Impact of single and multiple component interventions to improve medication adherence: a network meta-analysis

Fernanda S. Tonin, Elyssa Wiecek, **Andrea Torres-Robles**, Shalom I. Benrimoj, Fernando Fernandez-Llimos, Victoria Garcia-Cardenas

Background

      Medication adherence **X** complex interventions

      Network meta-analysis

Research
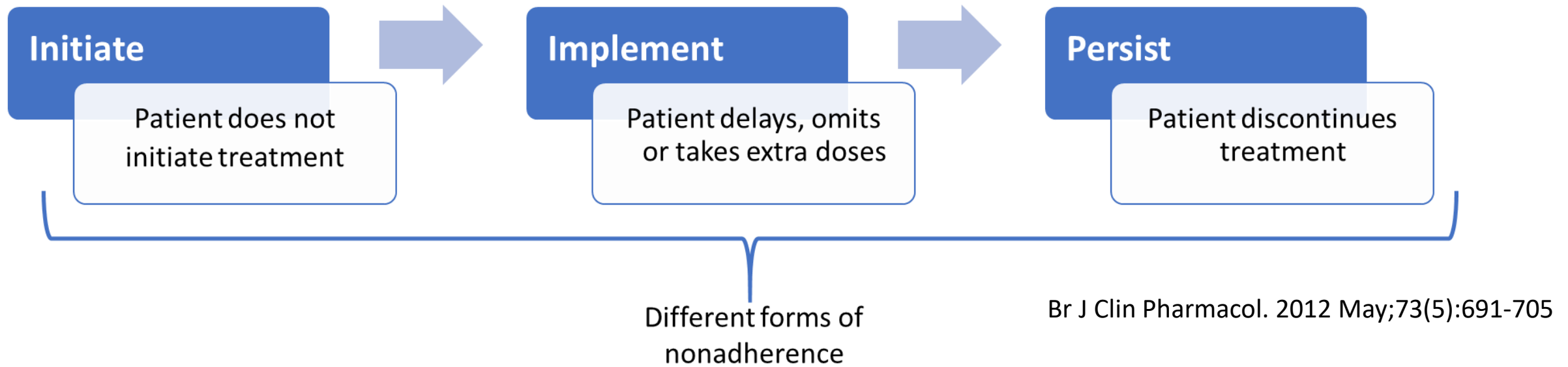
      Main goals

      Methods

      Results

Conclusions

      Highlights

➤ **Conflict of interest**: none to declare

Interventions to improve medication adherence

Initiate →	Implement →	Persist
Patient does not initiate treatment	Patient delays, omits or takes extra doses	Patient discontinues treatment

Different forms of nonadherence

Br J Clin Pharmacol. 2012 May;73(5):691-705

🙂 Different interventions exist to improve medication adherence
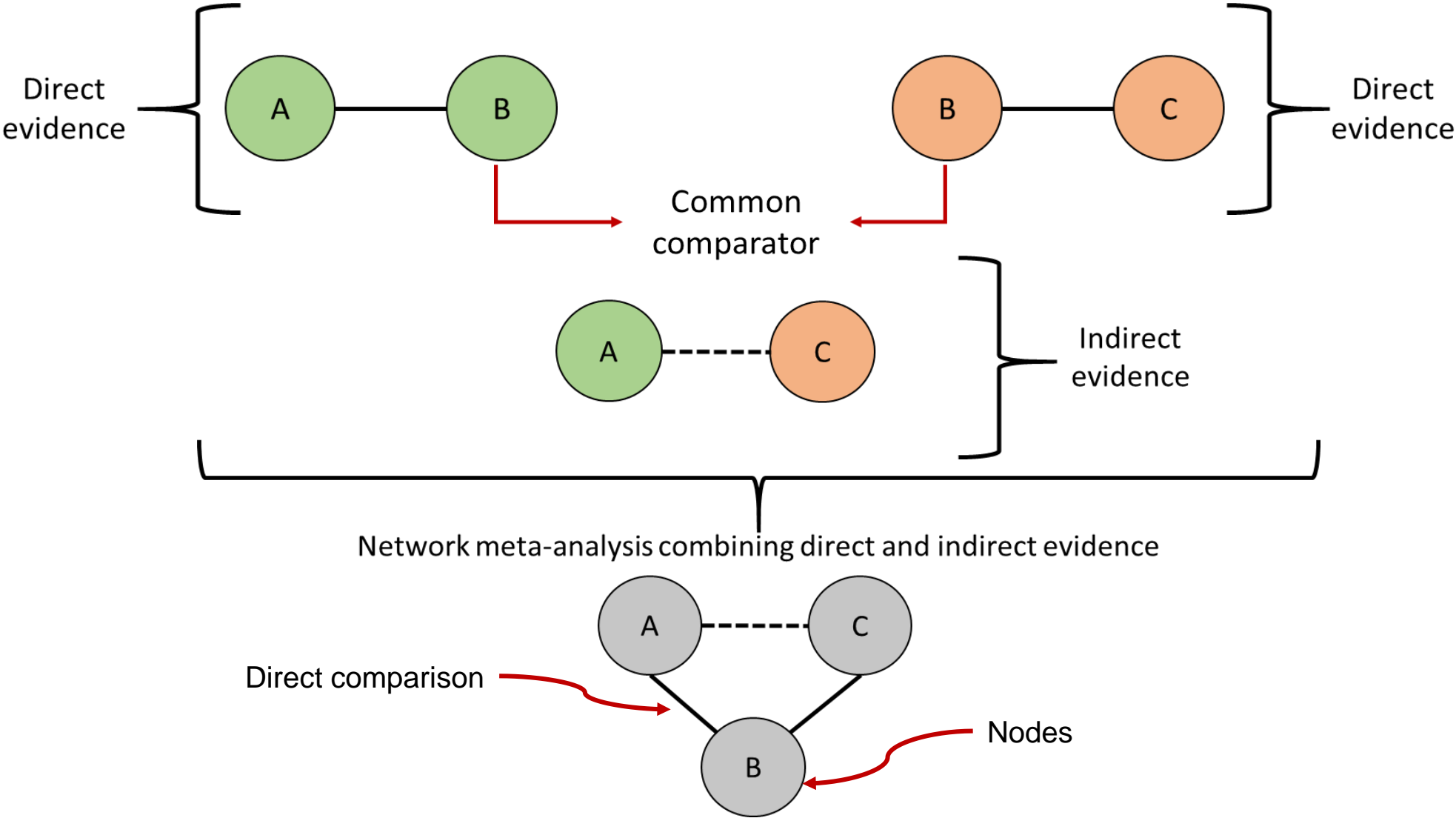➤ *Single-component interventions*
➤ *Multiple-component interventions*
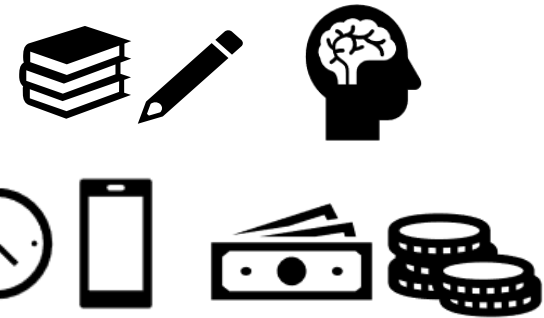
🙁 Inconsistency: limited robust evidence on the comparative effect of complex interventions to enhance medication adherence exists

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for enhancing medication adherence (Review)

Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB

"….effects were inconsistent from study to study, and only a minority of lowest risk of bias RCTs improved both adherence and clinical outcomes. Current methods of improving medication adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized…"

Cochrane Database Syst Rev. 2014 Nov 20;(11):CD000011

Network meta-analysis

Network meta-analysis

How are the results presented?
Consistency analysis

Pool effect sizes (95% CrI)
for all pairs of comparisons
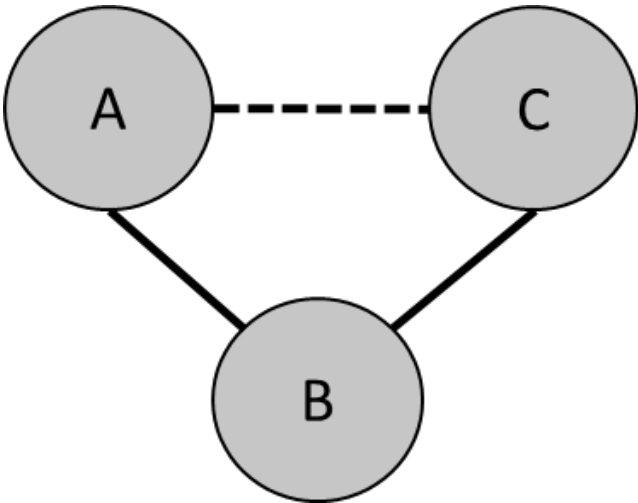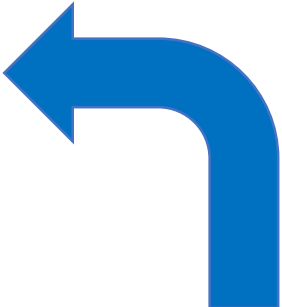
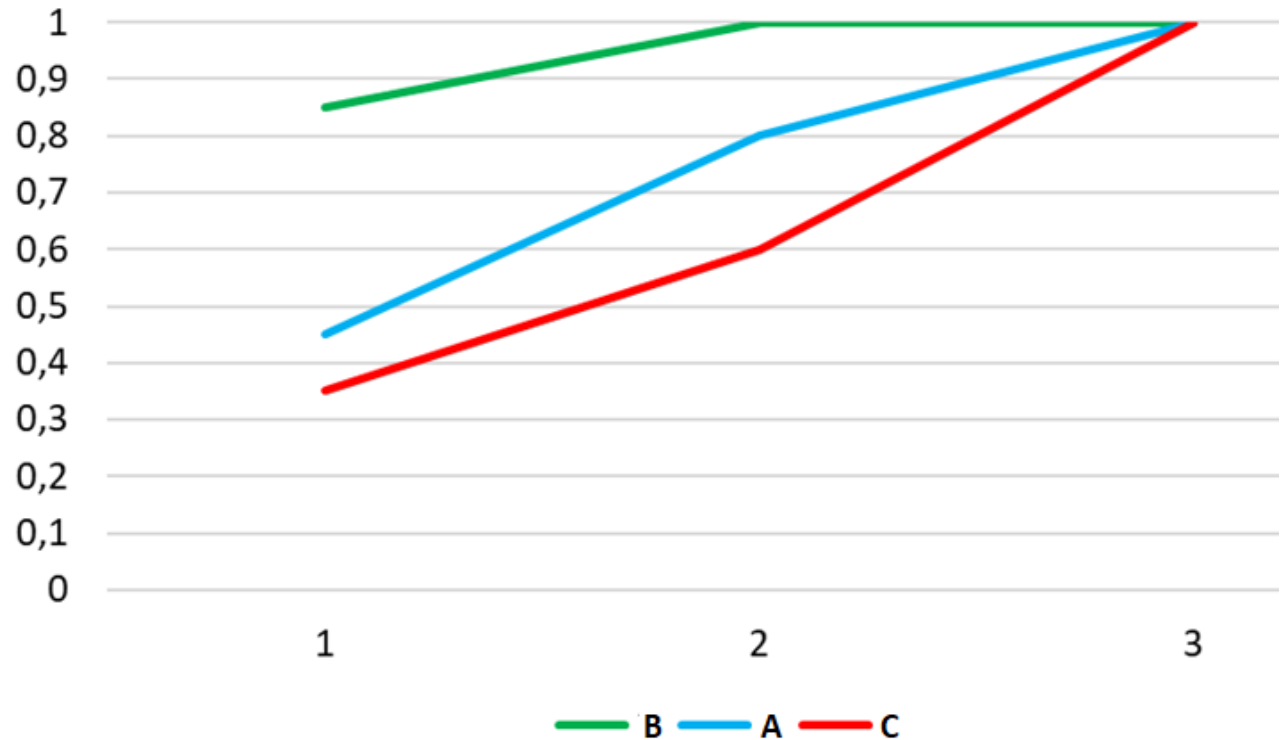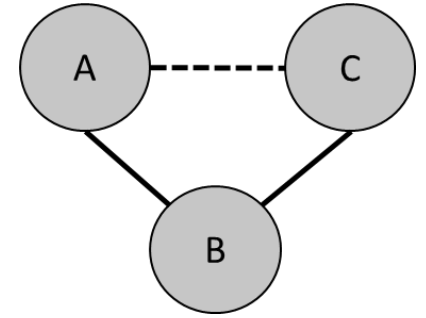| A	1.14 [1.04 - 1.28]	0.87 [0.47 – 1.25]
	B	0.73 [0.44 – 0.93]
		C

Network meta-analysis

How are the results presented?
Rank order

Surface under the cumulative curve analysis (SUCRA)

0% = worst option
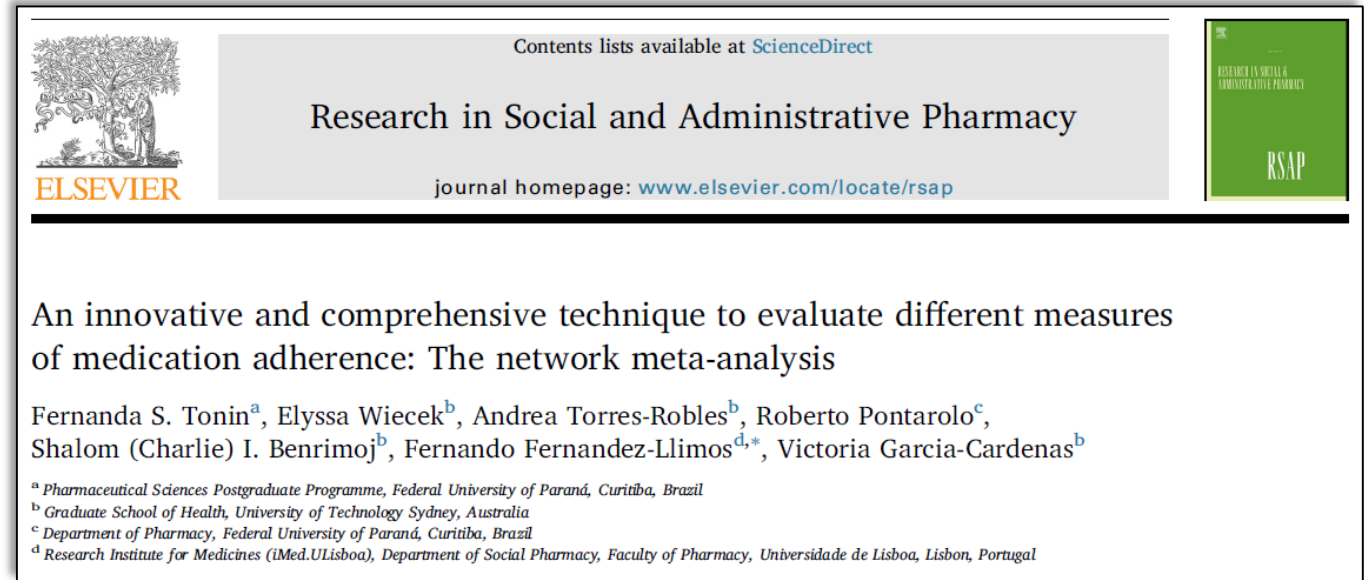100% = best option

A = 62%
B = 92%
C = 45%

Probability of each intervention to be the best, second best, and so on...

Systematic review with network meta-analysis
(PROSPERO CRD42018054598)

<div>

OBJECTIVE

to compare the impact of single- and multiple-component interventions to enhance patient's medication adherence in the implementation phase

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An innovative and comprehensive technique to evaluate different measures of medication adherence: The network meta-analysis

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- Systematic searches: PubMed (two-steps approach)
- Inclusion criteria: trials assessing interventions aiming to improve medication adherence
- Measures of adherence: self-report, pill count, medication event monitoring system
- Validated composite measure: to standardize the results obtained of the measures
- Follow-up: short (<3 months – 1st trimester) and long (>10 months – 4th trimester) periods

Systematic review with network meta-analysis
(PROSPERO CRD42018054598)

Interventions

Single-component
Multiple-component

Category	Definitions
Educational	Interventions providing information regarding the medication, disease state or importance of adherence to a patient with the aim of increasing patient's knowledge or skills that facilitate adherence
Attitudinal	Interventions aiming to modify behavioral intention based on modifying patient's attitudes, beliefs or subjective norm related to their disease state or medication
Technical	Interventions providing any gadget, instrument, or system that facilitate the medication intake or increase convenience of the medication taking process
Rewards	Interventions that provide incentives, awards or penalties to facilitate medication adherence
Standard of care	Usual care defined in the primary study (e.g. regular medication pick-ups including consultations with physician or pharmacist)

Systematic review with network meta-analysis
(PROSPERO CRD42018054598)

- Network meta-analysis: for 3 different scenarios
- Results: short (< 3 months) and long (> 10 months) follow-up periods

| **(I) Scenario**	All interventions: single- and multiple component interventions in one model
(II) Scenario	Single-component interventions (i.e. atitudinal, educational, technical, rewards)
(III) Scenario	Multiple-component interventions (e.g. combination of the of single-component interventions)

Results

Short follow-up (< 3 months)
(I) Scenario: 91 trials included
**(II) Scenario:** 67 trials included
(III) Scenario: 24 trials included

Interventions:
Attitudinal
Attitudinal + Technical
Attitudinal + Technical + Rewards
Educational
Educational + Technical
Educational + Attitudinal
Educational + Attitudinal + Technical
Rewards
Rewards + Technical
Technical
Standard of care

Results
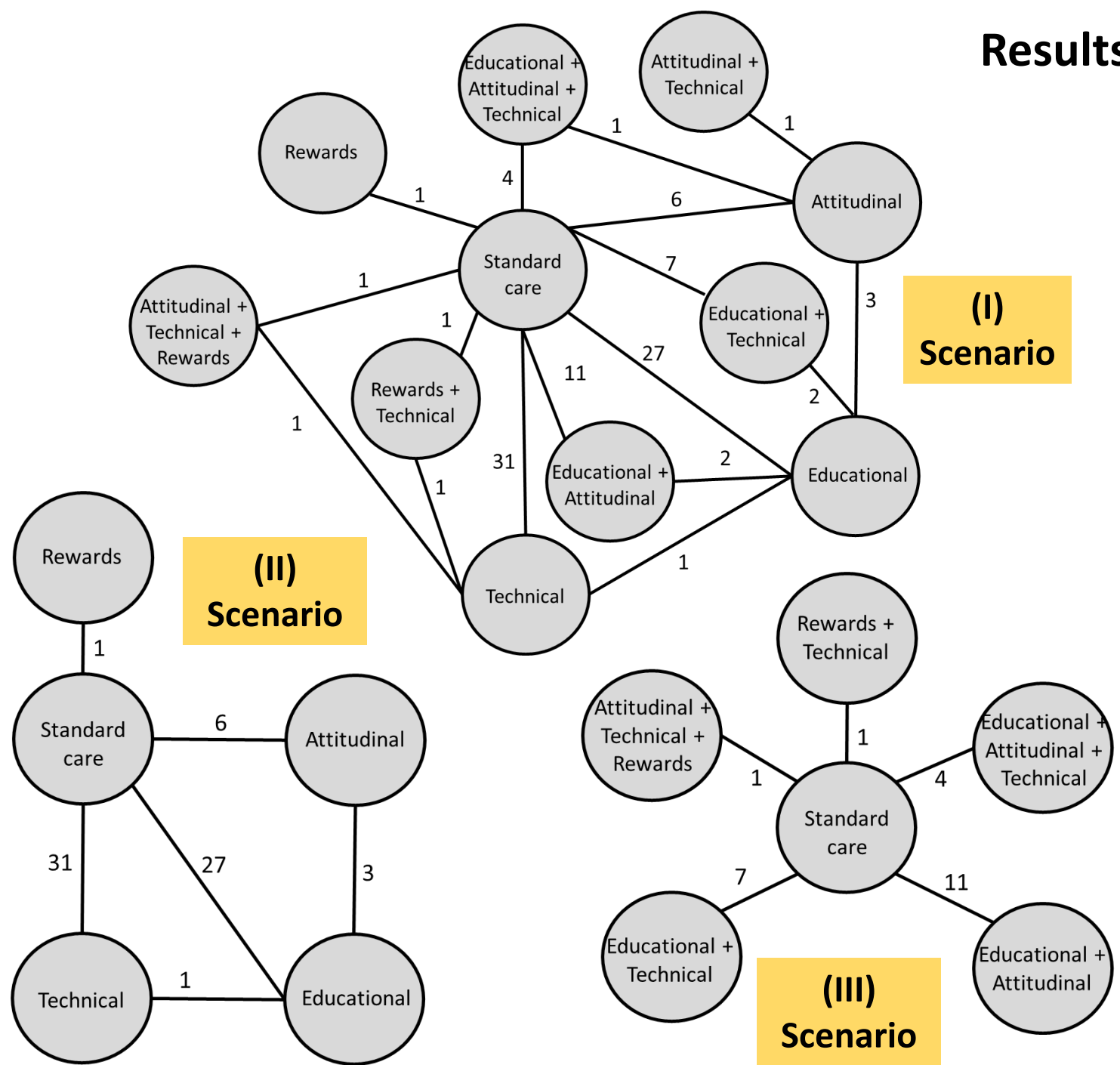
Short follow-up (< 3 months)
(I) Scenario

Rewards + Technical vs. Standard care
Odds ratio 95% CrI 0.09 [0.02-0.34]
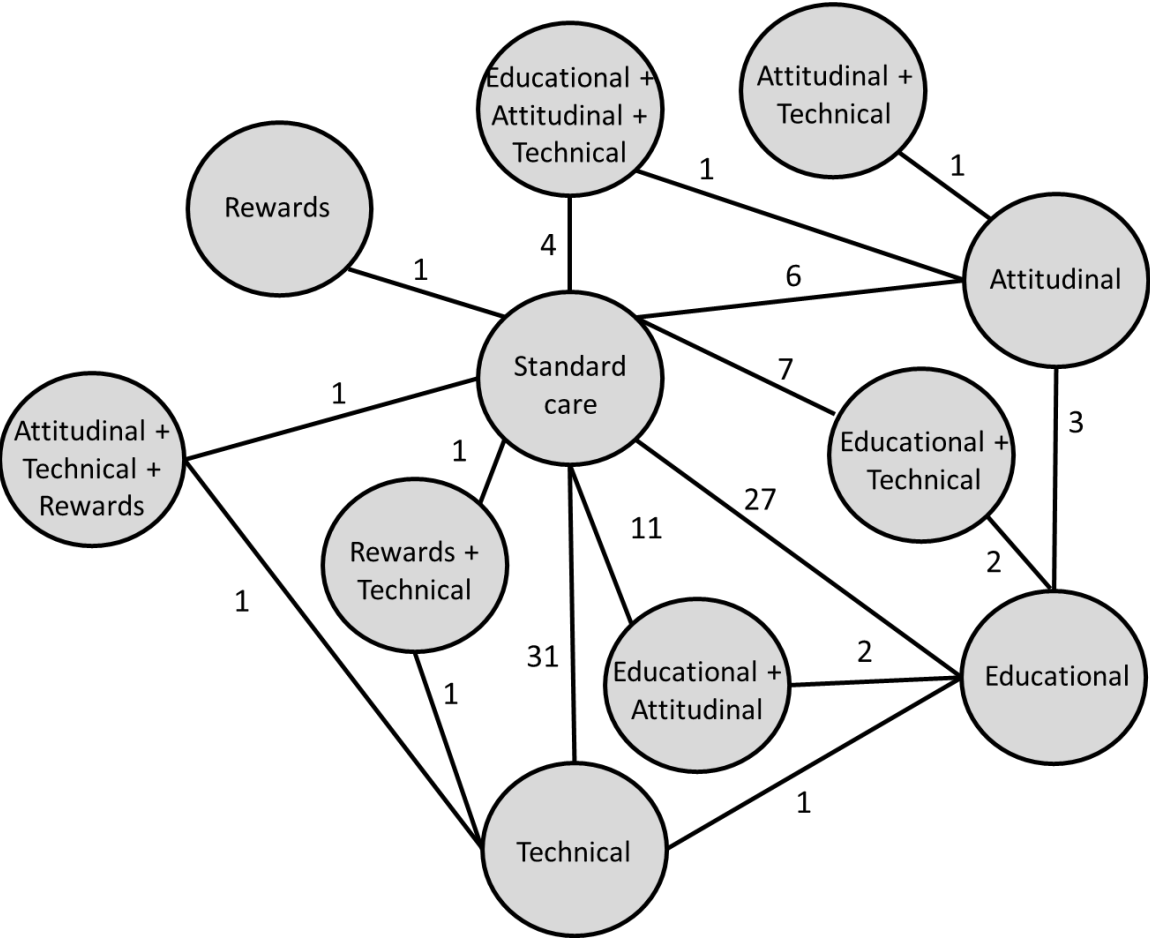
Consistency analysis

ATT + TEC + REW	1.30 (0.11, 13.91)	0.49 (0.07, 2.78)	2.83 (0.28, 25.11)	1.70 (0.07, 71.09)	0.37 (0.05, 2.20)	0.57 (0.08, 3.24)	0.55 (0.07, 3.30)	0.41 (0.06, 2.21)	0.25 (0.04, 1.35)	0.46 (0.07, 2.46)
	ATT + TEC	0.37 (0.08, 1.79)	2.19 (0.26, 19.10)	1.30 (0.07, 56.82)	0.28 (0.05, 1.59)	0.44 (0.08, 2.48)	0.41 (0.07, 2.34)	0.31 (0.06, 1.59)	*0.19 (0.04, 0.97)*	0.34 (0.06, 1.78)
		ATT	*5.96 (1.37, 26.53)*	3.36 (0.28, 115.75)	0.75 (0.34, 1.65)	1.18 (0.59, 2.34)	1.12 (0.54, 2.30)	0.84 (0.50, 1.42)	*0.52 (0.33, 0.84)*	0.93 (0.54, 1.64)
			REW + TEC	0.58 (0.04, 23.76)	*0.13 (0.03, 0.57)*	*0.16 (0.04, 0.69)*	*0.19 (0.04, 0.81)*	*0.14 (0.03, 0.57)*	*0.09 (0.02, 0.34)*	*0.16 (0.04, 0.60)*
				REW	0.22 (0.01, 2.84)	0.29 (0.01, 3.37)	0.33 (0.01, 4.13)	0.25 (0.01, 2.79)	0.16 (0.00, 1.73)	0.28 (0.01, 3.20)
					EDU + ATT + TEC	1.30 (0.59, 2.87)	1.53 (0.65, 3.65)	1.12 (0.54, 2.31)	0.68 (0.34, 1.35)	1.24 (0.60, 2.59)
						EDU + ATT	1.18 (0.62, 2.30)	0.87 (0.54, 1.38)	*0.53 (0.35, 0.79)*	0.96 (0.58, 1.56)
							EDU + TEC	0.75 (0.41, 1.35)	*0.46 (0.27, 0.78)*	0.83 (0.45, 1.52)
								EDU	*0.61 (0.47, 0.80)*	1.11 (0.76, 1.65)
									SOC	*1.82 (1.39, 2.40)*
										TEC

Network diagram (Standard care connected to: Rewards 1, Educational + Attitudinal + Technical 4, Attitudinal + Technical 1, Attitudinal 6, Educational + Technical 7, Educational 27, Rewards + Technical 1, Educational + Attitudinal 11, Technical 31; Attitudinal to Attitudinal + Technical 1, Attitudinal to Educational 3; Educational + Technical to Educational 2; Educational + Attitudinal to Educational 2; Technical to Educational 1; Attitudinal + Technical + Rewards to Standard care 1, to Technical 1; Educational + Attitudinal + Technical to Attitudinal 1)

SUCRA RESULTS	I scenario	II scenario	III scenario
REW + TEC	92%	-	95%
REW	76%	87%	-
ATT + TEC	75%	-	-
ATT + TEC + REW	68%	-	59%
EDU + TEC	53%	-	52%
ATT	45%	60%	-
EDU + ATT	43%	-	51%
TEC	40%	55%	-
EDU	29%	47%	-
EDU + ATT + TEC	25%	-	36%
SOC	3%	2%	8%

SUCRA: surface under the cumulative ranking curve. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first). ATT: attitudinal; REW: rewards; EDU: educational; TEC: technical; SOC: standard of care.
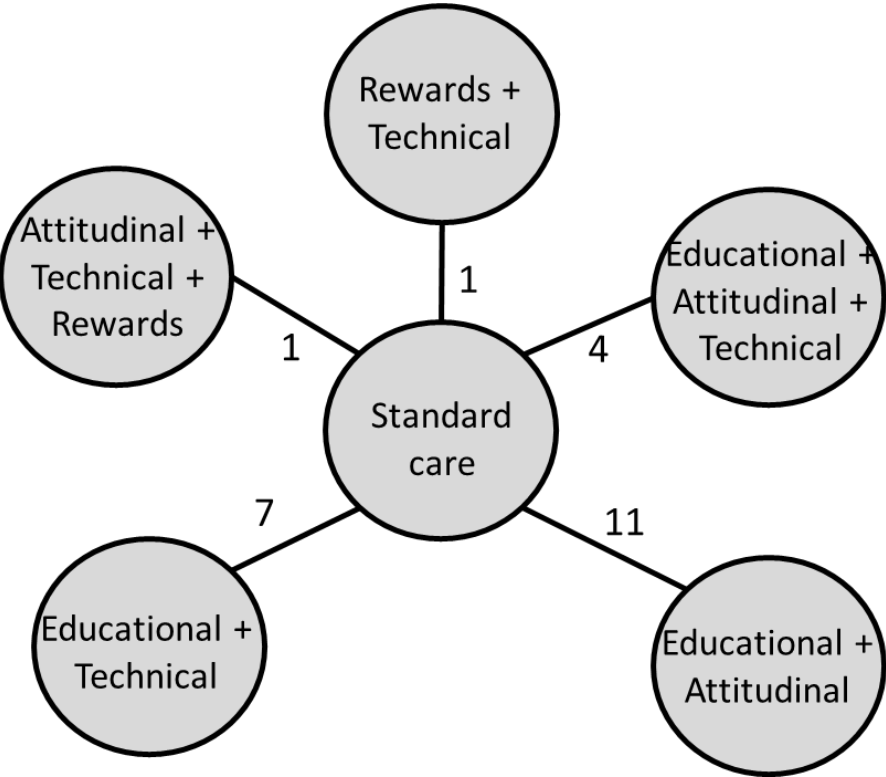
Short follow-up (< 3 months)
(II) Scenario

Rewards vs. Standard care
Odds ratio 95% CrI 0.15 [0.01-1.45]
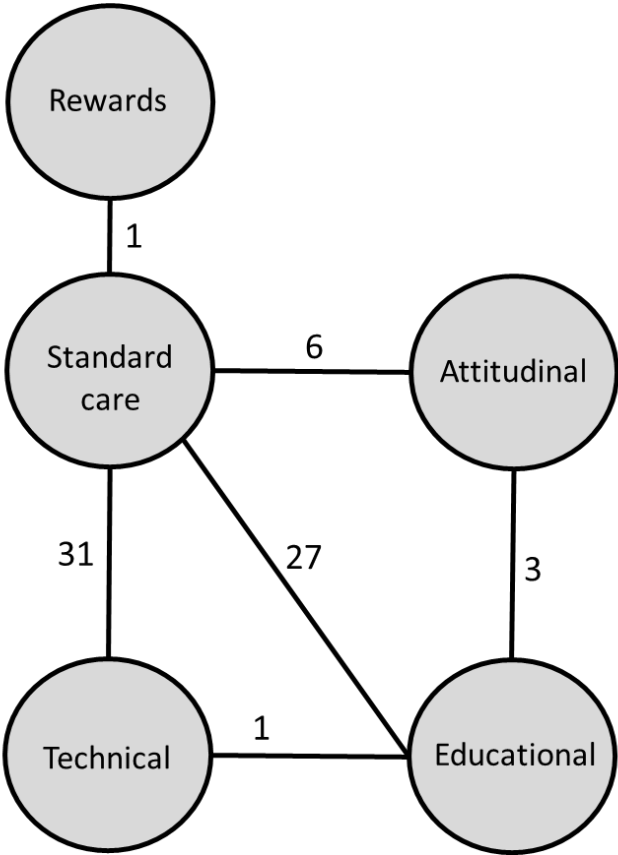
Consistency analysis

ATT	3.38 (0.33, 115.94)	0.91 (0.57, 1.44)	*0.52 (0.34, 0.80)*	0.94 (0.57, 1.52)
	REW	0.27 (0.01, 2.64)	0.15 (0.00, 1.49)	0.27 (0.01, 2.77)
		EDU	*0.57 (0.45, 0.74)*	1.03 (0.74, 1.48)
			SOC	*1.81 (1.41, 2.31)*
				TEC

| SUCRA RESULTS			
	I scenario	**II scenario**	**III scenario**
REW + TEC	92%	-	95%
REW	76%	87%	-
ATT + TEC	75%	-	-
ATT + TEC + REW	68%	-	59%
EDU + TEC	53%	-	52%
ATT	45%	60%	-
EDU + ATT	43%	-	51%
TEC	40%	55%	-
EDU	29%	47%	-
EDU + ATT + TEC	25%	-	36%
SOC	3%	2%	8%

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Results

Short follow-up (< 3 months)
(III) Scenario

Rewards + Technical vs. Standard care
Odds ratio 95% CrI 0.07 [0.01-0.56]

Consistency analysis

ATT + TEC + REW	4.91 (0.22, 125.64)	0.51 (0.04, 6.24)	0.66 (0.06, 7.53)	0.67 (0.06, 8.00)	0.34 (0.03, 3.64)
	REW + TEC	*0.11 (0.01, 0.99)*	0.13 (0.01, 1.14)	0.14 (0.01, 1.26)	*0.07 (0.01, 0.56)*
		EDU + ATT + TEC	1.28 (0.44, 3.99)	1.31 (0.42, 4.31)	0.66 (0.26, 1.72)
			EDU + ATT	1.01 (0.39, 2.61)	*0.52 (0.28, 0.90)*
				EDU + TEC	0.51 (0.23, 1.04)
					SOC

SUCRA RESULTS

	I scenario	II scenario	III scenario
REW + TEC	92%	-	95%
REW	76%	87%	-
ATT + TEC	75%	-	-
ATT + TEC + REW	68%	-	59%
EDU + TEC	53%	-	52%
ATT	45%	60%	-
EDU + ATT	43%	-	51%
TEC	40%	55%	-
EDU	29%	47%	-
EDU + ATT + TEC	25%	-	36%
SOC	3%	2%	8%

SUCRA: surface under the cumulative ranking curve. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first). ATT: attitudinal; REW: rewards; EDU: educational; TEC: technical; SOC: standard of care.

Results

Long follow-up (> 10 months)
(I) **Scenario:** 90 trials included
(II) **Scenario:** 53 trials included
(III) **Scenario:** 36 trials included

Interventions:
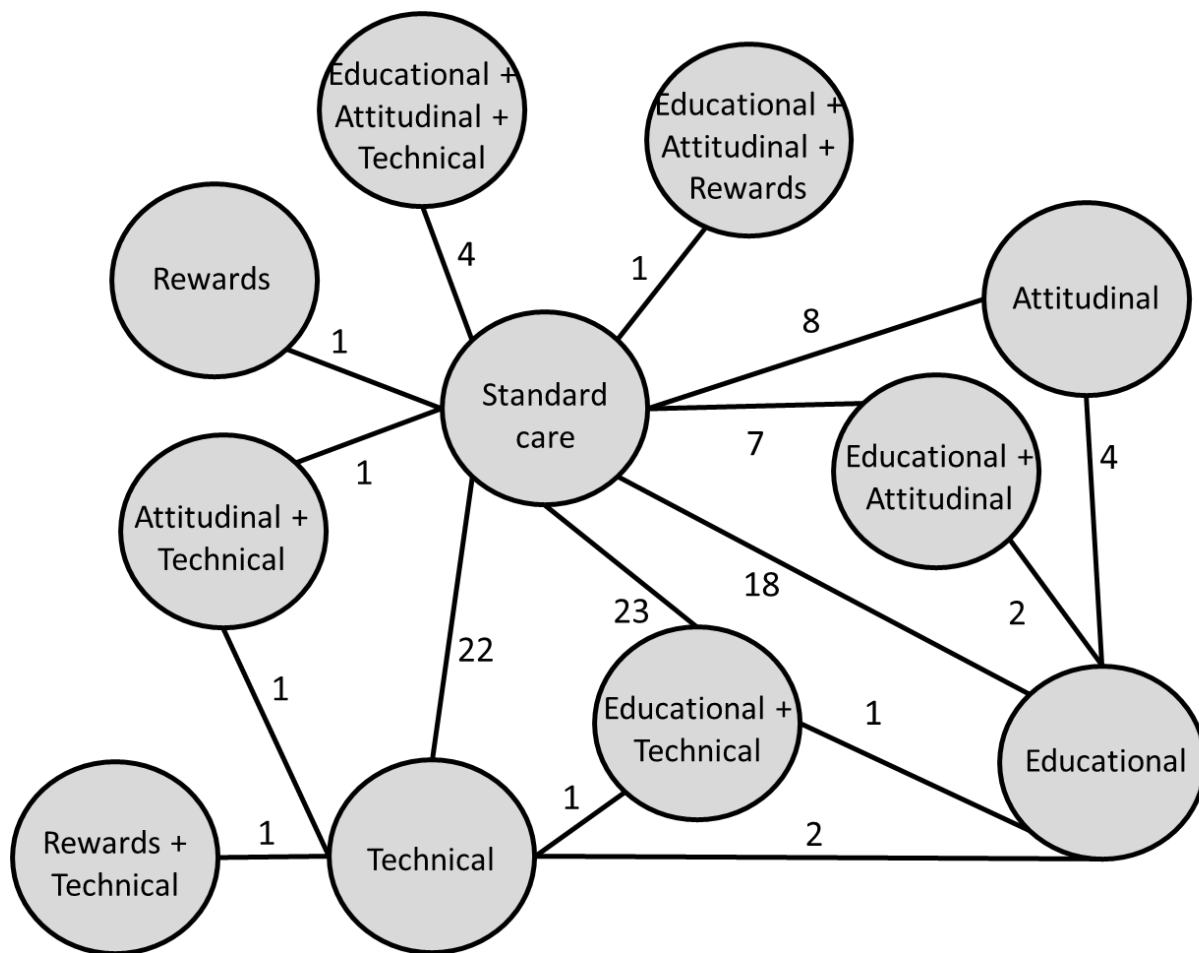
Attitudinal
Attitudinal + Technical
Educational
Educational + Technical
Educational + Attitudinal
Educational + Attitudinal + Technical
Educational + Attitudinal + Rewards
Rewards
Rewards + Technical
Technical
Standard of care

Results
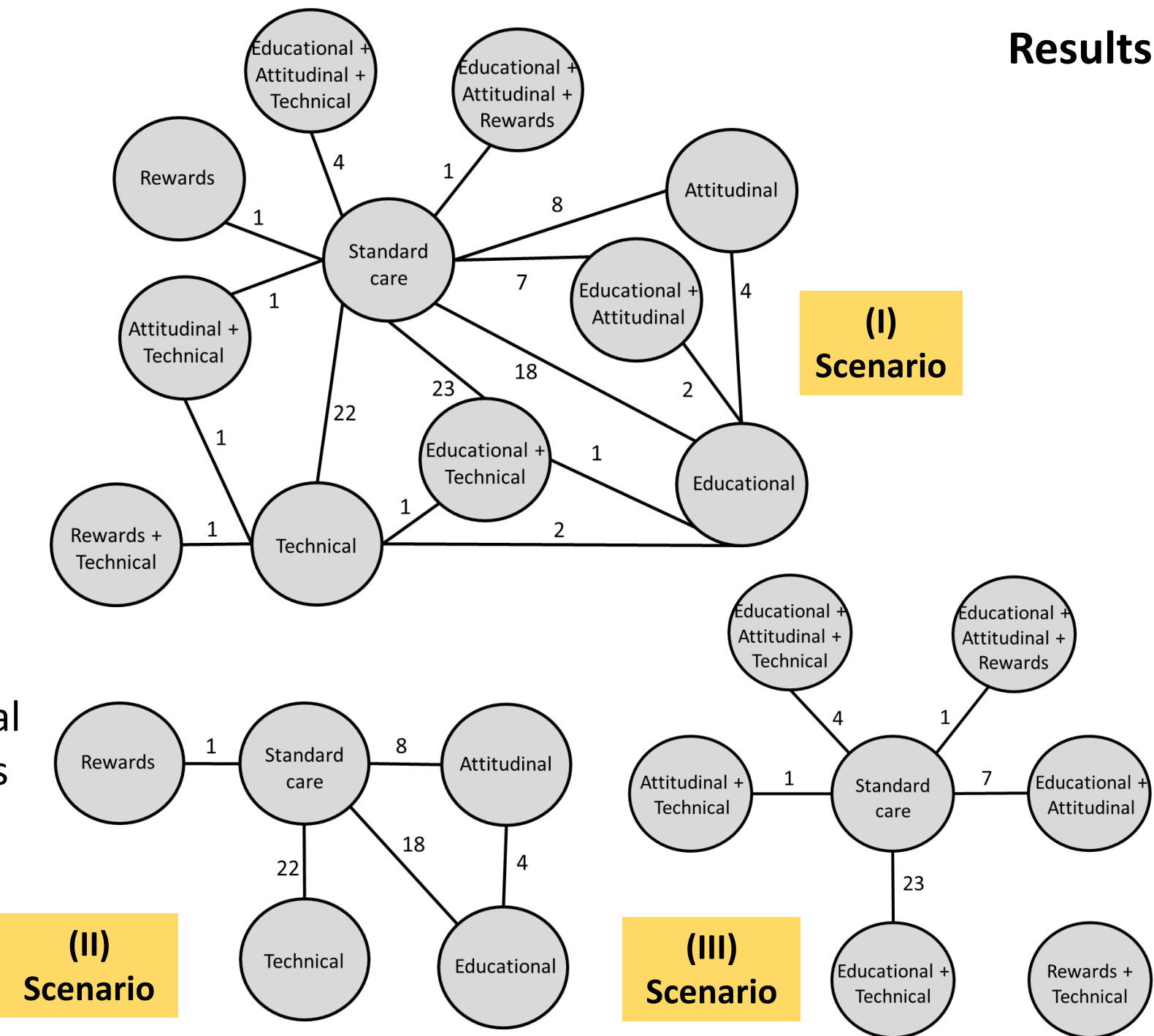
Long follow-up (> 10 months)
(I) Scenario

Rewards + Technical vs. Standard care
Odds ratio 95% CrI 0.05 [0.01-0.22]

Consistency analysis

SUCRA RESULTS	I scenario	II scenario	III scenario
REW + TEC	100%	-	-
EDU + ATT + TEC	73%	-	79%
EDU + ATT + REW	60%	-	65%
EDU + TEC	57%	-	65%
EDU	53%	74%	-
TEC	49%	62%	-
ATT	48%	61%	-
REW	36%	46%	-
EDU + ATT	34%	-	38%
ATT + TEC	31%	-	35%
SOC	8%	6%	15%

SUCRA: surface under the cumulative ranking curve. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first). ATT: attitudinal; REW: rewards; EDU: educational; TEC: technical; SOC: standard of care.

Long follow-up (> 10 months)
(II) Scenario

| Educational vs. Standard care |
| Odds ratio 95% CrI 0.57 [0.44-0.75] |
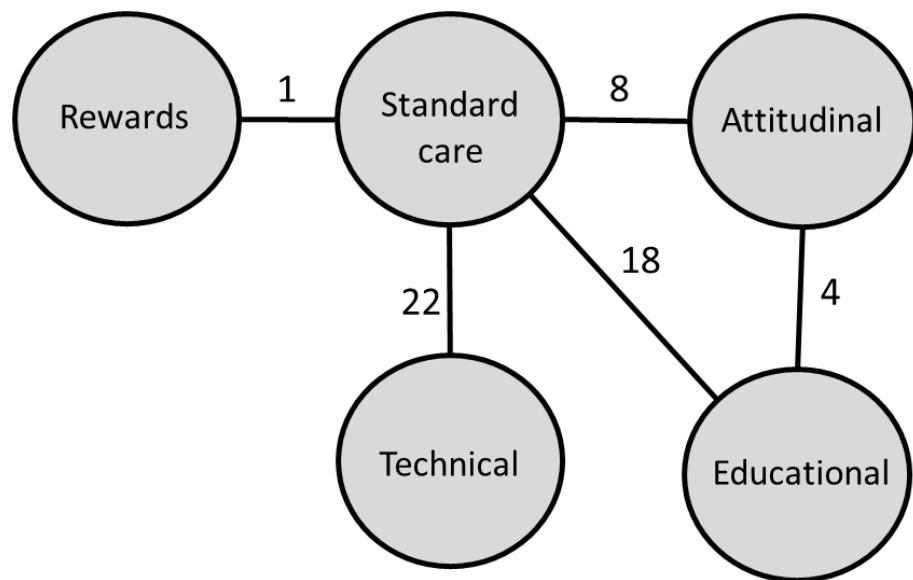
ATT	0.83 (0.31, 2.31)	1.05 (0.72, 1.52)	**_0.60_** **_(0.42, 0.86)_**	0.98 (0.64, 1.53)
	REW	1.26 (0.46, 3.36)	0.72 (0.27, 1.86)	1.18 (0.44, 3.19)
		EDU	**_0.57_** **_(0.44, 0.75)_**	0.93 (0.66, 1.33)
			SOC	**_1.63_** **_(1.29, 2.08)_**
Consistency analysis				TEC

SUCRA RESULTS			
	I scenario	**II scenario**	**III scenario**
REW + TEC	100%	-	-
EDU + ATT + TEC	73%	-	79%
EDU + ATT + REW	60%	-	65%
EDU + TEC	57%	-	65%
EDU	53%	74%	-
TEC	49%	62%	-
ATT	48%	61%	-
REW	36%	46%	-
EDU + ATT	34%	-	38%
ATT + TEC	31%	-	35%
SOC	8%	6%	15%

SUCRA: surface under the cumulative ranking curve. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first). ATT: attitudinal; REW: rewards; EDU: educational; TEC: technical; SOC: standard of care.

Long follow-up (> 10 months)
(III) Scenario

Educational + Attitudinal + Technical
vs. Standard care
Odds ratio 95% CrI 0.42 [0.18-0.97]
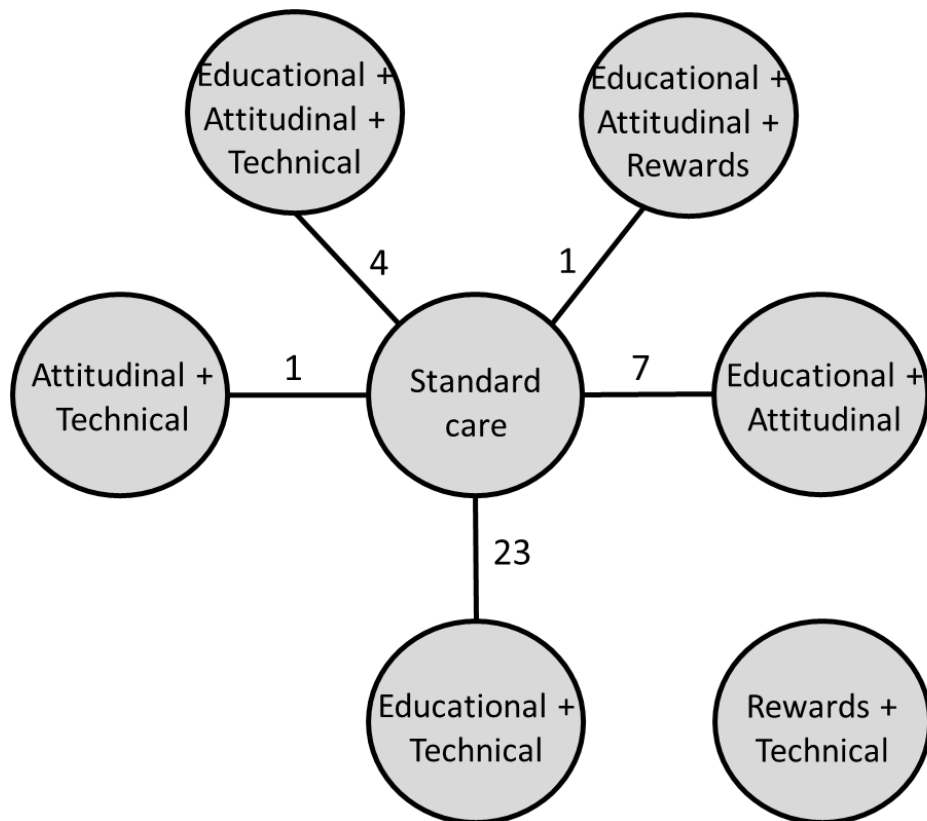
ATT + TEC	1.74 (0.18, 18.02)	1.97 (0.35, 11.35)	1.02 (0.19, 5.48)	1.55 (0.33, 7.47)	0.82 (0.18, 3.82)
	EDU + ATT + REW	1.12 (0.17, 7.23)	0.58 (0.09, 3.53)	0.87 (0.15, 5.07)	0.47 (0.08, 2.52)
		EDU + ATT + TEC	0.53 (0.17, 1.47)	0.80 (0.33, 1.98)	*0.42 (0.18, 0.97)*
			EDU + ATT	1.52 (0.75, 3.29)	0.80 (0.43, 1.57)
				EDU + TEC	*0.53 (0.37, 0.74)*
					SOC

Consistency analysis

SUCRA RESULTS			
	I scenario	**II scenario**	**III scenario**
REW + TEC	100%	-	-
EDU + ATT + TEC	73%	-	79%
EDU + ATT + REW	60%	-	65%
EDU + TEC	57%	-	65%
EDU	53%	74%	-
TEC	49%	62%	-
ATT	48%	61%	-
REW	36%	46%	-
EDU + ATT	34%	-	38%
ATT + TEC	31%	-	35%
SOC	8%	6%	15%

SUCRA: surface under the cumulative ranking curve. SUCRA values can range from 0% (i.e. the intervention always ranks last) to 100% (i.e. the intervention always ranks first). ATT: attitudinal; REW: rewards; EDU: educational; TEC: technical; SOC: standard of care.

Highlights

- The efficacy of the different components remained similar when used in single-component or multiple-component interventions.

- However, multiple-component interventions presented higher impact on medication adherence than similar components when used in single-component interventions.

- Differences in the profile of complex interventions can be observed over time.

- The use of techniques such as network meta-analysis can contribute towards evidence synthesis on the comparative effect of complex interventions to enhance medication adherence.