCS	TBI Severity [n]		
			Mild	Moderate	Severe
Alvarez et al., 2008 [23]	23 months	5.5	4	3	32
Alvarez et al., 2003 [24]	23 and 1107 days	6.1	3	1	16
Chet et al., 2012 [25]	24 h	>14	32	0	0
Khalil et al., 2017 [20]	1 month	6.02	*0*	*0*	129
Lucena et al., 2022 [26]	<1 month	5.84	*0*	*0*	87
Poon et al., 2019 [27]	6 h	9.9	0	40	
Ashgari et al., 2014 [21]	48 h	6.75	0	0	53
Murescanu et al., 2015 [22]	48 h	12.72	5125	587	1227

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This meta-analysis compares the treatment result among the clinical studies found in Pub Med, Cinahl, Web Of Science, and Embase from database inception until 11th July 2022 describing the effect of Cerebrolysin on patients diagnosed with TBI.

The studies included both prospective randomized studies [15,25,27] and observational or historical cohorts [20,21,22,23,26].

In most of the analyzed studies, the authors point out the heterogeneity of the groups and the lack of consensus regarding the dose of the drug and the duration of its use [15,27].

Most studies have proven that Cerebrolysin has a positive treatment effect in TBI patients in terms of cognitive functions, GOS, and GCS, but does not alter the mortality rate or LOS [21,22,28,29].

The positive effect of Cerebrolysin has been proven in vitro (decrease in microglial activity, excitotoxicity, production of free radicals, increase in neuronal survival) and has also been demonstrated in vivo in animal studies, as well as in clinical studies

In particular, the role of modeling the immune response deserves attention. Acting through influencing the activity of GABA and cholinergic pathways, Cerebrolysin, affects the response to the primary injury and could have an influence on the secondary injury in the damaged brain.

It is worth noticing that Cerebrolysin could moderate the processes at all stages after the initial trauma because of its neuroprotective properties. That also means that it could be beneficial after introducing the treatment at every level after the initial TBI—in the first 24 h, but also after 20 months since the injury.

Data from comprehensive meta-analyses confirm Cerebrolysin‘s positive outcomes

CAPTAIN META-ANALYSIS Vester J.C. et al.

The Captain meta-analysis included 2 clinical trials (phase IIIb/IV prospective, randomized, double-blind, placebo-controlled).

Results shows benefits of a Cerebrolysin add-on therapy for moderate-severe TBI:

- Higher chance of survival
- The effective treatment after TBI
- Save lives
- Early recovery
- Better quality of life

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Vester, J. C., et al. “Cerebrolysin after moderate to severe traumatic brain injury: prospective meta-analysis of the CAPTAIN trial series.” Neurological Sciences (2021): 1-11.

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Vester, 2021 – Captain Meta-Analysis

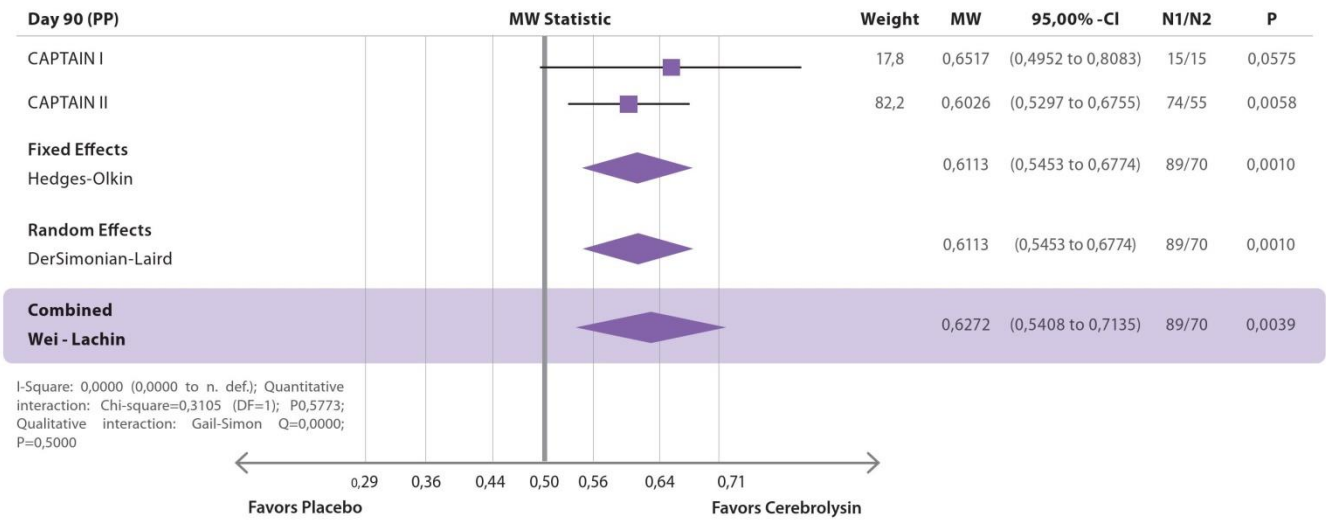

Figure: Confirmatory Multivariate Outcome Ensemble at Day 90, PP (Neurorecovery Phase)

Effective treatment after TBI

Cerebrolysin leads to

- improved functional and cognitive outcomes
- Faster reintegration into work and social live

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Vester, 2021 – Captain Meta-Analysis

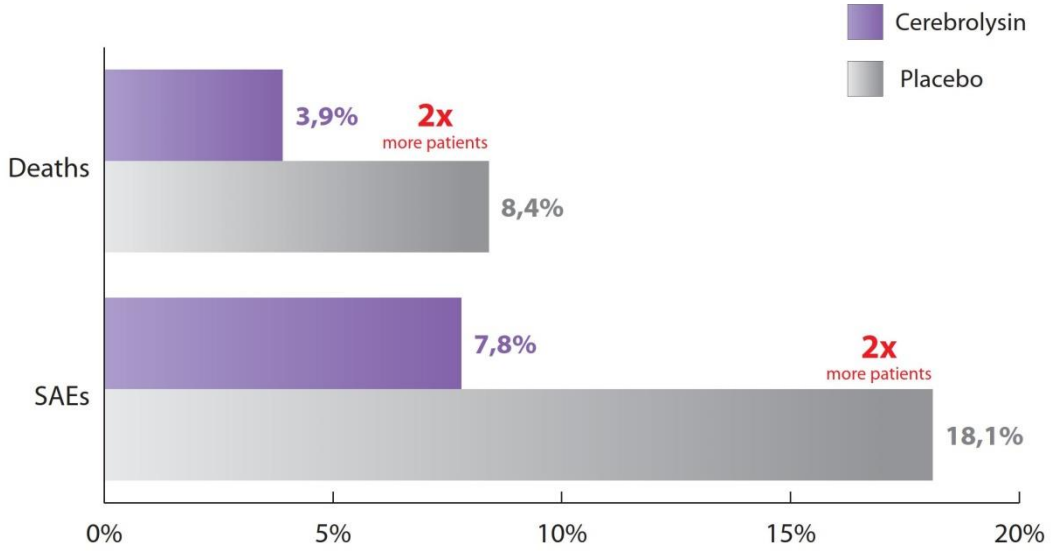

Figure: Safety Meta-Analyses

Cerebrolysin saves lives

- Higher chance of survival and lower rate of severe complications.
- Mortality in the Cerebrolysin group reduced by 50%.

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Vester, 2021 – Captain Meta-Analysis

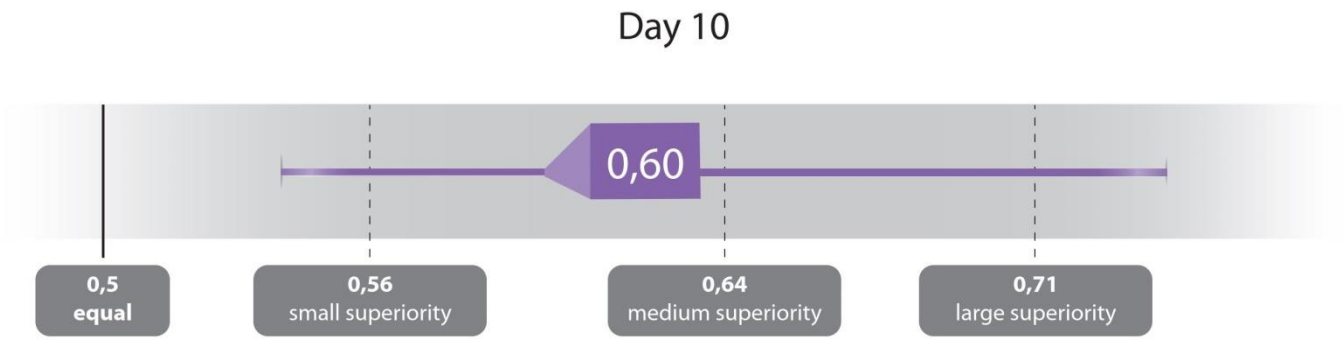


Figure: Confirmatory Multivariate Outcome Ensemble at Day 10, PP (Neuroprotection Phase) (Wert = 6,0)

Early recovery!

Cerebrolysin leads to higher probability of early discharge from hospital

Significant results already on day 10

Vester, 2021 – Captain Meta-Analysis

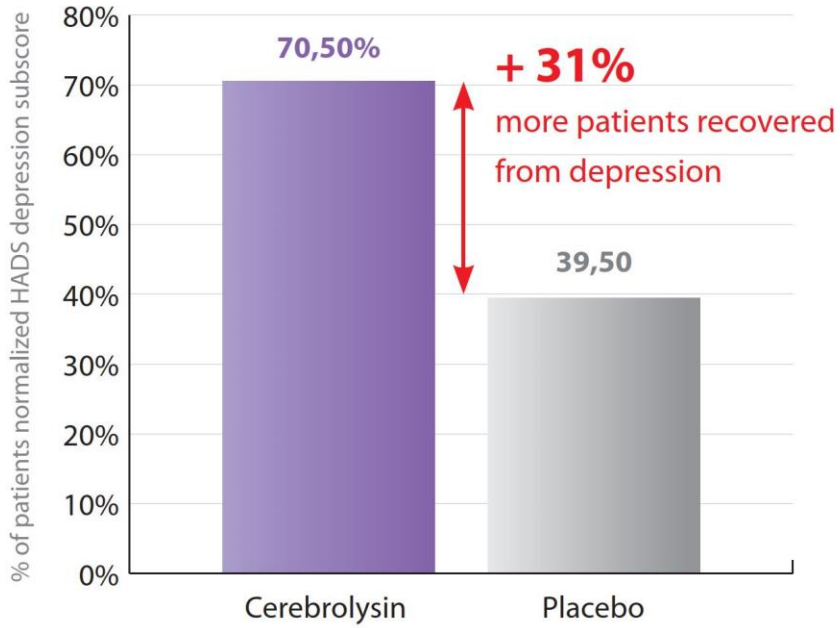
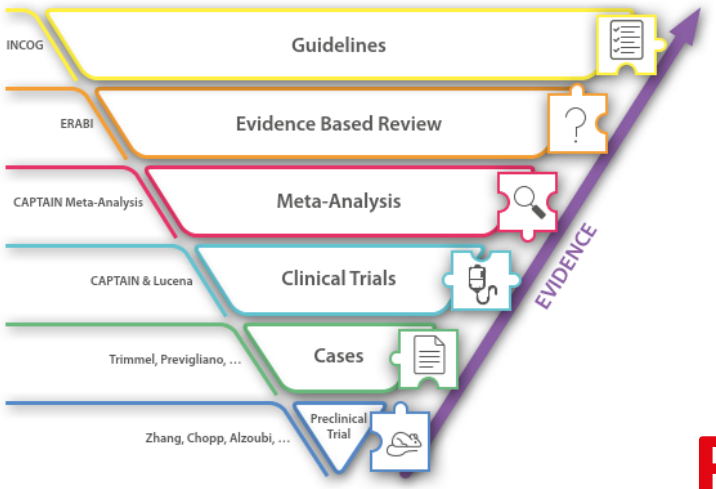


Figure: Normalization of the HADS score (Score 0-7) at Day 90

Better quality of life

- Cerebrolysin leads to a better quality of life by reducing the burden of depression after TBI
- 70,5% of Cerebrolysin patients recovered from depression after TBI and 31% more Cerebrolysin patients showed normalization in HADS depression score



Evidenced Based Review (ERABI)

Evidenced Based Review

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Efficacy and benefits confirmed by independent committees

Independent systematic reviews by leading experts confirm that Cerebrolysin is effective in improving attention deficits.

The review confirms that:

- Cerebrolysin improves attention
- Is the only evidenced based agent in brain trauma
- Cerebrolysin – is the recommended agent for attention improvement after TBI
- Takes care of the main consequences of TBI – attention and concentration deficits

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Levels of Evidence 1B Physiotherapy Evidence Database (PEDro) rating scale

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6
	Prospective Controlled Trial (PCT)	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post Trial	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

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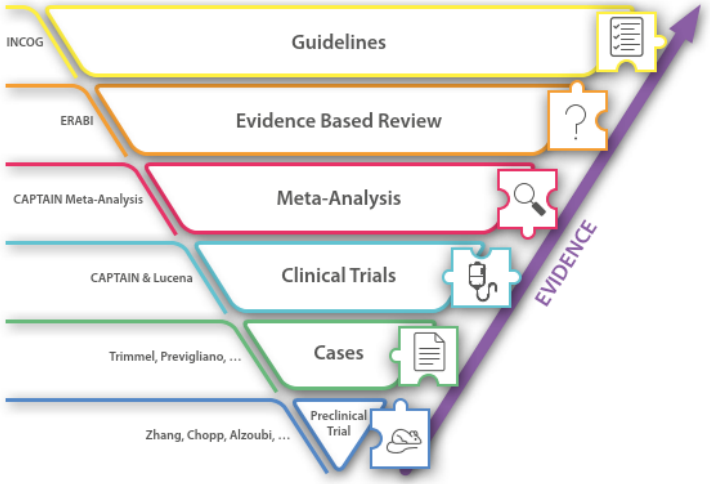
Guidelines for Cognitive Rehabilitation Following Traumatic Brain Injury, Part III: Executive Functions

Traumatic brain injury (TBI) is a leading cause of death and disability. Mild TBI (mTBI) is often unnoticed or misdiagnosed because of missing visible physical signs without obvious tissue lesions in the brain.

Although mTBI symptoms typically resolve within days to weeks, more than 15% of patients with mTBI have a measurable cognitive deficit at 1 year following an injury.

The pathologies underlying cognitive deficits after mTBI are poorly understood, and most clinical trials involve moderate to severe injury, neglecting efforts to treat mTBI.

The failure of clinical trials for TBI may, in part, be a result of heterogeneity of the population of TBI patients and variability in treatment approaches.



INCOG Guidelines

Guidelines

Another important aspect is that most strategies to date have used drugs in clinical trials targeting a single pathophysiological mechanism that contributes to early cell death.

Cerebrolysin is a neuropeptide preparation derived from purified brain proteins with both neuroprotective and neurotrophic properties that target multiple pathways to improve functional recovery after neurological diseases and injuries.

Cerebrolysin consists of amino acids (80%)

INCOG Guidelines

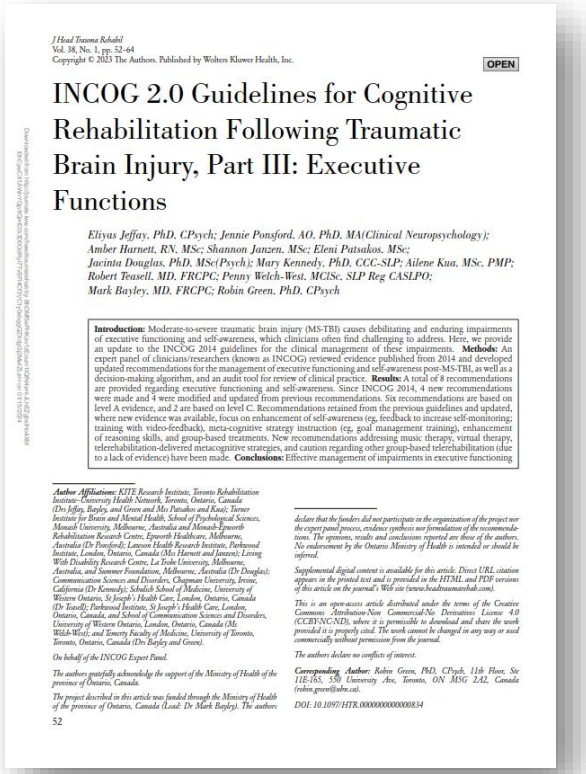
An expert panel of clinicians/researchers known as INCOG group.

INCOG = **IN**ternational **COG**nitive

These guidelines aim to improve patient outcomes and reduce the impact of cognitive deficits on individuals after TBI.

Guidelines for the management of executive dysfunction following moderate to severe TBI were provided by the INCOG group.

Evidence published from 2014 was reviewed by this expert team, and **developed updated recommendations for the management of executive funtioning** as well as decison-making algorithm and an audit tool for review of clinical practice.



J Head Trauma Rehabil
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OPEN

INCOG 2.0 Guidelines for Cognitive Rehabilitation Following Traumatic Brain Injury, Part III: Executive Functions

Eliyas Jeffay, PhD, CPsych; Jennie Ponsford, AO, PhD, MA(Clinical Neuropsychology); Amber Harnett, RN, MSc; Shannon Janzen, MSc; Eleni Patsakos, MSc; Jacinta Douglas, PhD, MSc(Psych); Mary Kennedy, PhD, CCC-SLP; Ailene Kua, MSc, PMP; Robert Teasell, MD, FRCPC; Penny Welch-West, MCISc, SLP Reg CASLPO; Mark Bayley, MD, FRCPC; Robin Green, PhD, CPsych

Introduction: Moderate-to-severe traumatic brain injury (MS-TBI) causes debilitating and enduring impairments of executive functioning and self-awareness, which clinicians often find challenging to address. Here, we provide an update to the INCOG 2014 guidelines for the clinical management of these impairments. **Methods:** An expert panel of clinicians/researchers (known as INCOG) reviewed evidence published from 2014 and developed updated recommendations for the management of executive functioning and self-awareness post-MS-TBI, as well as a decision-making algorithm, and an audit tool for review of clinical practice. **Results:** A total of 8 recommendations are provided regarding executive functioning and self-awareness. Since INCOG 2014, 4 new recommendations were made and 4 were modified and updated from previous recommendations. Six recommendations are based on level A evidence, and 2 are based on level C. Recommendations retained from the previous guidelines and updated, where new evidence was available, focus on enhancement of self-awareness (eg, feedback to increase self-monitoring; training with video-feedback), meta-cognitive strategy instruction (eg, goal management training), enhancement of reasoning skills, and group-based treatments. New recommendations addressing music therapy, virtual therapy, telerehabilitation-delivered metacognitive strategies, and caution regarding other group-based telerehabilitation (due to a lack of evidence) have been made. **Conclusions:** Effective management of impairments in executive functioning

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On behalf of the INCOG Expert Panel.

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The authors declare no conflicts of interest.

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These guidelines provide recommendations for managing executive dysfunctions based on the latest evidence and support their implementation.


Any
Questions?

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