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Transdermal Rivastigmine for HIV-Associated Cognitive Impairment: Preliminary Results from a Randomized Trial

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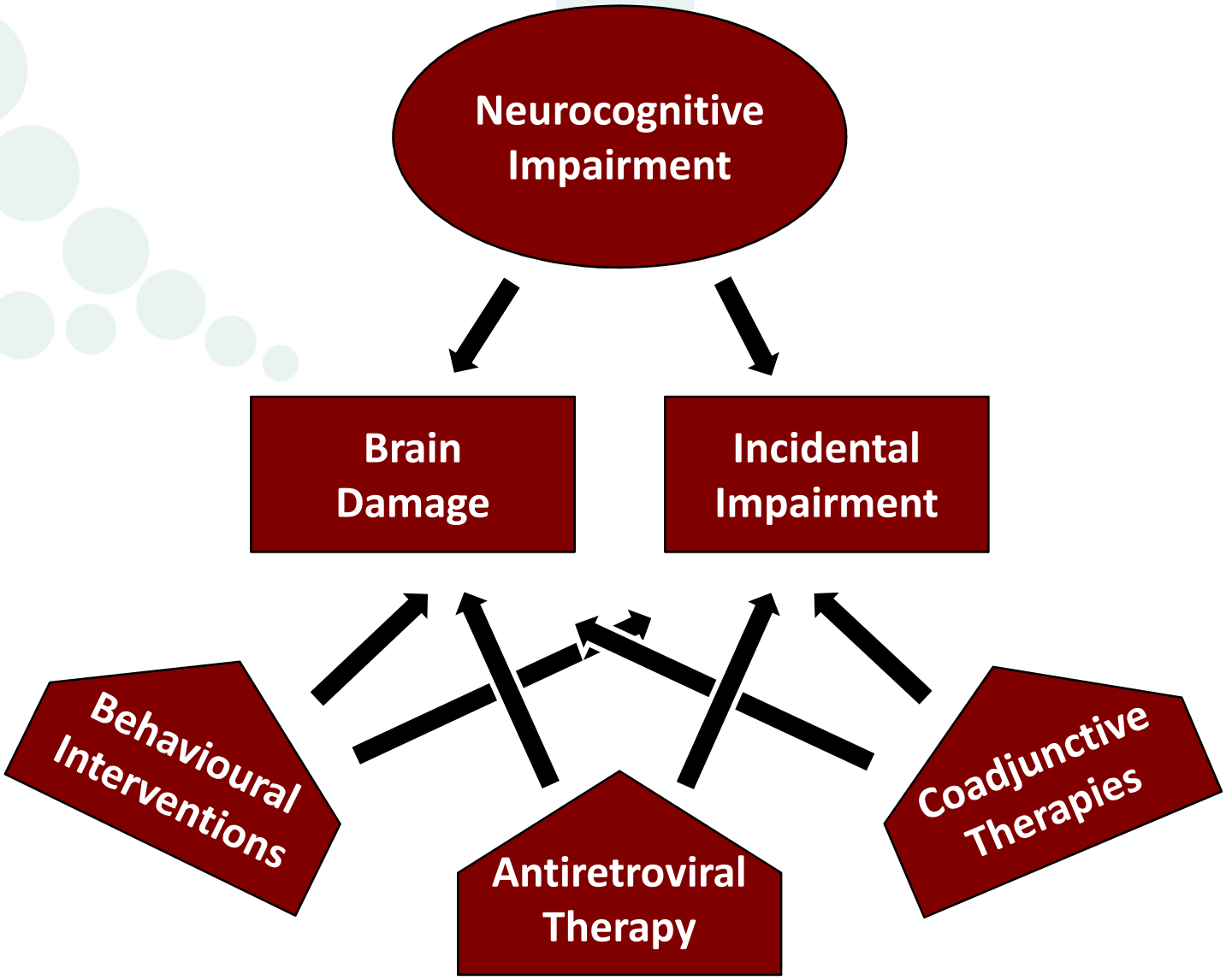
Background


Neurocognitive Impairment
Brain Damage
Incidental Impairment
Behavioural Interventions
Antiretroviral Therapy
Coadjunctive Therapies

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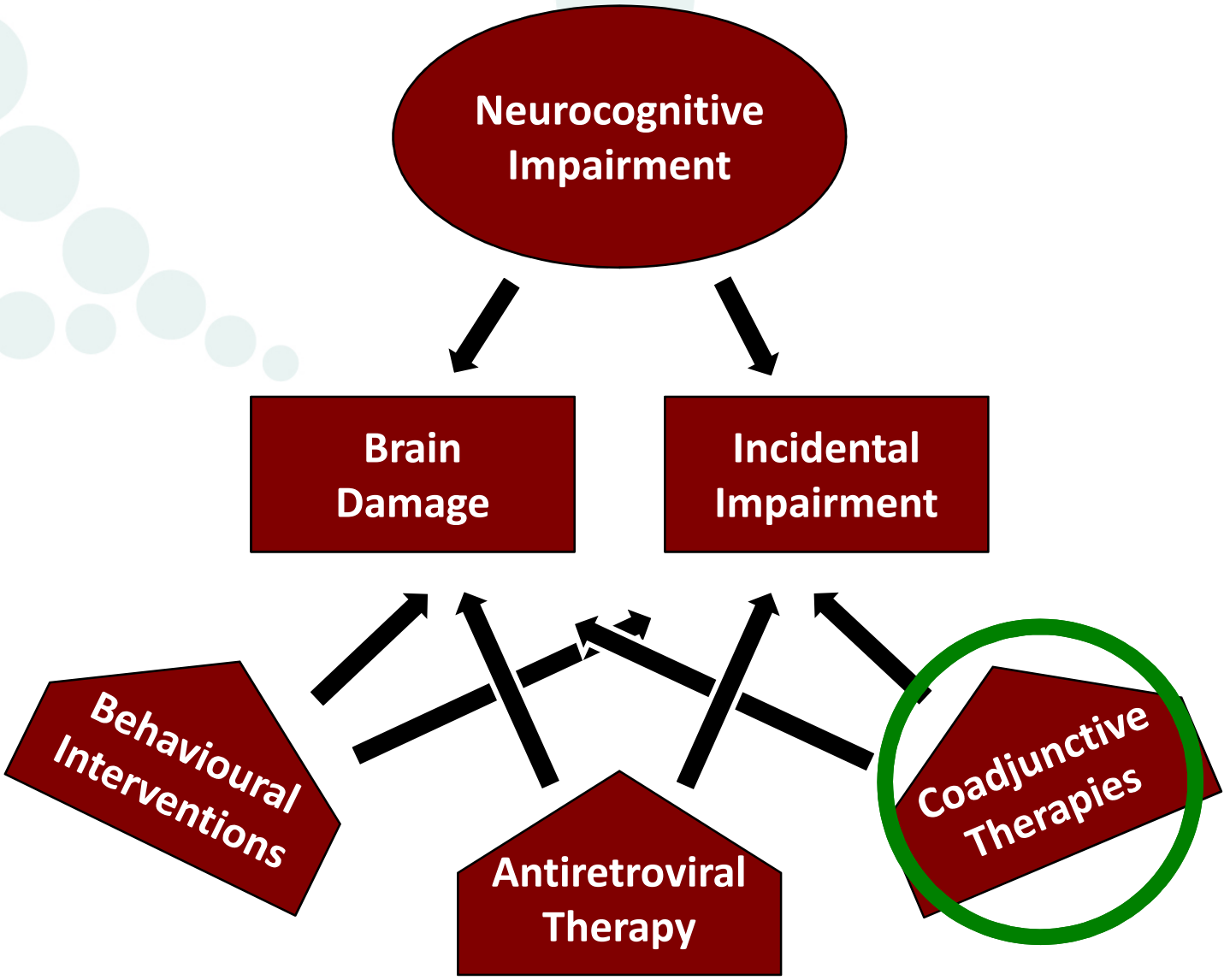
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TOTAL	*Observational / Non-pharmacological*	*Coadjunctive trials*	*Therapies*	*Sample size*	*Comorbidities*	*Primary endpoint*
125	107	18	12	14 (77%): <100 subjects 0 (0%): >215 subjects	Not excluded or unreported	NPZ change wk 10 – wk 24

Adapted from McGuire et al, 2014

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Therapy	Authors / Journal	Publication year	Design / Sample size	Timepoint / Endpoint	Main results	Limitations
Valproic Acid	Cysique et al, *BMC Neurology*	2006	Cohort, retrospective n=40 (8 vs 32)	72 wks (24-108) RCI	⇩ global	- retrospective - variable timepoint
	Schifitto et al, *Neurology*	2006	Pilot, placebo n=22 (11 vs 11)	10 wks NPZ11, MRS, DTI	⇗ memory ⇗ MRS, ⇗ DTI	- small sample - baseline differences
Memantine	Schifitto et al, *AIDS*	2007	Double-blind, placebo n=140 (70 vs 70)	16 wks NPZ8, MRS	⇔ global ⇗ MRS	- short-term follow-up
	Zhao et al, *HIV Clin Trials*	2010	Open-label n=99 (51 vs 48)	60 wks NPZ8	⇔ global	- open-label design
Transdermal Selegiline	Evans et al, *HIV Clin Trials*	2007	Open-label n=86 (4 arms)	24 wks NPZ6, NPZ8	⇔ global ⇗ motor	- open-label design - safety-targeted
	Schifitto et al, *Neurology*	2009	Placebo-controlled n=52 (19 vs 18 vs 25)	24 wks NPZ8, MRS, CSF	⇔ global ⇔ MRS, ⇔ CSF	- small sample
Lithium	Letendre et al, *AIDS*	2006	Pilot, single-arm n=8	12 wks GDS	⇧ global ⇗ emotional	- small sample - single-arm design
	Schifitto et al, *J Neurovirol*	2011	Single-arm n=15	10 wks NPZ10, MRS, DTI	⇔ global ⇗ MRS, ⇔ DTI	- short-term follow-up - single-arm design
Minocycline	Sacktor et al, *Neurology*	2011	Double-blind, placebo n=107 (52 vs 55)	24 wks NPZ8	⇔ global	- ⇧ comorbidities - ⇩ dosage
	Nakasujja et al, *Neurology*	2013	Double-blind, placebo n73 (36 vs 37)	24 wks NPZ9	⇔ global	- ⇧ comorbidities - ⇩ representation
Oral Rivastigmine	Simioni et al, *Neurology*	2013	Pilot, crossover n=17 (9 vs 8)	20 wks ADAS-Cog	⇔ global ⇗ inf pro speed	- small sample - ⇩ adherence

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Study Design

Randomized Controlled Pilot Study to Compare the Safety and Efficacy of Two Different Coadjuvant Therapies for HIV-Associated Cognitive Impairment. The TRIANT-TE Trial.

Population:

- HAND required
- On stable CART (>6 months)
- No comorbidities (Frascati, 2007)

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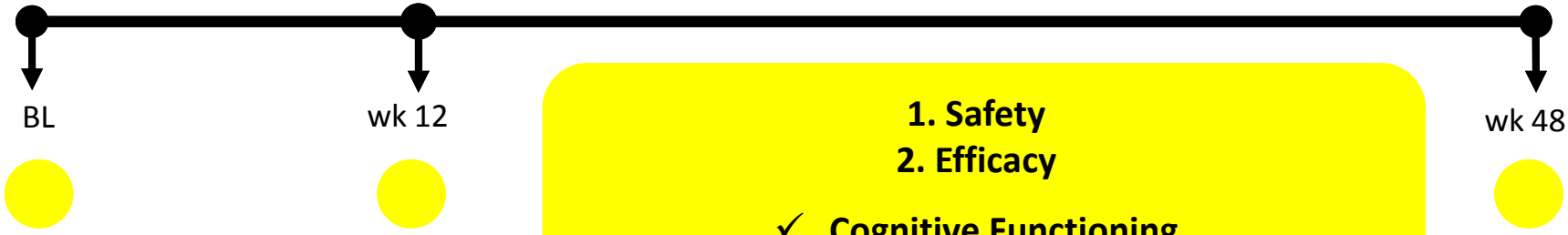
* stratification by CPE score (<8 vs ≥8)

Arm 1:
Transdermal rivastigmine (*4.6 mg ⇨ 9.5 mg*)

Arm 2:
Lithium (*400 mg ⇨ 0.4-0.8 mEq/l*)

Arm 3:
Control group (*no therapy initiation*)



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2. Efficacy

✓ **Cognitive Functioning**
✓ **Functional Outcomes**

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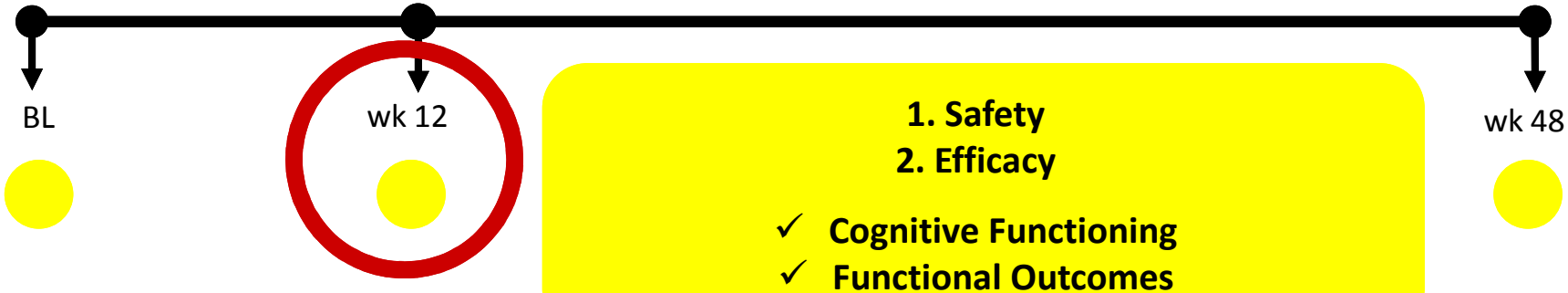

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Variables / Instruments

Demographic + Clinical / Safety Variables

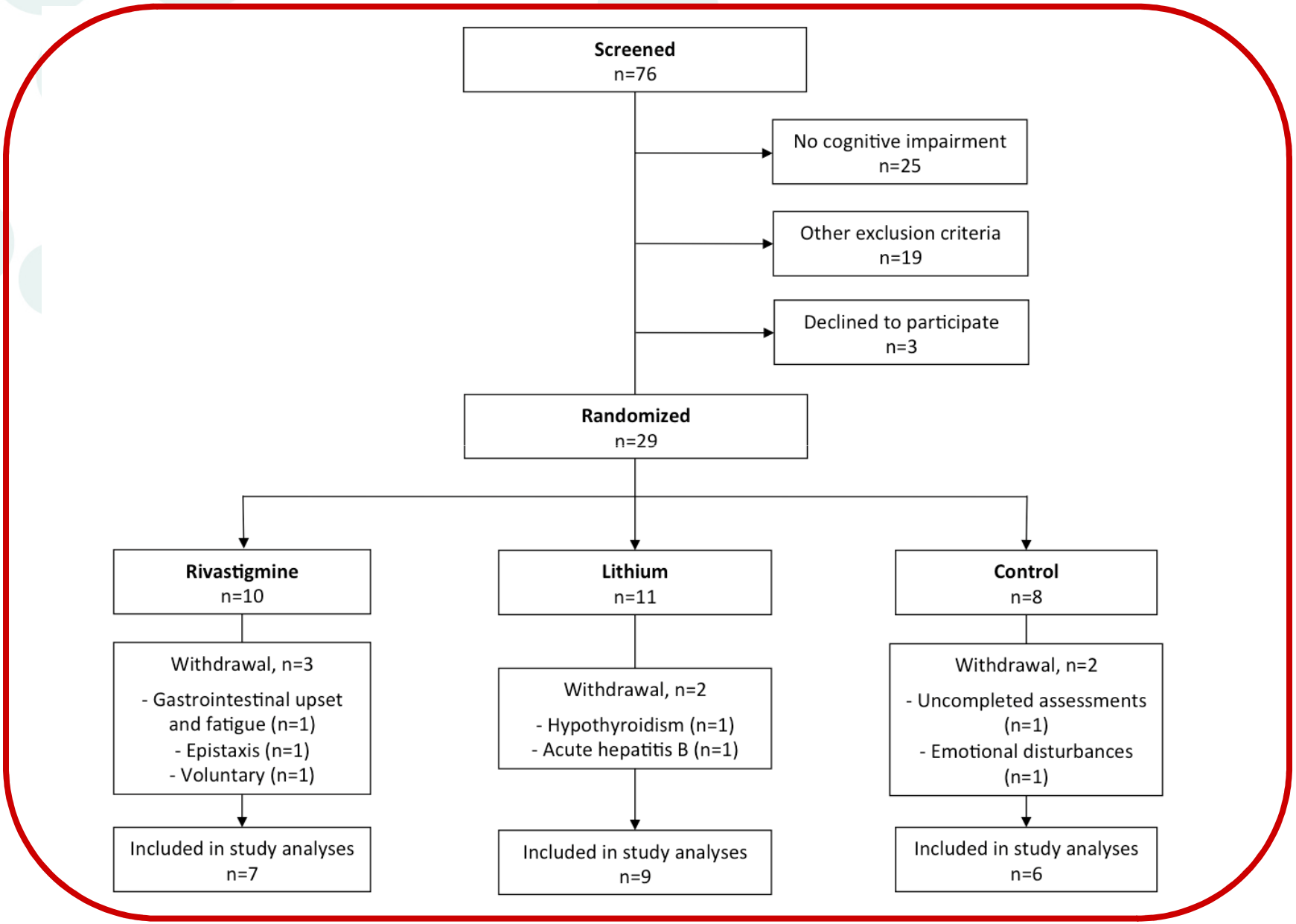
Cognitive Functioning

- ✓ **Global composite score (*NPZ7*)**
- ✓ 7 cognitive domains
- ✓ Frequency of impairment
- ✓ Frequency of cognitive complaints
- ✓ Distribution of HAND

Functional Outcomes

- ✓ Daily functioning (*15 areas, IADL*)
- ✓ Emotional status (*depressive + anxiety symptoms, HADS*)
- ✓ Quality of life (*4 scales, MOS-HIV*)
- ✓ Satisfaction outcomes

Results: Flow Diagram



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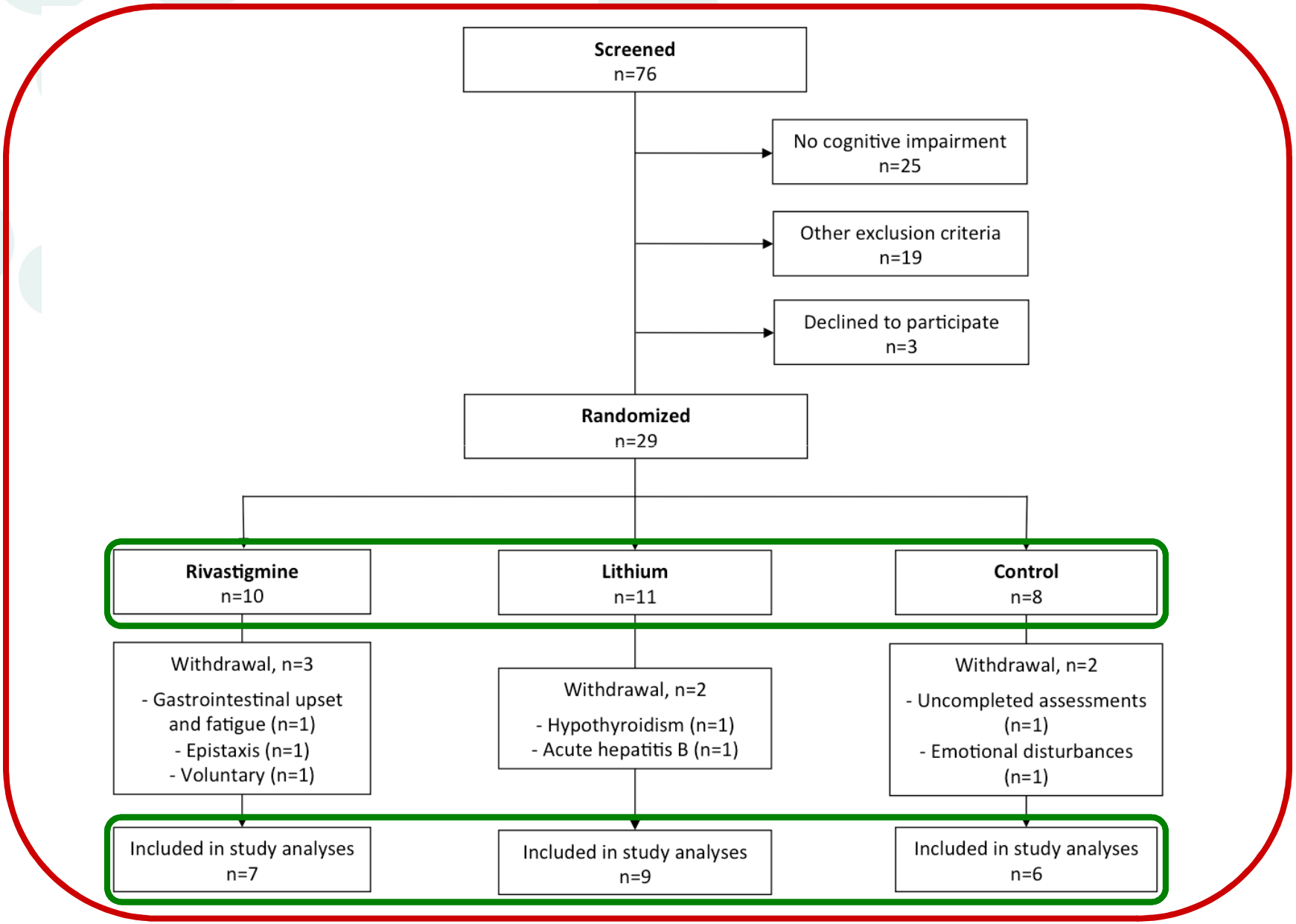

Results: Baseline Characteristics

	Rivastigmine (n=10)	Lithium (n=11)	Control (n=8)	*p* Value
Age, y, mean (SD)	45 (7)	43 (5)	45 (3)	0.592
Male, n (%)	7 (70)	9 (81)	7 (87)	0.640
Years of education, mean (SD)	11 (4)	13 (5)	12 (4)	0.497
HIV diagnosis, y, mean (SD)	17 (7)	8 (4)	12 (7)	***0.020***
Months on current ARV regimen, mean (SD)	34 (30)	31 (24)	64 (77)	0.282
CPE score, mean (SD) [a]	7 (1)	7 (2)	7 (1)	0.633
CD4 cell count, mean (SD)	591 (211)	649 (206)	463 (218)	0.180
Nadir CD4 cell count, mean (SD)	180 (126)	280 (100)	194 (123)	0.124
Undetectable viral load, n (%) [b]	10 (100)	11 (100)	8 (100)	-
Depressive symptoms, mean (SD) [c]	8 (5)	6 (4)	7 (4)	0.789
Anxiety symptoms, mean (SD) [c]	9 (4)	10 (3)	8 (4)	0.765
GDS, mean (SD)	0.84 (0.54)	0.57 (0.22)	0.77 (0.23)	0.229
NPZ7, mean (SD)	-0.67 (0.57)	-0.08 (0.28)	-0.49 (0.30)	***0.017***
HAND, n (%) [i]				
ANI	2 (20)	0 (0)	1 (12)	
MND	8 (80)	11 (100)	7 (88)	0.196
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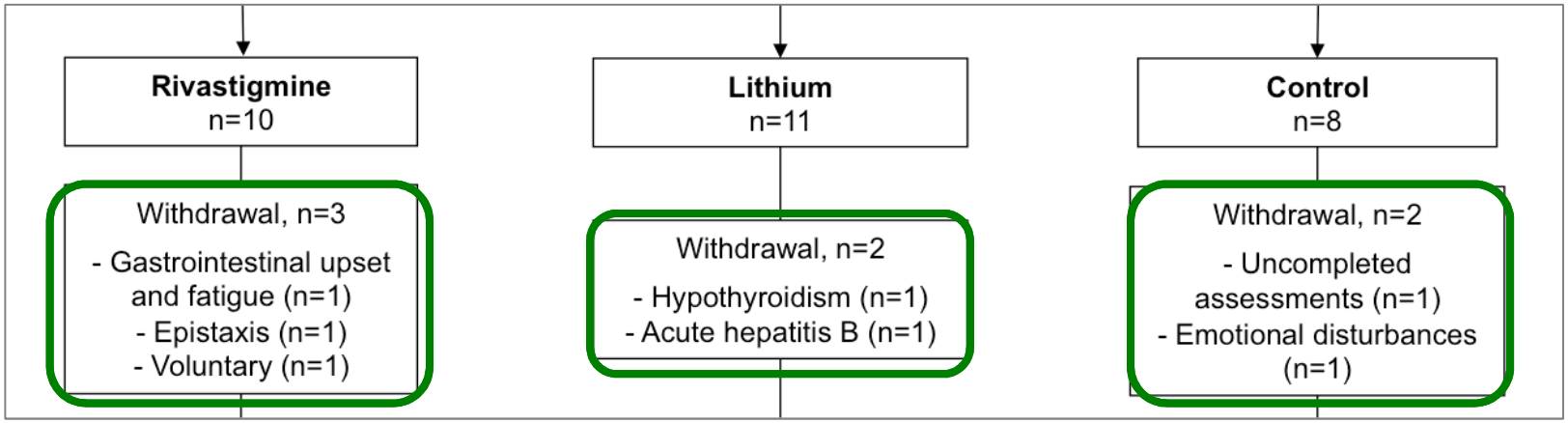
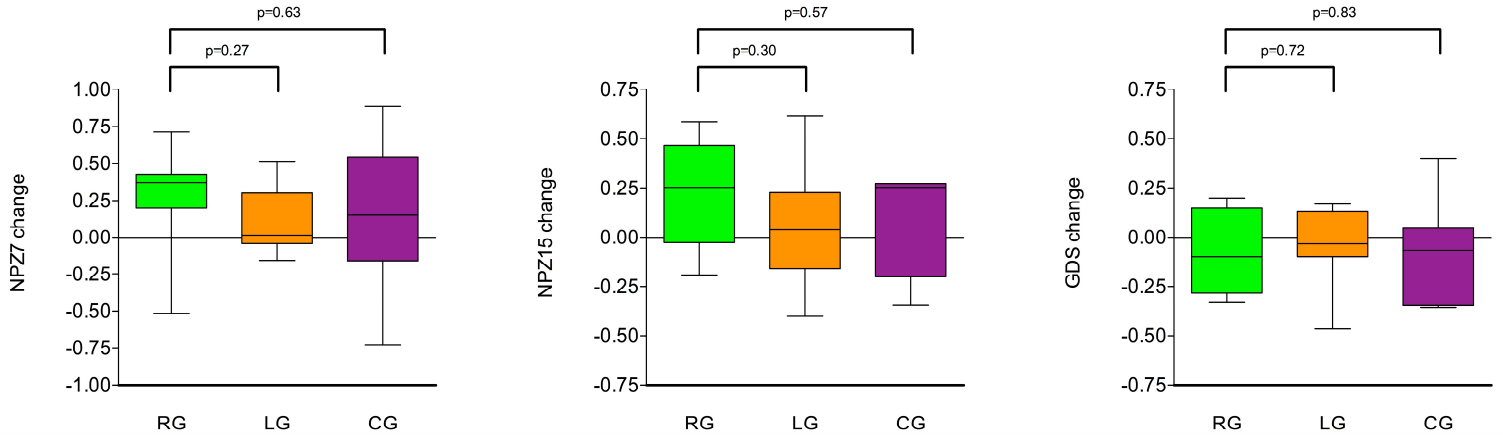
Results: Safety



- ✓ Rate of drop-outs: *3 (30%) vs 2 (18%) vs 2 (25%)*.
- ✓ Related to new medication:

  1 (10%) in RG (abdominal upset and fatigue),
  1 (9%) in LG (hypothyroidism).
- ✓ No severe adverse events.
- ✓ No relevant changes in blood count, biochemistry or immunology.

Results: Primary Endpoint



- ✓ No significant improvement in any group.
- ✓ No differences in specific measures or domains.
- ✓ A trend regarding attention/working memory:

  RG: 0.19 vs LG: -0.03; p=0.17.
- ✓ Rates of impairment: *71% vs 55% vs 100%; p=0.08*.
- ✓ No changes in cognitive complaints or HAND.

Results: Secondary Endpoints

- ✓ No significant improvement in any area.
- ✓ Trend towards **daily functioning** benefits in RG:

  Economy management (p=0.08) and medication management (p=0.05).
- ✓ Trend towards **emotional** benefits in LG:

  Depressive symptoms (p=0.10) and anxiety symptoms (p=0.15).
- ✓ Trend towards benefits in **quality of life** in RG:

  Physical quality of life (p=0.05).
- ✓ Similar **satisfaction** levels:

  Effort (p=0.19), easiness (p=0.43) and general satisfaction (p=0.69).

Limitations

- ☞ Small sample.
- ☞ Differences in baseline characteristics.
- ☞ Non-blinded design.

Conclusions

- ☑ *Transdermal rivastigmine was safe and well-tolerated in HIV-infected patients on stable CART with a 12-week follow-up.*
- ☑ *No significant improvement was observed in cognitive functioning or functional parameters.*
- ☑ *There were some trends towards slight benefits linked to the use of transdermal rivastigmine.*
- ☑ *Our results are consistent with prior findings regarding oral rivastigmine, although we observed a lower adverse events rate.*
- ☑ *Data at week 48 will provide key long-term information about transdermal rivastigmine for HIV-associated cognitive impairment.*

Thanks!

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