Determining the Effectiveness and safety of Citicoline among Ischemic Stroke Patients through Systematic Review of Clinical Evidence

EVIDENCE AND JUDGMENTS

[Basis for HTAC Preliminary Recommendation]

DOST

CONTEXT

DOST

CONTEXT

Nominated Intervention	Citicoline (as an add on therapy)
Proponent/Nominator	Philippine Neurological Association
Date of Submission	January 2019 under Transitory Formulary Executive Council (TFEC)

SUMMARY OF JUDGMENTS PER CRITERION

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Summary of Judgments per Criterion

RQ	Direction of Judgment
C1: What is the **magnitude and severity** of Ischemic Stroke?	Significant burden
C2.1: Among adult patients who had ischemic stroke, what is the **efficacy/effectiveness** of Citicoline (vs placebo, and SOC only) in terms of (1) All-cause mortality, (2) Degree of disability or dependence in daily activities (mRs), (3) Functional recovery (BI), (4) Neurological function (NIHSS), and (5) Quality of life?	vs Placebo: Comparable vs SOC: Comparable
C2.2: Among adult patients who had ischemic stroke, what is the **safety** of Citicoline in terms of (1) severe adverse events and (2) non-severe adverse events?	vs Placebo: No difference vs SOC: No evidence
C2.3: What are the **recommendations and guidelines** of ministries of health, HTA agencies and medical societies on the use of Citicoline for ischemic stroke?	Not listed in the WHO EML • 3 societies (including local society) - Negative recommendation • 1 society - Alternative only (very limited evidence)

BACKGROUND

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Ischemic Stroke

Ischemic Stroke occurs when a clot or a mass clogs a blood vessel, cutting off the blood flow to brain cells. The underlying condition for this type of obstruction is the development of fatty deposits lining the vessel walls (atherosclerosis).

Atherosclerotic plaque reduces blood flow in the internal carotid artery

If the plaque ruptures, tiny pieces (plaque +clotted blood) can travel to the bloodstream to the brain

A foreign mass traveling through the bloodstream (embolus) may lodge in a small artery halting the blood flow to the brain

Ischemic stroke accounts for **87%** of all strokes.

https://www.stroke.org/en/about-stroke/types-of-stroke/ischemic-stroke-clots

Citicoline

- **Classification:** Other psychostimulants and nootropics.
- **MOA:** Citicoline is a complex organic molecule that stimulates the biosynthesis of structural phospholipids of the neuronal membrane. It preserves the neuronal energetic reserve, inhibits apoptosis and stimulates the synthesis of acetylcholine
- **Synonyms:** CDP-choline; cytidine diphosphate choline; cytidine 5'-diphosphocholine.
- **Dosage for Ischemic stroke**
  - **IM/IV:** 100-1000 mg/day (IM), slow IV injection for 3-5 mins, or IV infusion 40-60 drops/min
  - **Oral:** (as tablet) 500 mg 1 -2x/day, or 1000 mg/day; (as solution)100-200 mg 2x-3x/day, or 500-2000 mg/day

Reference: MIMS , 2024

Local Guidelines: Stroke Society of the Philippines

CPG on the Management of Acute Ischemic Stroke and Intracerebral Hemorrhage in the Philippines, 2024

Neuroprotective agents

Q15. Should we give citicoline as an add-on therapy for adult patients with acute stroke?

RECOMMENDATION 15:

Among patients with acute stroke, we do not recommend the use of citicoline as an add-on therapy.

Overall Level of Certainty: Moderate ⊕⊕⊕◯
Strength of Recommendation: **Strong**

Consensus Discussion

- **No additional benefit to placebo** in terms of improving functional outcomes and stroke severity
- **Associated with more central nervous system adverse events**
- This recommendation may encourage clinicians to focus more on other existing standard treatments for acute stroke and minimize the costs borne by patients for a drug that confers no clear benefit.

DOST

Not Recommending

Cost

[CPG on the Management of Acute Ischemic Stroke and Intracerebral Hemorrhage in the Philippines, 2024]

Table Q17.2. Estimated costs associated with citicoline.

Parameter	Estimated cost
Unit cost of treatment	Citicoline 1 gram ampule – P 245.50 Citicoline 1 gram tablet – P 102.75 to P 113.00
Dosing frequency	1 gram IV q 12 for 3 days then 1 gram tab BID
Duration of therapy	6 weeks
Total cost of treatment	PHP 10,287.00 for a full course

Policy Question and Research Questions

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Policy Question: Should Citicoline be included in the Philippine National Formulary for adult patients with Ischemic Stroke?

Research Questions

C1: Responsiveness to Magnitude and Severity

RQ.1. What is the **magnitude and severity** of ischemic stroke?

C2: Clinical efficacy, effectiveness and safety

RQ.2.1. Among adult patients who had ischemic stroke, what is the **efficacy/effectiveness** of Citicoline as compared with placebo and standard of care in terms of (1) All-cause mortality, (2) Degree of disability or dependence in daily activities (mRs), (3) Functional recovery (BI), (4) Neurological function (NIHSS) and (5) Quality of life?

RQ.2.2. Among adult patients who had ischemic stroke, what is the **safety** of Citicoline as compared with placebo and standard of care in terms of (1) severe adverse events and (2) non-severe adverse events?

RQ.2.3. What are the **recommendations and guidelines** of ministries of health, HTA agencies and medical societies on the use of Citicoline for ischemic stroke?

PICO

Population	Adult patient who suffered ischemic stroke
Intervention	Citicoline
Comparator	SOC alone Placebo (on top of SOC)

Efficacy Outcomes	Importance Rating
All-cause mortality	Critical
Degree of disability or dependence in daily activities (mRs)	Critical
Functional recovery (BI)	Critical
Neurological function (NIHSS)	Critical
Quality of life	Critical

Safety Outcomes	Importance Rating
Severe Adverse Events	
Cardiovascular	Critical
Central nervous system *(including hemorrhagic or ischemic stroke)*	Critical
Respiratory (including pneumonia)	Important
Gastrointestinal	Important
Musculoskeletal	Important
Hepatic dysfunction	Important
Renal and urologic disorders	Important
Hematological disorders	Important

Safety Outcomes	Importance Rating
Non-Severe Adverse Events	
Cardiac disorders	Critical
Pyrexia	Low importance
Constipation	Low importance
Urinary tract infections	Low importance
Headache	Critical
Nausea and Vomiting	Critical
Agitation	Critical
Hemorrhagic transformation stroke	Critical
Pneumonia	Important
Hypotension	Critical

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C1: DISEASE MAGNITUDE AND SEVERITY

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C1 Responsiveness to Magnitude and Severity

RQ 1: What is the magnitude and severity of Ischemic Stroke?

In 2021, stroke is the third most common cause of death globally (WHO, 2024). Ischemic stroke is the most frequent type of stroke. In 2030, there is an expected increase by 22% in the incidence of ischemic stroke from 7,862 cases in 2020 to 9,618 cases in 2030 (Pu et al., 2023). Similarly, local data showed that cerebrovascular disease which includes stroke ranks as the third most common cause of death among Filipinos as of July 2024 (PSA, 2024). Based on a systematic review (Collantes et al., 2022), stroke incidence in the country ranges from 3.95% to 5.61% while the national stroke prevalence ranges from 0.486% to 6.0%. Based on local mortality data, cerebrovascular diseases including ischemic stroke (which accounts for 7 our 10 stroke cases) are the leading cause of deaths in the country, thus, there is a need to look into the management of ischemic stroke to not further its existing disease magnitude and severity.

C1 Responsiveness to Magnitude and Severity

GLOBAL DATA

- Stroke is the **2nd** most common cause of death in 2000, 2019, 2020; and ranks **3rd** in 2021 *(WHO, 2024)*.
- Ischemic stroke is the most frequent type of stroke (**62.4%** of all stroke cases worldwide) in 2019, and will increase by **22%** (7,862 cases in 2020 → 9,618 cases in 2030) *(Pu et al., 2023)*

LOCAL DATA

- Cerebrovascular disease including stroke ranks as the **3rd** most common cause of death among Filipinos as of July 2024 *(PSA, 2024)*.
- National stroke incidence ranges from **3.95% to 5.61%** while prevalence ranges from **0.486% to 6.0%** (*Collantes et al., 2022*).

C2: EFFICACY, EFFECTIVENESS and SAFETY

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C2 Efficacy, Effectiveness, and Safety (1 of 2)

RQ.2.1. Among adult patients who had ischemic stroke, what is the efficacy/effectiveness of Citicoline (vs placebo, and SOC only) in terms of (1) All-cause mortality, (2) Degree of disability or dependence in daily activities (mRs), (3) Functional recovery (BI), (4) Neurological function (NIHSS), and (5) Quality of life?

Overall, in terms of critical outcomes such as all-cause mortality and functional outcomes measures (i.e. mRs, BI, and NIHSS), there is no difference in the efficacy of Citicoline (as an add-on therapy) compared to placebo on top of standard of care (SOC) and SOC alone in the treatment of ischemic stroke based on very low to low certainty of evidence.

In terms of comparing the efficacy of Citicoline as an add-on therapy to SOC vs placebo on top of SOC:
Among adult patients who had ischemic stroke, Citicoline was found to have no difference compared to placebo in reducing all-cause mortality (17.3% vs 18.5%, RR 1.06 , 95% CI 0.81 to 1.54) at 90 days follow-up, based on pooled data of 6 RCTs (N=4,222) with low certainty of evidence. In assessing the degree of disability or depence in daily activities, at 90 days using the modified Rankin scale (mRS)*, results showed little to no difference in comparing Citicoline vs placebo (26.2% vs 21.6 %, OR 1.27, 95% CI 1.12 to 1.27) based on seven (7) trials (N=4,314) with very low certainty of evidence. Similarly, in evaluating functional recovery using Barthel index (BI)** at 90 days follow-up, five (5) trials (N=3,819) with very low certainty of evidence comparing Citicoline with placebo showed no difference in results, (29.2% vs 27.3 %, OR 1.12, 95% CI 0.81 to 1.53). Further, based on the National Institute of Health Stroke Scale (NIHSS)***, no difference was reported in those who received Citicoline compared to those administered with placebo (30.7% vs 30.2%, OR 1.05, 95% CI 0.87 to 1.27) in six (6) trials (N=3,901, low certainty of evidence). None of the trials reported any information covering the quality of life as an outcome.

Notes:
*Cut off for favorable outcomes: for mRs: *<1, **BI: ≥95%, and ***NIHSS: <1*

C2 Efficacy, Effectiveness, and Safety (2 of 2)

RQ.2.1. Among adult patients who had ischemic stroke, what is the efficacy/effectiveness of Citicoline (vs placebo, and SOC only) in terms of (1) All-cause mortality, (2) Degree of disability or dependence in daily activities (mRs), (3) Functional recovery (BI), (4) Neurological function (NIHSS), and (5) Quality of life?

In terms of comparing the efficacy of Citicoline as an add on therapy vs SOC alone:

In the sole trial by *Ghosh, 2015* (N=65, very low certainty of evidence) comparing Citicoline (1000 mg/day) versus the standard stroke therapy (i.e. antihypertensives, osmotic diuretics, lipid-lowering agents, statins, and if necessary, aspirin or clopidogrel), an inconclusive result (25.0% vs 22.9%, RR 1.09 95% CI 0.45, 2.65) was reported at 90 days follow-up. In evaluating functional recovery using Barthel index (BI) at 90 days follow-up, the same trial (N=65) with very low certainty of evidence showed no difference in results (25.0% vs 22.9 %, RR 3.13, 95% CI 1.10 to 8.9). Meanwhile, a single study (Premi et al, 2022) comparing Citicoline versus SOC presented results on mRS and NIHSS in time points also showed no difference (no data on effect measure i.e. RR, OR were provided). In addition, no trials reported quality of life in comparing citicoline versus the standard stroke therapy

Notes:

*Cut off for favorable outcomes: for mRs: *<1, **BI: ≥95%, and ***NIHSS: <1*

DOST

C2 Efficacy, Effectiveness, and Safety

RQ.2.2. Among adult patients who had ischemic stroke, what is the safety of Citicoline in terms of (1) severe adverse events and (2) non-severe adverse events?

For critical serious adverse event, there is **no difference** in the risk of experiencing **central nervous system (CNS) serious adverse events** (RR 1.30, 95% CI: 1.07 to 1.59; 3 RCTs) with Citicoline as **compared with placebo** based on low certainty of evidence. Similarly, in terms of non-serious adverse events, there is **no difference** in the risk of **cardiac disorders** (RR 0.94, 95% CI: 0.82 to 1.08), **pyrexia** (RR 1.02, 95% CI: 0.87 to 1.19), **constipation** (RR 1.03, 95% CI: 0.88 to 1.20), **urinary tract infections** (RR 1.06, 95% CI: 0.89 to 1.26), **headache** (RR 0.96, 95% CI: 0.79 to 1.18), and **nausea and vomiting** (RR 0.95, 95% CI: 0.77 to 1.16) based on moderate certainty of evidence. For the rest of the serious AEs (**cardiovascular AE, respiratory AE, gastrointestinal AE, musculoskeletal AE, hepatic dysfunction, renal and urologic disorders, and hematological disorders**) and non-severe AEs (**agitation, hemorrhagic transformation stroke, pneumonia and hypotension**) there is **inconclusive evidence** to compare the risk of Citicoline and placebo.

Meanwhile, there is **no evidence** comparing the safety of Citicoline and **standard of care alone.**

Methodology

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Initial Scoping: Methodology

Search date	29 January 2020 (Marti-Carvajal last search date)
Database	MEDLINE via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar, and SCOPUS
Search terms	cerebrovascular infarct OR stroke OR ischemic stroke AND citicoline AND randomized controlled trial

Key Studies

- Sagaro and Amenta, 2023 [SR]
- Marti-Carvajal , 2020 [SR]
- Premi et al., 2023 [RCT]

Final Methodology

Citicoline vs **Placebo** *(on top of SOC)*	Citicoline vs **SOC** only
Adapt Sagaro and Amenta 2023 SR	De Novo SR (Ghosh 2015 and Guillen 1995 from Marti-Carvajal SR plus study of Premi et al., 2022)

Tabulation of Evidence per Outcome

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C2 Efficacy/Effectiveness: Overview of Available Evidence *[1 of 2]*

Efficacy Outcomes	Citicoline vs Placebo	Citicoline vs SOC
All-cause mortality	RCTs (k=6) • *Tazaki, 1988* • *Clark, 1997* • *Clark, 1999* • *Warach, 2000* • *Clark, 2001* • *Davalos/ICTUS, 2012*	RCTs (k=1) • *Ghosh, 2015*
Degree of disability or dependence in daily activities: modified Rankin Scale (mRS) <1	RCTs (k=7) • *Tazaki, 1988* • *Clark, 1997* • *Clark, 1999* • *Clark, 2001* • Warach, 2000 • *Davalos/ICTUS, 2012* • *Agarwal, 2022*	RCT (k=1) • *Premi, 2022*

C2 Efficacy/Effectiveness: Overview of Available Evidence *[2 of 2]*

Efficacy Outcomes	Citicoline vs Placebo	Citicoline vs SOC
Functional recovery: Barthel Index (BI) ≥95	RCTs (k=5) • Clark, 1997 • Clark, 1999 • Clark, 2001 • Davalos/ICTUS, 2012 • Agarwal, 2022	RCTs (k=1) • Ghosh, 2015
Neurological function: National Institutes of Health Stroke Scale (NIHSS) <1	RCTs (k=6) • Clark, 1997 • Clark, 1999 • Warach, 2000 • Clark, 2001 • Davalos/ICTUS, 2012 • Agarwal, 2022	RCT (k=1) • Premi, 2022
Quality of Life	*No evidence found.*	

C2. SAFETY: Overview of Available Evidence

Serious AEs	Citicoline vs Placebo	Non Serious AEs	Citicoline vs Placebo
Cardiovascular	RCTs (k=3) • Clark, 1999 • Clark, 2001 • Davalos/ICTUS, 2012	**Cardiac disorders**	RCTs (k=1) • Davalos/ICTUS, 2012
Central nervous system (including hemorrhagic or ischemic stroke)		**Pyrexia**	
Respiratory (including pneumonia)		**Constipation**	
Gastrointestinal	RCTs (k=2) • Clark, 1999 • Clark, 2001	**Urinary tract infections**	
Musculoskeletal	CTs (k=2) • Clark, 1999 • Clark, 2001	**Headache**	
Hepatic dysfunction	RCTs (k=1) • Tazaki, 1988	**Nausea and Vomiting**	
Renal and urologic disorders	RCTs (k=3) • Clark, 1999 • Clark, 2001 • Tazaki, 1988	**Agitation**	
Hematological disorders		**Hemorrhagic transformation stroke**	
		Pneumonia	
		Hypotension	

Tabulation of Results

DOST

C2 Efficacy/Effectiveness: Results *[1 of 2]*

Citicoline vs Placebo

Efficacy Outcome	No. of studies	Risk Ratio /Odds Ratio *Certainty of Evidence*
1. All-cause mortality (negative outcome)	6 RCTs (N=4,222)	**RR 1.06** (0.81 to 1.54) *Low*
2. Degree of disability or dependence in daily activities (mRS) < 1 (positive outcome)	7 RCTs (N=4,314)	**OR 1.27** (1.12 to 1.44) *Very Low*
3. Functional recovery: Barthel Index (BI) >95 (positive outcome)	5 RCTs (N=3,819)	**OR 1.12** (0.81 to 1.53) *Very Low*
4. Neurological function: National Institutes of Health Stroke Scale (NIHSS) <1 (positive outcome)	6 RCTs (N=3,901)	**OR 1.05** (0.87 to 1.27) *Low*
5. Quality of Life	*No evidence found.*	

LEGEND	
Favors Citicoline vs Placebo	
Non-inferior/Equivalent/ No difference between Citicoline and Placebo	
Inconclusive evidence	
Favors Placebo over Citicoline	

Key Findings: *No difference between Citicoline and Placebo for all efficacy outcomes*

DOST

C2 Efficacy/Effectiveness: Results *[2 of 2]*

Citicoline vs SOC

Efficacy Outcome	Reference study	Risk Ratio / Odds Ratio	
1. All-cause mortality (2000 mg/day)	1 RCT ***Ghosh, 2015*** (N=63)	**RR 1.09** (0.45 to 2.65) *Very Low*	
2. Functional recovery: Barthel Index (BI) >95	1 RCT ***Ghosh, 2015*** (N=63)	**OR 3.13** (1.10 to 8.91) *Low*	
3. Degree of disability or dependence in daily activities (mRS) < 1	1 RCT ***Premi, 2022*** *(N=128)*	Citicoline: T0: 1.3 +/- 1.6 T1: 0.5 +/- 0.7	SOC: T0: 1.5 +/ 1.6 T1: 0.7 +/0.8
4. NIHSS <1	1 RCT ***Premi, 2022*** *(N=128)*	Citicoline: T0: 4.6 +/- 6.2 T1: 0.9 +/1.5	SOC: T0: 5.1 +/4.2 T1: 0.9 +/1.1
5. Quality of Life		*No evidence found.*	

LEGEND	
Favors Citicoline vs Placebo	
Non-inferior/Equivalent/ No difference between Citicoline and Placebo	
Inconclusive evidence	
Favors Placebo over Citicoline	

Key Findings:

- Inconclusive evidence comparing Citicoline vs SOC for all-cause mortality.
- No difference between Citicoline and Placebo in terms of functional recovery.
- For dependence in daily activities (mRS) and neurological function (NIHSS) outcomes, SOC was was found to have higher scores as compared to Citicoline on both timepoints (T0 baseline, T1 8 weeks follow-up).

DOST

GRADE Evidence Profile: Efficacy Outcomes

Citicoline vs Placebo

Certainty assessment							Summary of findings				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Effect (Effectiveness or relative risk etc.) (95% CI)	Certainty	Importance
All-cause mortality (follow-up: 90 days)											
6	RCT	Serious	Not Serious	Not Serious	Very Serious [d,f]	None	388/2247 (17.3%)	366/1975 (18.5%)	**RR 1.06 (0.81 to 1.54)**	⨁⨁◯◯ Low	CRITICAL
Degree of disability or dependence in daily activities: modified Rankin Scale (mRs) <1 (follow-up: 90 days)*											
7	RCT	very serious[a,b,c,d,e,]	Serious[f]	Not Serious	Not serious	None	601/2293 (26.2%)	436/2021 (21.6%))	**OR 1.27 (1.12 to 1.27)**	⨁◯◯◯ Very low	CRITICAL
Functional recovery: Barthel Index (BI) ≥95 (follow-up: 90 days)*											
5	RCT	Very serious[a,b,c,d,e,]	Serious[f]	not serious	Serious[g]	None	578/1982 (29.2%)	501/1837 (27.3%)	**OR 1.12** (0.81 to 1.53)	⨁◯◯◯ Very low	CRITICAL
Neurological function: National Institutes of Health Stroke Scale (NIHSS) <1 (follow-up: 90 days)*											
6	RCT	very serious[a,b,c,d,e,]	Not serious	Not Serious	Not Serious	None	621/2024 (30.7%)	566/1877 (30.2%)	**OR 1.05 (0.87 to 1.27)**	⨁⨁◯◯ Low	CRITICAL

[a] Unclear risk for selection bias [b] Unclear risk for detection bias [c] Unclear risk for others [d] High risk for attrition bias [e] High risk for other bias [f] Moderate Heterogeneity [g] Wide CI
*Positive outcome

GRADE Evidence Profile: Efficacy Outcomes

Citicoline vs SOC

Certainty assessment							Summary of findings				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Effect (Effectiveness or relative risk etc.) (95% CI)	Certainty	Importance
All-cause mortality (follow-up: 90 days)											
1	RCT	Serious[a,b,c,d,e]	None	Not Serious	Very Serious [f, g]	None	7/28 (25.0%)	8/35 (22.9%)	**RR 1.09** (0.45 to 2.65)	⊕◯◯◯ Very low	CRITICAL
Functional recovery: Barthel Index (BI) ≥95 (follow-up: 90 days) *											
1	RCT	serious[a,b,c,d,e]	None	Not Serious	Serious[g]	none	7/28 (25.0%)	8/35 (22.9%)	**RR 3.13** (1.10 to 8.91)	⊕⊕◯◯ Low	CRITICAL

[a] Unclear risk for selection bias [b] Unclear risk for detection bias [c] Unclear risk for others [d] High risk for attrition bias [e] High risk for other bias [f] Moderate Heterogeneity [g] Wide CI
*Positive outcome

DOST

C2. SAFETY: Results *[1 of 2]*

Citicoline vs Placebo

Serious AE	# of Studies	Risk Ratio *Certainty of Evidence*
Cardiovascular	3 RCTs	1.04 (0.84 to 1.29) *Low*
CNS	3 RCTs	1.30 (1.07 to 1.59) *Low*
Respiratory	3 RCTs	1.01 (0.78 to 1.31) *Very Low*
Gastrointestinal*	2 RCTs	0.93 (0.49 to 1.78) *Very Low*
Musculoskeletal	2 RCTs	1.52 (0.50 to 4.60) *Very Low*
Hepatic dysfunction	1 RCT	0.78 (0.18 to 3.41) *Very Low*
Renal and urologic disorders	3 RCTs	2.04 (0.99 to 4.22) *Very Low*
Hematological disorders	3 RCTs	1.27 (0.46 to 3.5)] *Very Low*

LEGEND	
Favors Citicoline vs Placebo	
Non-inferior/Equivalent/ No difference between Citicoline and Placebo	
Inconclusive evidence	
Favors Placebo over Citicoline	

Key Findings:

- Inconclusive evidence on the comparison of Citicoline vs Placebo for the following safety outcomes: cardiovascular AE, respiratory AE, GI AE, musculoskeletal AE, hepatic dysfunction, renal and urologic disorders and hematological disorders.
- No difference in risk for CNS AE between Citicoline and Placebo.

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C2. SAFETY: Results *[2 of 2]*

Citicoline vs Placebo

Non Serious AE	# of Studies	Risk Ratio *Certainty of Evidence*
Cardiac disorders	1 RCT	0.94 (0.82 to 1.08) *Moderate*
Pyrexia		1.02 (0.87 to 1.19) *Moderate*
Constipation		1.03 (0.88 to 1.20) *Moderate*
Urinary tract infections		1.06 (0.89 to 1.26) *Moderate*
Headache		0.96 (0.79 to 1.18) *Moderate*
Nausea and Vomiting		0.95 (0.77 to 1.16) *Moderate*
Agitation		1.20 (0.94 to 1.54) *Very Low*
Hemorrhagic transformation stroke		0.98 (0.74 to 1.29) *Very Low*
Pneumonia		1.02 (0.73 to 1.41) *Very Low*
Hypotension		0.92 (0.63 to 1.36) *Very Low*

LEGEND	
Favors Citicoline vs Placebo	
Non-inferior/Equivalent/ No difference between Citicoline and Placebo	
Inconclusive evidence	
Favors Placebo over Citicoline	

Key Findings:

- No difference in risk for cardiac disorders, pyrexia, constipation, UTI, headache, nausea and vomiting between Citicoline and Placebo.
- Inconclusive evidence on the comparison of Citicoline vs Placebo for the following safety outcomes: agitation, hemorrhagic transformation stroke, pneumonia and hypotension

GRADE Evidence Profile: Safety Outcomes *[1 of 2]*

Citicoline vs Placebo

Certainty assessment							Summary of findings				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Effect (Effectiveness or relative risk etc.) (95% CI)	Certainty	Importance
Serious AE: Cardiovascular											
3	RCT	Serious[a,b,c]	Not Serious	Not Serious	Serious[d]	None	251/1868	134/1723	RR 1.04 (0.84-1.29)	Low ⊕⊕◯◯	*CRITICAL*
Serious AE: Central nervous system											
3	RCT	Serious[a,b,c]	Serious[e]	Not Serious	Not Serious	None	251/1868	155/1723	RR 1.30 (1.07-1.59)	Low ⊕⊕◯◯	*CRITICAL*
Serious AE: Respiratory											
3	RCT	Serious[a,b,c]	Not Serious	Not Serious	Very Serious[d,f]	None	120/1868	100/1723	RR 1.01 (0.78-1.31)	Very Low ⊕◯◯◯	*IMPORTANT*
Serious AE: Gastrointestinal											
2	RCT	Serious[a,bc]	Serious[e]	Not Serious	Very Serious[d,f]	None	29/720	35/573	RR 0.93 (0.49 -1.78)	Very Low ⊕◯◯◯	*IMPORTANT*

[a] Unclear risk for selection bias [b] Unclear risk for detection bias [c] High risk for attrition bias [d] Crosses appreciable benefit or harm [e] Moderate to high heterogeneity
[f] Wide CI [g] High risk for other bias

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GRADE Evidence Profile: Safety Outcomes *[2 of 2]*

Citicoline vs Placebo

Certainty assessment							Summary of findings				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Effect (Effectiveness or relative risk etc.) (95% CI)	Certainty	Importance
Serious AE: Musculoskeletal											
2	RCT	Serious[a,b]	Not Serious	Not Serious	Very Serious[d,f]	None	10/720	5/573	RR 1.52 (0.50-4.60)	Very Low ⊕◯◯◯	*IMPORTANT*
Serious AE: Hepatic dysfunction											
1	RCT	Serious[a,g]	None	Not Serious	Very Serious[d,f]	None	3/131	4/136	RR 0.78 (0.18-3.41)	Very Low ⊕◯◯◯	*IMPORTANT*
Serious AE: Renal and urologic disorders											
3	RCT	Serious[a,b]	Not Serious	Not Serious	Very Serious[d,f]	None	28/851	11/709	RR 2.04 (0.99-4.22)	Very Low ⊕◯◯◯	*IMPORTANT*
Serious AE: Hematological disorders											
3	RCT	Serious[a,b,g]	Not Serious	Not Serious	Very Serious[d,f]	None	10/851	6/709	RR 1.27 (0.46-3.51)	Very Low ⊕◯◯◯	*IMPORTANT*

[a] Unclear risk for selection bias [b] Unclear risk for detection bias [c] High risk for attrition bias [d] Crosses appreciable benefit or harm [e] Moderate to high heterogeneity
[f] Wide CI [g] High risk for other bias

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GRADE Evidence Profile: Safety Outcomes *[1 of 2]*

Citicoline vs Placebo

Certainty assessment							Summary of findings				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Effect (Effectiveness or relative risk etc.) (95% CI)	Certainty	Importance
Non Serious AE: Cardiac Disorder											
1	RCT	Serious[c,g]	None	Not Serious	Not Serious	None	277/1148	295/1150	RR 0.94 (0.82-1.08)	Moderate ⊕⊕⊕◯	*CRITICAL*
Non Serious AE: Pyrexia											
1	RCT	Serious[c,g]	None	Not Serious	Not Serious	None	258/1148	254/1150	RR 1.02 (0.87-1.19)	Moderate ⊕⊕⊕◯	*LOW IMPORTANCE*
Non Serious AE: Constipation											
1	RCT	Serious[c,g]	None	Not Serious	Not Serious	None	245/1148	239/1150	RR 1.03 (0.88-1.20)	Moderate ⊕⊕⊕◯	*LOW IMPORTANCE*
Non Serious AE: Urinary tract infections											
1	RCT	Serious[c,g]	None	Not Serious	Not Serious	None	219/1148	207/1150	RR 1.06 (0.89-1.26)	Moderate ⊕⊕⊕◯	*LOW IMPORTANCE*
Non Serious AE: Headache											
1	RCT	Serious[c,g]	None	Not Serious	Not Serious	None	154/1148	160/1150	RR 0.96 (0.79-1.18)	Moderate ⊕⊕⊕◯	*CRITICAL*

[a] Unclear risk for selection bias [b] Unclear risk for detection bias [c] High risk for attrition bias [d] Crosses appreciable benefit or harm [e] Moderate to high heterogeneity
[f] Wide CI [g] High risk for other bias

GRADE Evidence Profile: Safety Outcomes *[2 of 2]*

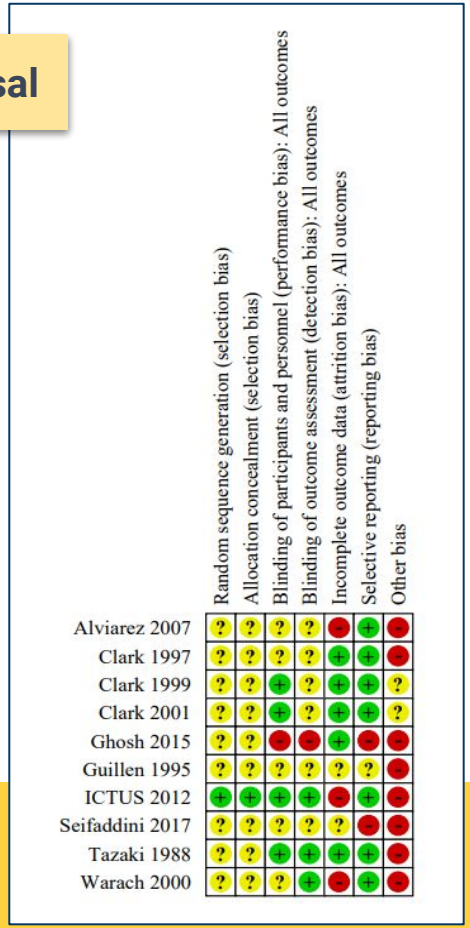
Citicoline vs Placebo

Certainty assessment							Summary of findings				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Effect (Effectiveness or relative risk etc.) (95% CI)	Certainty	Importance
Non Serious AE: Nausea and Vomiting											
1	RCT	Serious[c,g]	None	Not Serious	Not Serious	None	153/1148	162/1150	RR 0.95 (0.77-1.16)	Moderate ⊕⊕⊕◯	*CRITICAL*
Non Serious AE: Agitation											
1	RCT	Serious[c,g]	None	Not Serious	Very Serious[d,f]	None	125/1148	104/1150	RR 1.20 (0.94-1.54)	Very Low ⊕◯◯◯	*CRITICAL*
Non Serious AE: Hemorrhagic transformation stroke											
1	RCT	Serious[c,g]	None	Not Serious	Very Serious[d,f]	None	91/1148	93/1150	RR 0.98 (0.74-1.29)	Very Low ⊕◯◯◯	*CRITICAL*
Non Serious AE: Pneumonia											
1	RCT	Serious[c,g]	None	Not Serious	Very Serious[d,f]	None	68/1148	67/1150	RR 1.02 (0.73-1.41)	Very Low ⊕◯◯◯	*IMPORTANT*
Non Serious AE: Hypotension											
1	RCT	Serious[c,g]	None	Not Serious	Very Serious[d,f]	None	48/1148	52/1150	RR 0.92 (0.63-1.36)	Very Low ⊕◯◯◯	*CRITICAL*

[a] Unclear risk for selection bias [b] Unclear risk for detection bias [c] High risk for attrition bias [d] Crosses appreciable benefit or harm [e] Moderate to high heterogeneity
[f] Wide CI [g] High risk for other bias

Critical Appraisal: ROB

Marti-Carvajal Appraisal



DOST

Critical Appraisal: AMSTAR 2 - Sagaro & Amenta, 2022

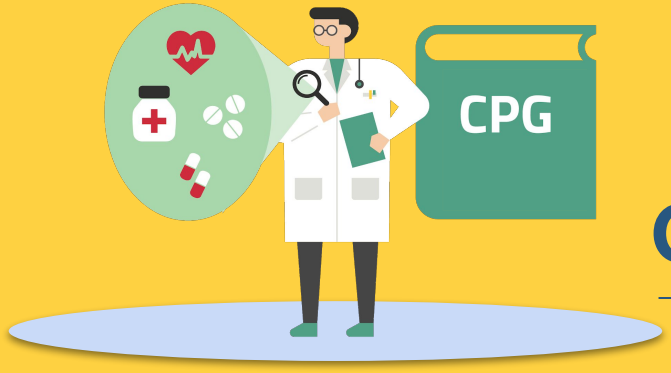
AMSTAR 2			
Domain	Judgment	Domain	Judgment
1	N I= for Placebo only O= No all-cause mortality	9*	Y
2*	PY	10	N. Source of funding of included studies were not included
3	N. No explanation for including RCTs and case control studies	11*	N. No further investigation on the causes of heterogeneity
4*	PY	12	N. No assessment of the potential impact of RoB in individual studies on the results.
5	Y	13*	N. Did account for RoB in individual studies when interpreting/ discussing the results
6	Y	14	N. Did not provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results
7*	N. No list of excluded studies	15*	N. Did not carry out an adequate investigation of publication bias and likely impact on the results
8	PY	16	Y

Critically Low

- 5 non critical weakness
- 4 critical flaw

DOST

HTAD AMSTAR 2 Appraisal



C2: REVIEW OF GUIDELINES

DOST

C2 Review of Guidelines

RQ.2.1. What are the recommendations and guidelines of ministries of health, HTA agencies and medical societies on the use of Citicoline for ischemic stroke?

Scoping of recommendations and guidelines on ministries of health, HTA agencies, and medical societies across 13 countries (US, UK, Australia, Canada, Malaysia, Thailand, Colombia, Philippines, Vietnam, Laos, Cambodia, Nepal, and India) with varying classifications of income level was performed.

Based on the scoping review, Citicoline for ischemic stroke is not recommended by the Stroke Society Philippines (2024) due to its unclear clinical benefits and associated with central nervous system (CNS) adverse events. This is consistent with the non-recommendation of countries such as Australia and Colombia. Meanwhile, the national CPG for Management of Stroke in Malaysia (2020) considers Citicoline as an alternative treatment based on very limited evidence. For the other countries, no recommendation on Citicoline for stroke was found across ministries of health, HTA Agencies and medical societies. Additionally, Citicoline is not included in the WHO EML.

Review of Guidelines

Country	Ministry of Health	HTA Agency	Medical Society
WHO	*No recommendation*		
High Income Countries (n=4)			
United States	*No recommendation*	-	*No recommendation*
United Kingdom	*No recommendation*	*No recommendation*	*No recommendation*
Australia	*No recommendation*	*No recommendation*	Not recommending
Canada	*No recommendation*	*No recommendation*	*No recommendation*
Upper Middle Income Countries (n=3)			
Malaysia	*Alternative treatment*	*Alternative treatment*	*Alternative treatment*
Thailand	*No recommendation*	*No recommendation*	*No recommendation*
Colombia	*No recommendation*	*No recommendation*	Not recommending
Low Middle Income Countries (n=6)			
Philippines	*No recommendation*	*No recommendation*	Not recommending
Vietnam	*No recommendation*	*No recommendation*	*No recommendation*
Laos	*No recommendation*	*No recommendation*	*No recommendation*
Cambodia	*No recommendation*	*No recommendation*	*No recommendation*
Nepal	*No recommendation*	*No recommendation*	*No recommendation*
India	*No recommendation*	*No recommendation*	*No recommendation*

LEGEND	
	Recommended Citicoline for treatment of Stroke
	Alternative only *"May be recommended"*
	Not recommended (e.g. with study on non-inclusion)
	No recommendation found on Citicoline for treatment of stroke

OTHER SUPPORTING EVIDENCE

DOST

Cost

CPG on the Management of Acute Ischemic Stroke and Intracerebral Hemorrhage in the Philippines, 2024

Additional cost to be incurred for citicoline ON TOP of cost of SoC

Table Q17.2. Estimated costs associated with citicoline.

Parameter	Estimated cost
Unit cost of treatment	Citicoline 1 gram ampule – P 245.50 Citicoline 1 gram tablet – P 102.75 to P 113.00
Dosing frequency	1 gram IV q 12 for 3 days then 1 gram tab BID
Duration of therapy	6 weeks
Total cost of treatment	PHP 10,287.00 for a full course

HTAC Clinical Judgment

DOST

OVERALL CLINICAL JUDGMENT

	Overall Clinical Judgment	Next Steps for Costing Analysis
Option A *[Superior]*	In terms of efficacy, Citicoline has **superior efficacy** vs Placebo and SCC	**CUA/CEA + BIA** *CUA= Cost Utility Analysis* *CEA = Cost Effectiveness Analysis* *BIA = Budget Impact Analysis*
Option B *[Non-inferior]*	Citicoline has **comparable efficacy/ effectiveness** vs Placebo and SOC Citicoline has a **manageable/tolerable safety** profile	**CMA + BIA** *CMA = Cost Minimization Analysis* *BIA = Budget Impact Analysis*
Option C *[Inferior]*	Citicoline has **comparable efficacy** vs Placebo and SOC Citicoline has an **comparable safety profile** vs Placebo With negative recommendation of Stroke Society of the Philippines	**Do not proceed to Economic Assessment**

KEY CONSIDERATION:

- Non-inferior to standard of care as an add on therapy → more expensive and without clinically significant benefit
- Negative recommendation of Stroke Society of the Philippines

Thank you!