CAUSALITY IN GUIDELINES

Causal language use and assumptions in clinical practice guidelines: evaluation of causality

Keling Wang
keling.wang@erasmusmc.nl

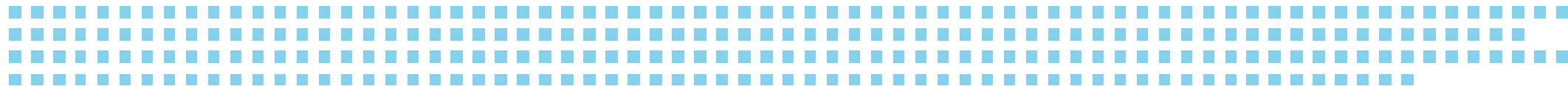**RM Health Sciences student**
Dept. of Epidemiology, Erasmus MC
Supvr.: Dr. Jeremy Labrecque

Presentation of research proposal

Erasmus MC
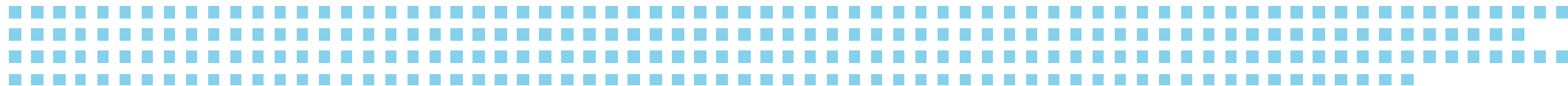Universitair Medisch Centrum Rotterdam

ABOUT ME

- First-year research master student
- Area of interest:

  Causal inference

  Endocrinology & Metabolism

  Transgender health

  Qualitative research

Email: keling.wang@erasmusmc.nl

TABLE OF CONTENTS

BACKGROUND
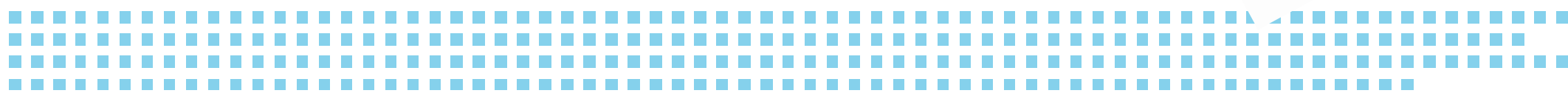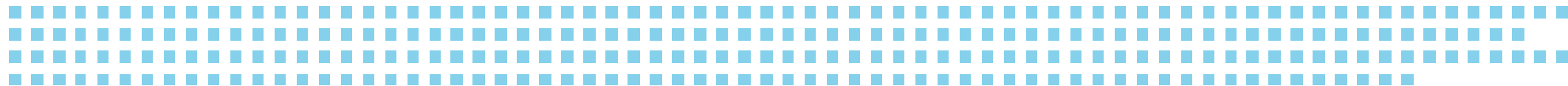
Causal statements in clinical guidelines: what, where, why, how?
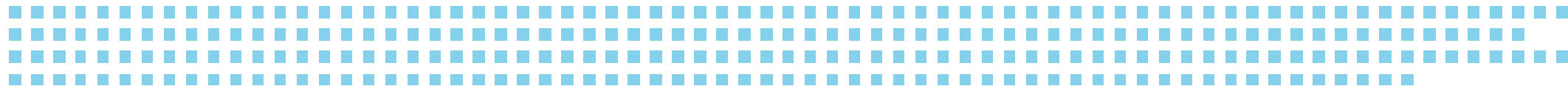
BACKGROUND
Clinical practice guidelines

- Clinical practice guideline (CPG):

  "a set of **statements** that include **recommendations** intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the **benefits and harms** of alternative care options"

- "Clinical practice guidelines are ubiquitous in our healthcare system." [1]

- Most real-world clinical practices **are ruled by** CPGs to date!

  --from cold and flu to cancers

Erasmus MC
Universitair Medisch Centrum Rotterdam

Diabetes Care.

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

JANUARY 2023 | VOLUME 46 | SUPPLEMENT 1

Standards of Care in Diabetes—2023

American Diabetes Association.

ISSN 0149-5992

2023 AHA/ACC Guideline for the Management of Patients with Chronic Coronary Disease

Developed in Collaboration with and Endorsed by the American College of Clinical Pharmacy, American Society for Preventive Cardiology, National Lipid Association and Preventive Cardiovascular Nurses Association

Endorsed by Society for Cardiovascular Angiography and Interventions

ESC European Society of Cardiology

2018 ESC Pocket Guidelines
Committee for Practice Guidelines
MYOCARDIAL REVASCULARIZATION

2018 ESC Pocket Guidelines
Committee for Practice Guidelines
CVD DURING PREGNANCY

2018 ESC Pocket Guidelines
Committee for Practice Guidelines
HYPERTENSION

2018 ESC Pocket Guidelines
Committee for Practice Guidelines
SYNCOPE

2018 ESC Pocket Guidelines
Committee for Practice Guidelines
4ᵗʰ Universal MI

BACKGROUND

What does a guideline look like?

Guideline

Recomm-endations

Supporting Statements

Supporting Studies

section 5

Rec. 5.1

Rec. 5.2

SS5.1.1

SS5.1.2

SS5.2.1

Cohort 1

RCT 2

SR 3

Case-control 4
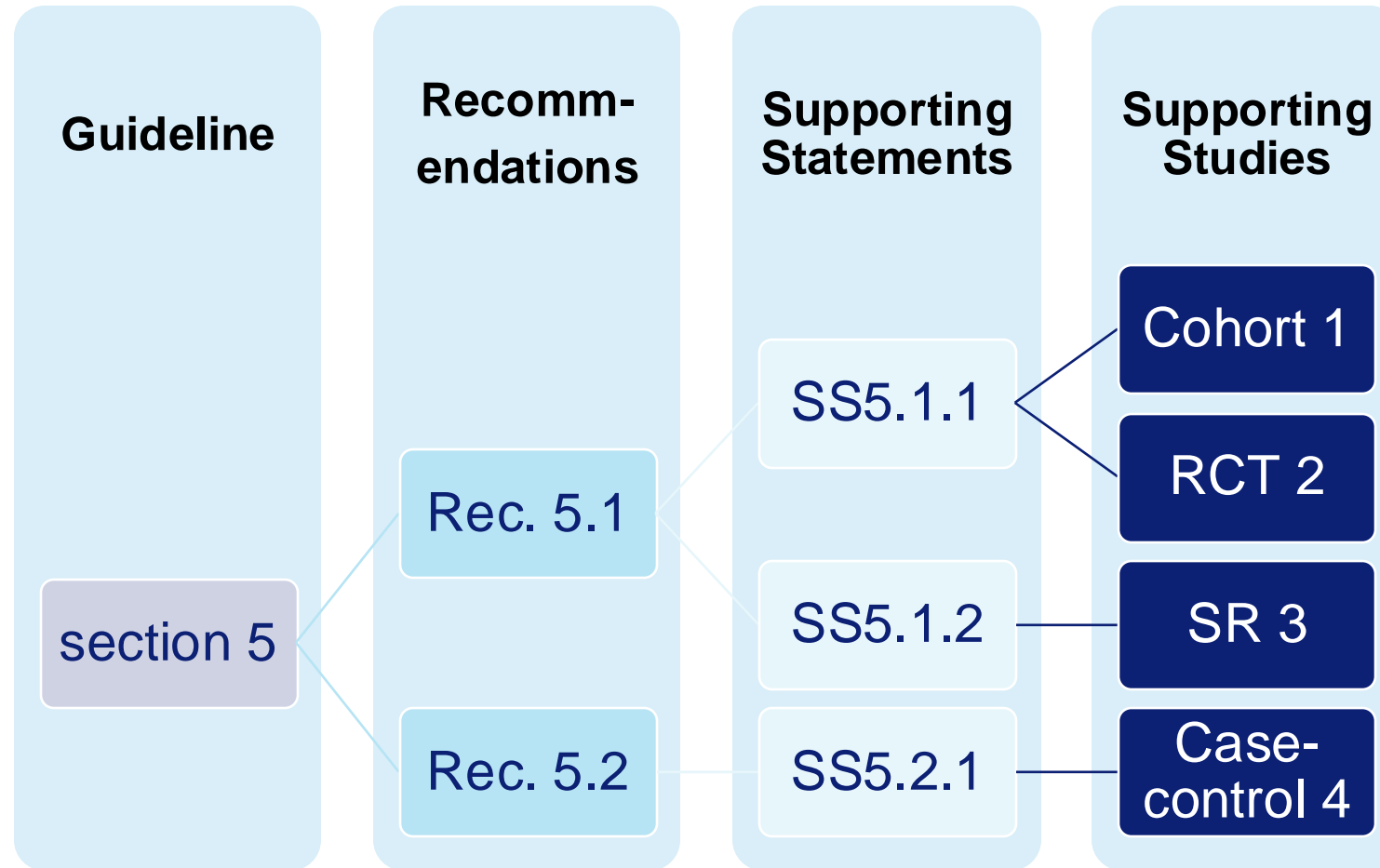
BACKGROUND
Causation in guidelines

- Recommendations attempt to **inform clinical practice**, and contain causal statements about **treatment effect**, benefits and harms, care strategy selection, etc.

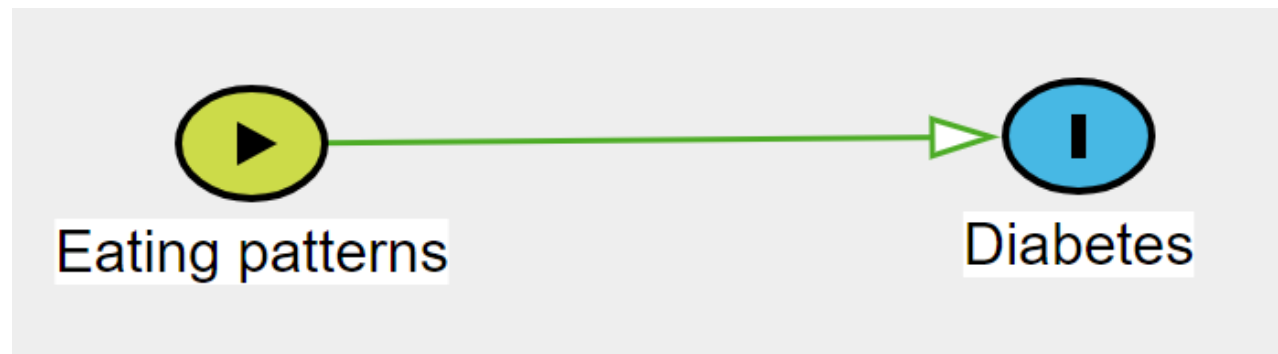- Supporting statements also contain causal language.

BACKGROUND
Causation in guidelines

- Example:

    Recommendation 3.3 (ADA Diabetes SoC 2023)

    A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. **B** [2]
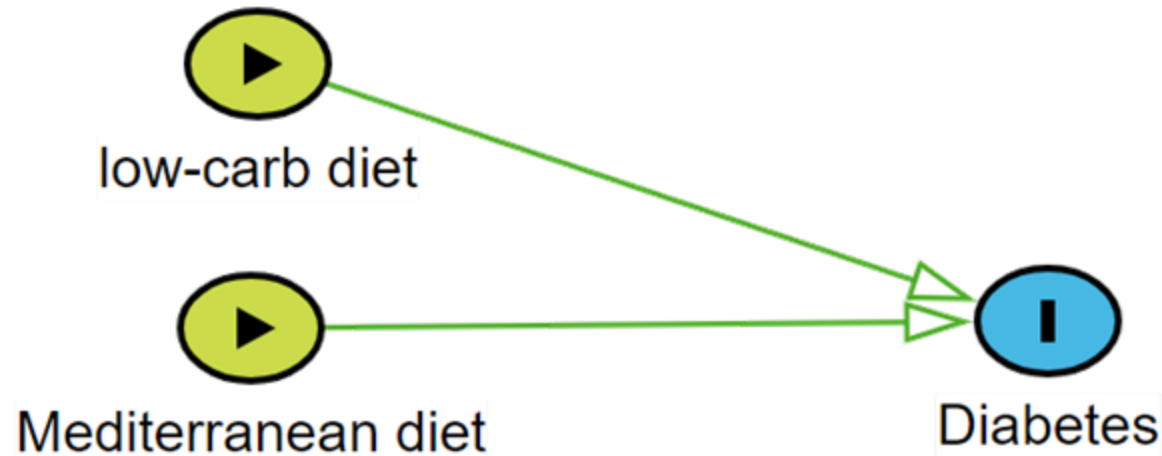

$A \longrightarrow Y^a$

BACKGROUND
Causation in guidelines

- Example:
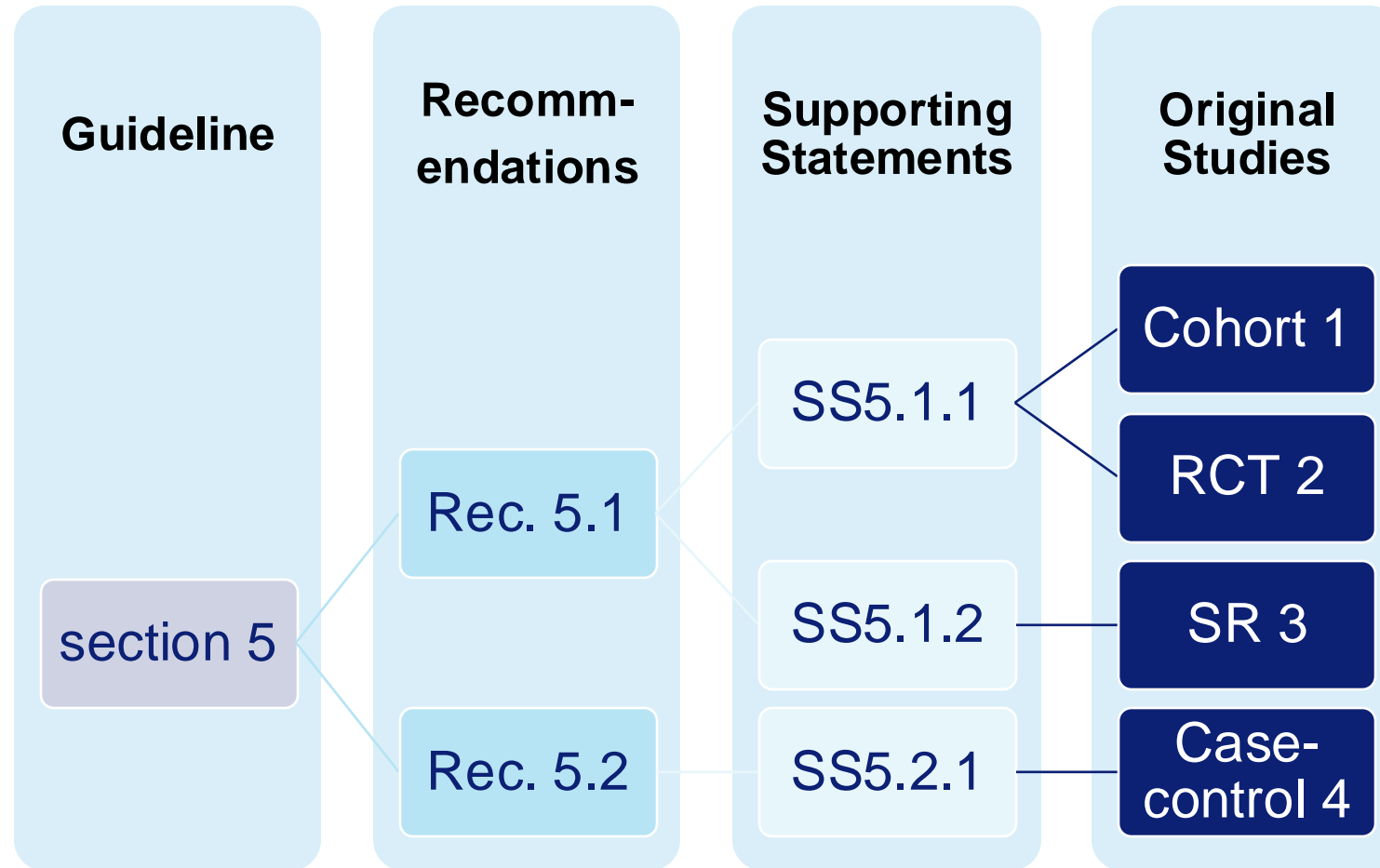
    Supporting statement for Recommendation 3.3

    Based on other intervention trials, a variety of eating patterns… may also be appropriate for individuals with prediabetes (**10**), including Mediterranean-style and low-carbohydrate eating plans (**12**–**15**).[2]
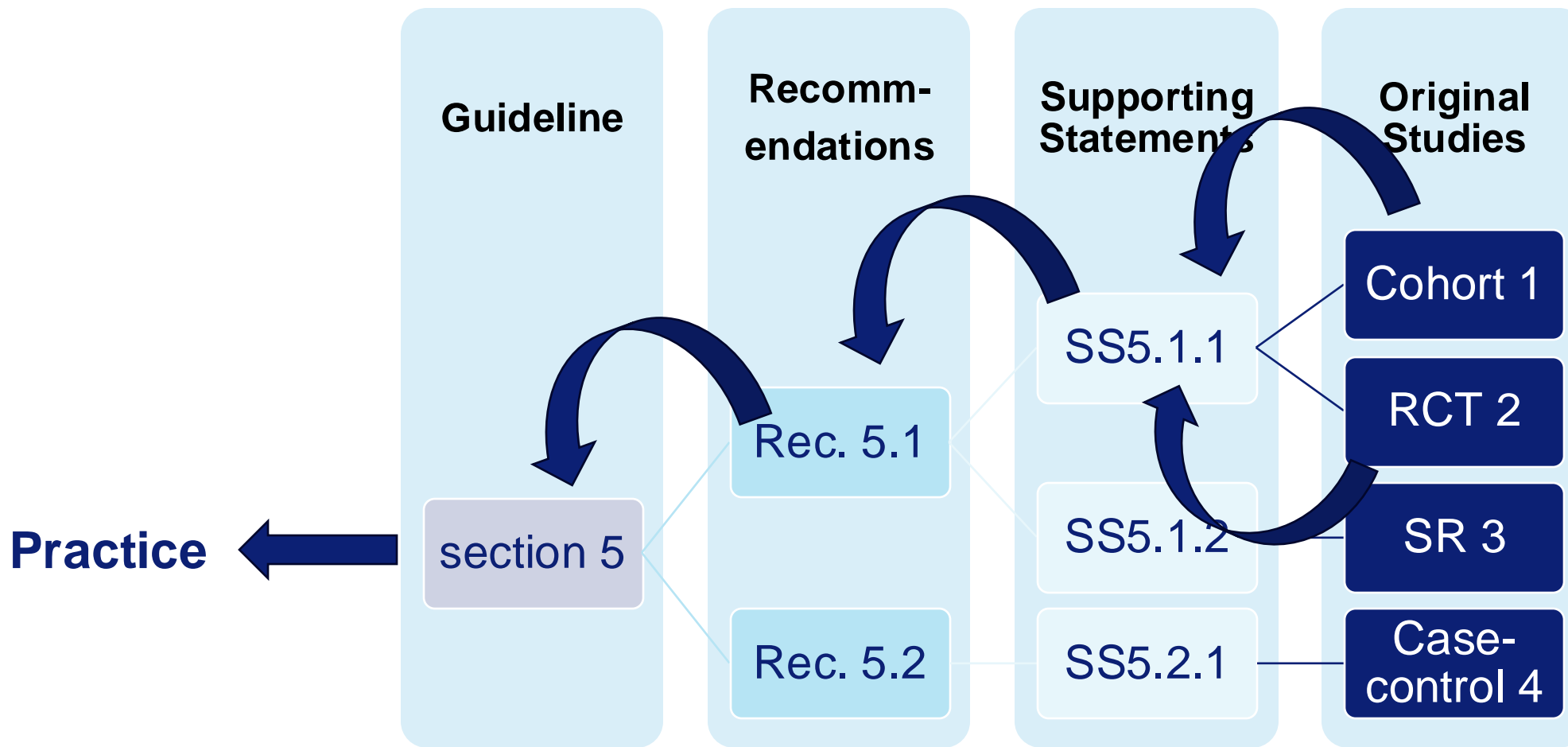
BACKGROUND
Evidence passing

Practice

Guideline	Recomm-endations	Supporting Statements	Original Studies

- section 5
- Rec. 5.1
- Rec. 5.2
- SS5.1.1
- SS5.1.2
- SS5.2.1
- Cohort 1
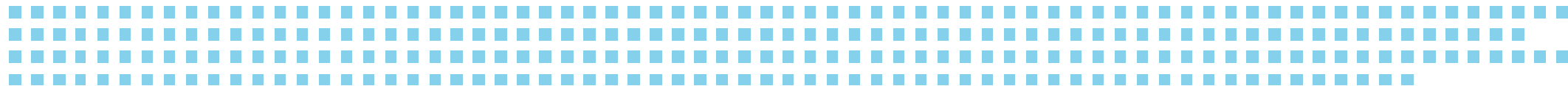- RCT 2
- SR 3
- Case-control 4
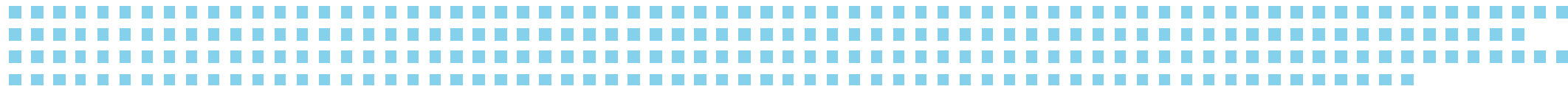
BACKGROUND
Evidence passing

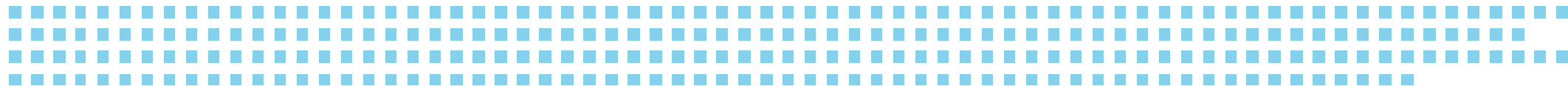**Therefore, if a recommendation statement is causal, this causation should come from...**

Therefore, if a recommendation statement is causal, this causation should come from...

Original studies!

However...
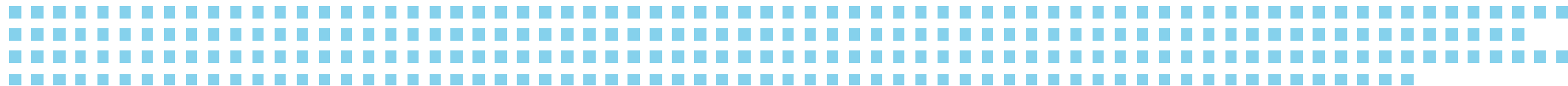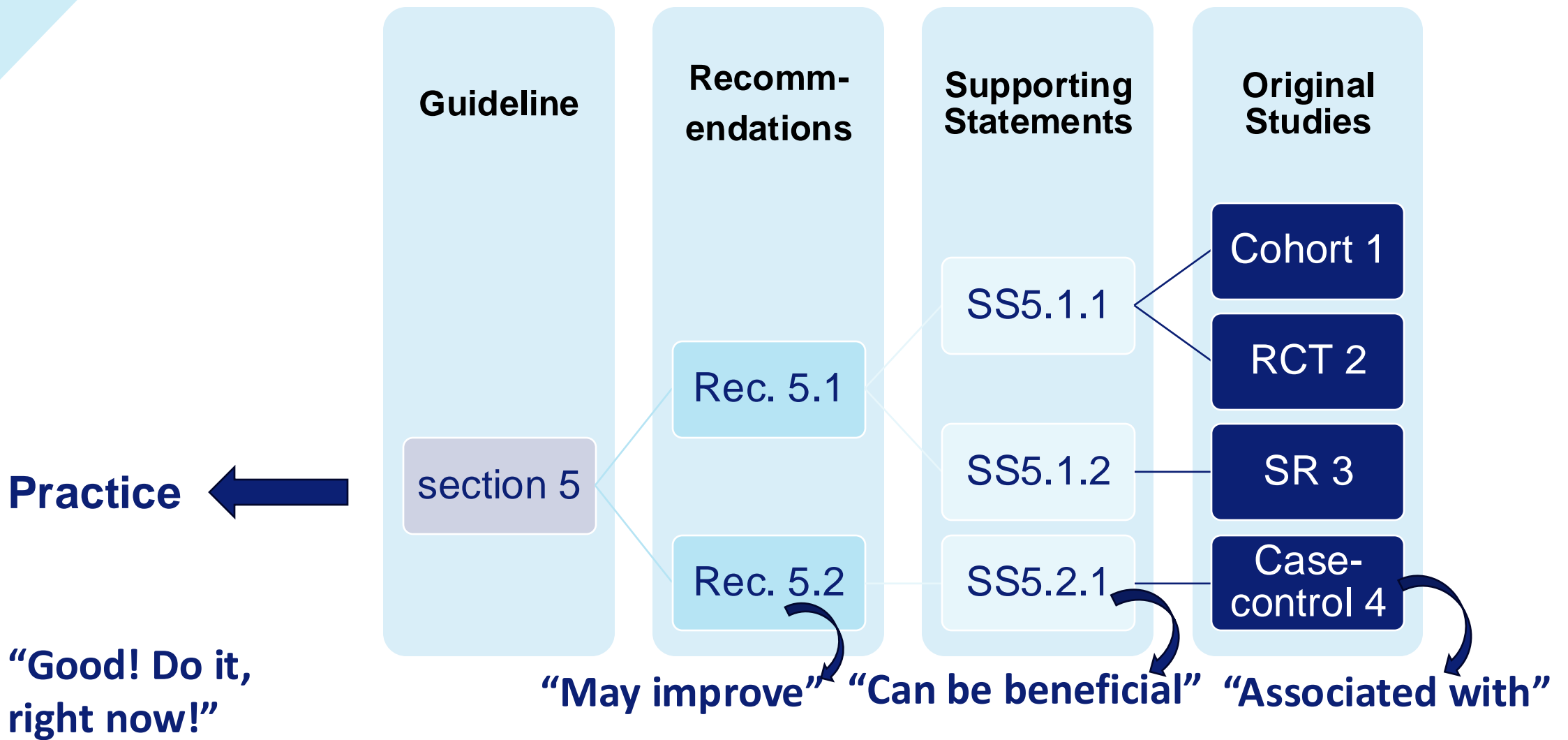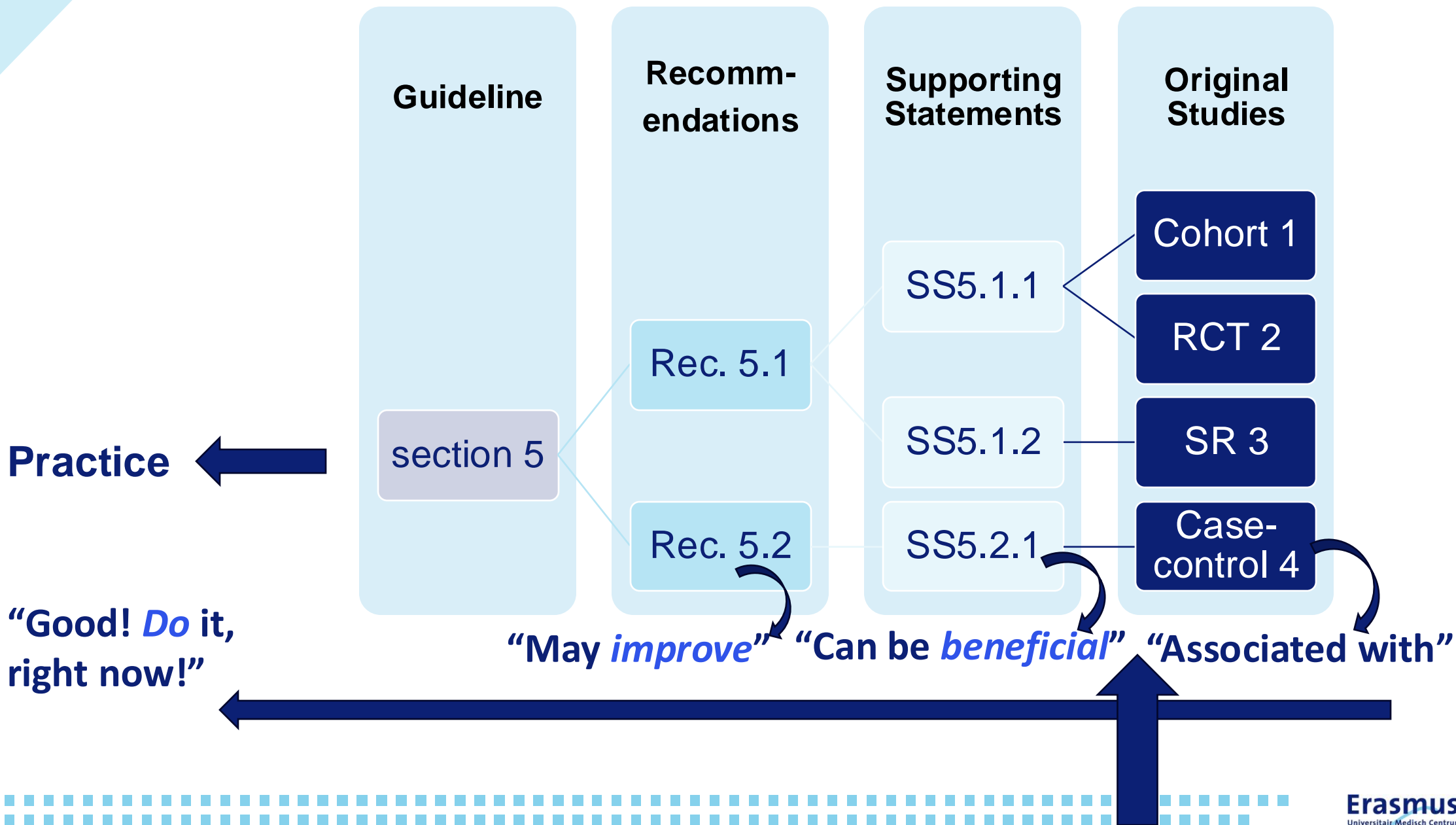
Causation *jump*…

BACKGROUND
Causation jump

- Example: (ADA diabetes SoC 2023 Sec. 5)[2]

  Original study: *For every kilogram of weight loss, there was a 16% reduction in risk, adjusted for changes in diet and activity.*

BACKGROUND
Causation jump

- Example: (ADA diabetes SoC 2023 Sec. 5)[2]

  Original study: *For every kilogram of weight loss, there was a 16% reduction in risk, adjusted for changes in diet and activity.*

  Supp. Statements: *In prediabetes, the weight loss goal is 7–10% for preventing progression to type 2 diabetes.* *(???)*
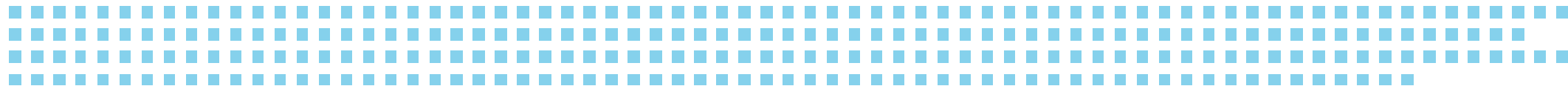
BACKGROUND
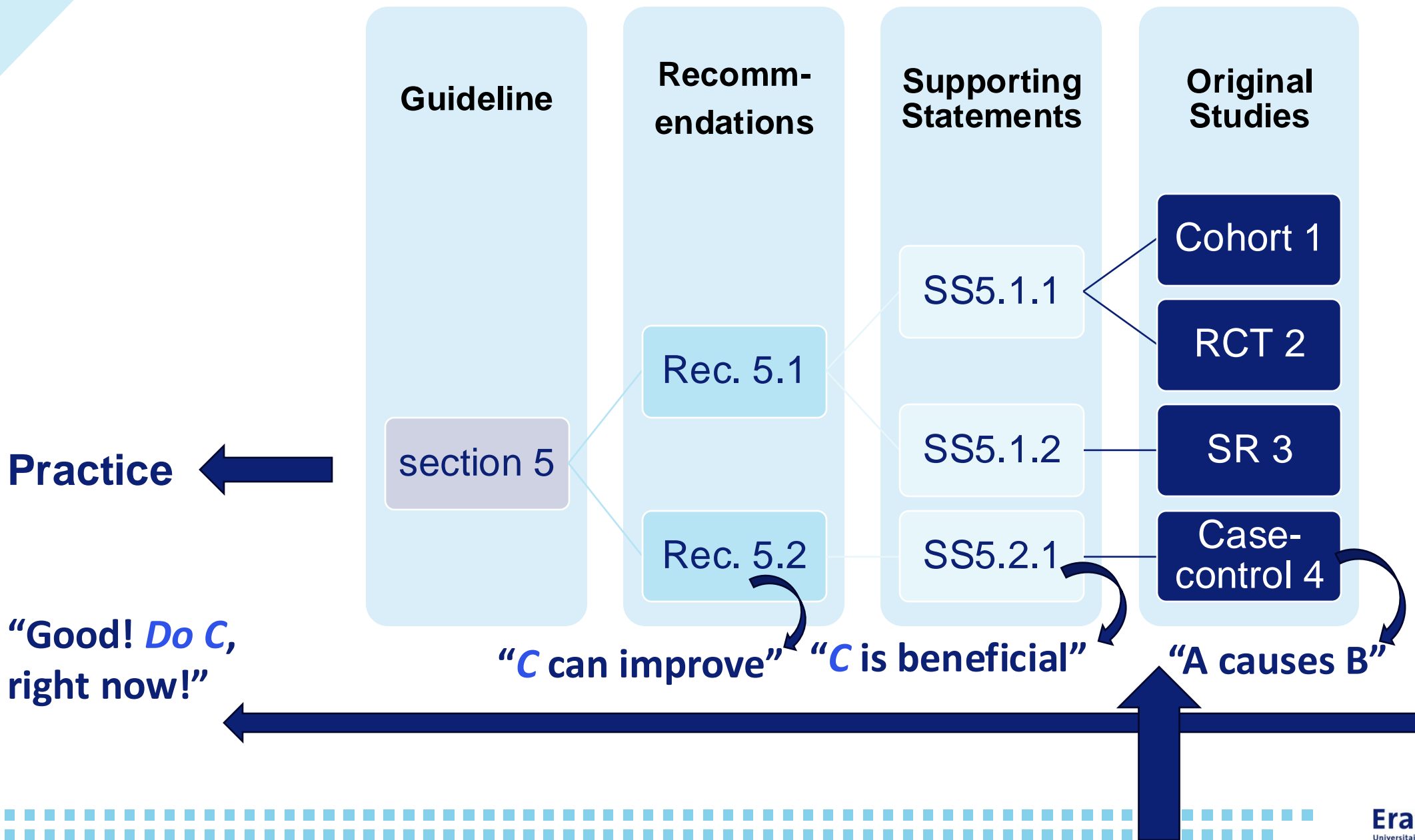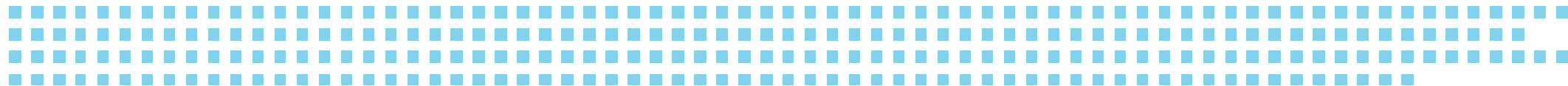**Causation jump**

- Example: (ADA diabetes SoC 2023 Sec. 5)[2]

  Original study: *For every kilogram of weight loss, there was a 16% reduction in risk, adjusted for changes in diet and activity.*

  Supp. Statements: *In prediabetes, the weight loss goal is 7–10% for preventing progression to type 2 diabetes.* **(???)**

  Recommendation: *For all people with overweight or obesity, behavioral modification to achieve and maintain a minimum weight loss of 5% is recommended.*

BACKGROUND
Our interest

- ***Evaluate the use of causal language*** both in guideline recommendations and in underlying original studies.

- Check sentences in guidelines → check original studies;

Erasmus MC
Universitair Medisch Centrum Rotterdam

BACKGROUND
Our interest

- ***Evaluate the use of causal language*** both in guideline recommendations and in underlying original studies.

- Check sentences in guidelines → check original studies;

   "Is causation adequately passed down without jumps?"
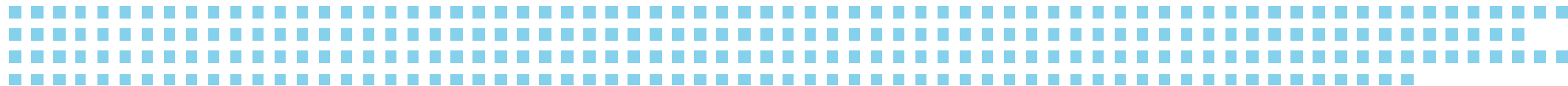
BACKGROUND
Our interest

- ***Evaluate the use of causal language*** both in guideline recommendations and in underlying original studies.

- Check sentences in guidelines → check original studies;

- Check original studies → check causal assumptions made.

Erasmus MC
Universitair Medisch Centrum Rotterdam

BACKGROUND
Our interest

- ***Evaluate the use of causal language*** both in guideline recommendations and in underlying original studies.

- Check sentences in guidelines → check original studies;

- Check original studies → check causal assumptions made.

   "Do causal statements come with necessary assumptions in original studies?"

Erasmus MC
Universitair Medisch Centrum Rotterdam
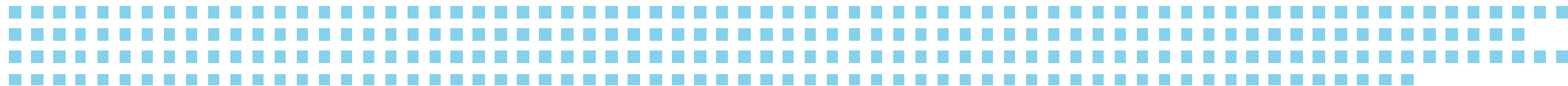
AIMS

AIMS

- 1. How different is the language with respect to causality different between the recommendations and the original studies?

- 2. How often are causal assumptions mentioned in the original studies, and how are their reporting quality?

- 3. How many statements in guidelines are causal or implying causation?

MATERIAL & METHODS

All you want to know about our study…
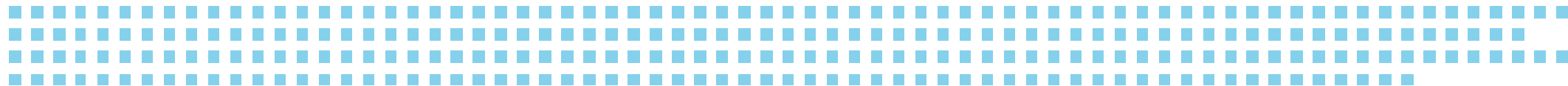
Material & Methods

- Study design
- Data source
- Eligibility criteria
- Data selection
- Data extraction
- Data analysis
- Evidence synthesis

MATERIAL & METHODS
Study design

- Scoping review
- Semi-systematic approach for data source
- Will register *a priori* at OSF (Open Science Framework)

MATERIAL & METHODS
Data source

We want a semi-systematic approach to pick guidelines out…

MATERIAL & METHODS
Data source

We want a semi-systematic approach to pick guidelines out…

We want to pick the most important ones…

Global disease burden, DALYs [6]

Global
Both sexes, All ages, 2019, DALYs attributable to All risk factors

- CVD
- Neoplasms
- Oth NCD
- Mat+Neonat
- Resp+TB
- MSK
- Diabetes+CKD
- Digestive
- Sense
- Enteric Infect
- HIV/AIDS+STIs
- Other+Diseases
- Chr Resp
- NTD+Malaria
- Nutr Def
- Mental
- Neuro
- Skin
- Subs Use
- Unint Inj
- Trans Inj
- Self-harm & IPV
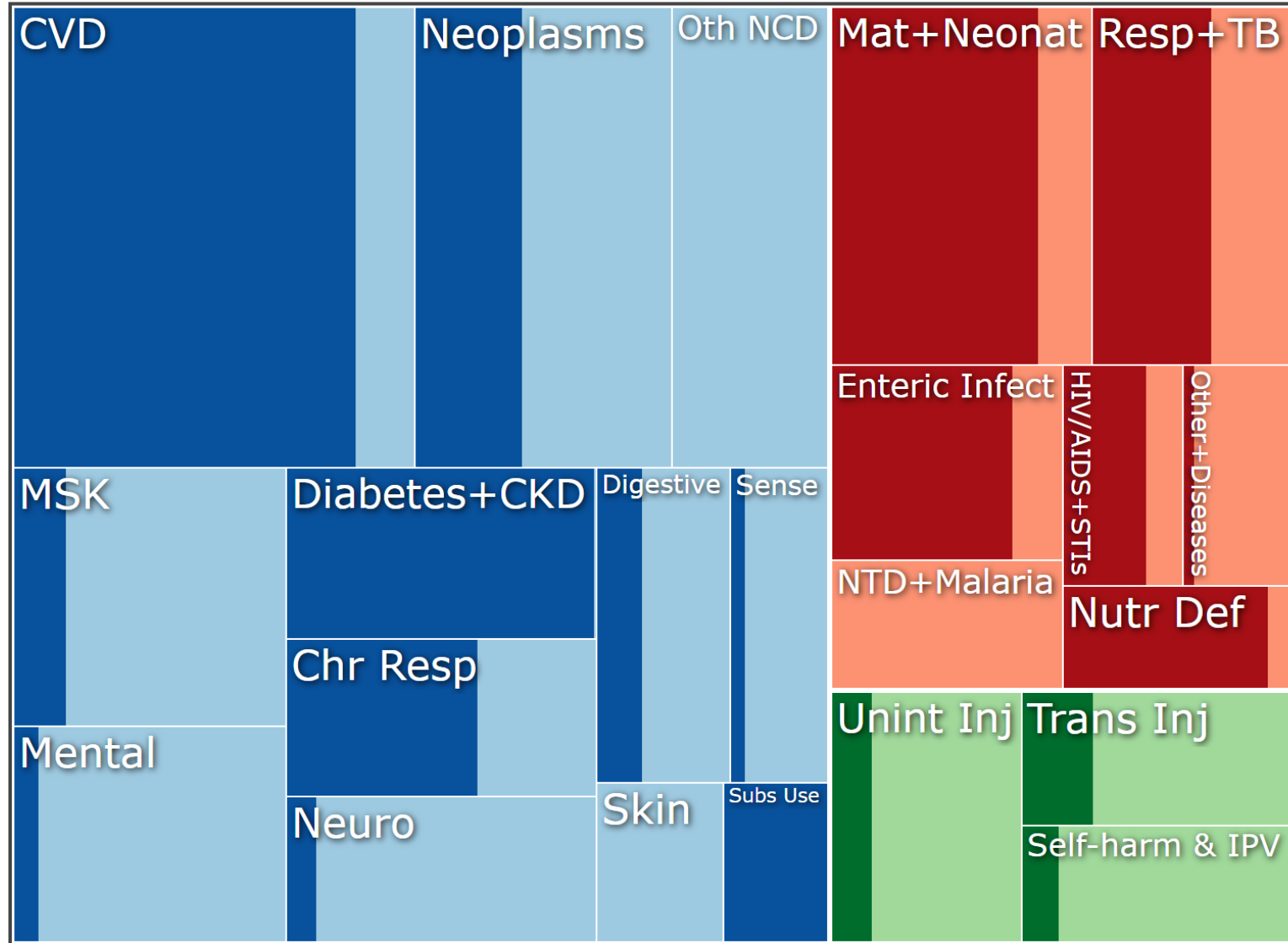
Table 1: **Eligible clinical practice guidelines**

Disease	CPGs
CVD	2023 AHA guideline: management of chronic CD [13]
	2023 ESC guideline: management of acute CD [14]
	2019 AHA guideline: CVD primary prevention [15]
	2021 ESC guideline: CVD prevention [16]
Diabetes	2023 ADA guideline: Standard of Care [2]
	2019 Endocrine Society guideline: prevention [17]
Obesity	2020 Canadian MA: Obesity in adults [18]
	2016 AACE/ACE guideline: obesity [19]
Cirrhosis and CLD	2023 AASLD guideline: NAFLD [20]
	2022 AACE/AASLD guideline: NAFLD [21]

CPG, clinical practice guideline; CVD, cardiovascular disease; AHA, American Heart Association; CD, coronary disease; ESC, European Society of Cardiology; ADA, American Diabetes Association; MA, medical association; AACE, American Association of Clinical Endocrinology; ACE, American College of Endocrinology; CLD, chronic liver disease; AASLD, American Association for the Study of Liver Diseases; NAFLD, non-alcoholic fatty liver disease.

MATERIAL & METHODS
Eligibility criteria

Eligible sentences:

(1) part of formal recommendations and supporting statements that are intended to provide evidence;

(2) focus on **non-pharmaceutical treatment or preventive** strategies;

(3) explicitly **contain** causal linking terms or imply causation.

MATERIAL & METHODS
Eligibility criteria

Eligible sentences:

(1) part of formal recommendations and supporting statements that are intended to provide evidence;

(2) focus on **non-pharmaceutical treatment or preventive** strategies;

(3) explicitly **contain** causal linking terms or imply causation.

Eligible studies:

All citations (interventional/observational/SR studies) following the sentence.

Erasmus MC
Universitair Medisch Centrum Rotterdam

MATERIAL & METHODS
Eligibility criteria

Eligible sentences:

(1) part of formal recommendations and supporting statements that are intended to provide evidence;

(2) focus on **non-pharmaceutical treatment or preventive** strategies;

(3) explicitly **contain** causal linking terms or imply causation.

Eligible studies:

All citations (interventional/observational/SR studies) following the sentence.

Sometimes a causal statement is not supported by any citations.

… A variety of eating plans, varying in macronutrient composition, *can be used effectively and safely* in the short term (1–2 years) to achieve weight loss in people with diabetes. These plans include *structured low-calorie meal plans with meal replacements (106,117,119),* a *Mediterranean eating pattern (120),* and *low-carbohydrate meal plans* with additional support (121,122).
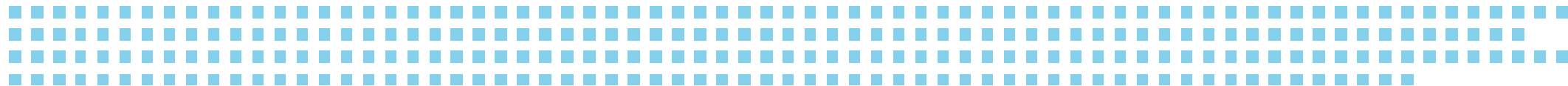
MATERIAL & METHODS
Data selection

However, a guideline often has thousands of sentences and hundreds of recommendations…

MATERIAL & METHODS
Data selection

However, a guideline often has thousands of sentences and hundreds of recommendations…

We have a maximal capacity of approx. 300 sentences and 300 original studies. We have to sample from the entire guideline (or eligible sections).

Stratified sampling if there are multiple guidelines (or guideline sections).

If one of the capacities (sentence or study) is reached we will stop sampling.
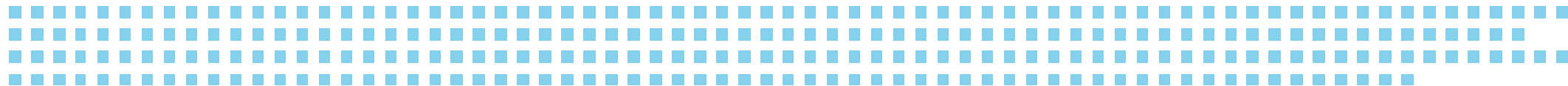
Erasmus MC
Universitair Medisch Centrum Rotterdam

MATERIAL & METHODS
Data selection

Data selection will be performed by at least two researchers independently.

(But sampling will not be.)

MATERIAL & METHODS
Data extraction

A pre-defined data extraction form…

Will be double-checked.

	A	B	C	D
	Name	Meaning	Type	Length
	glInfo	guideline information	table	13
	glSent	guideline sentences (statements)	table	10
	recInfo	recommendation information	table	4
	osInfo	original study information	table	10
	osStatements	statements in original studies	table	11
	osComponents	Trial emulation components	table	13
	osArms	Arms (different treatment strategies) in origir	table	5
	gl_No	guideline identifier	integer	1
	gl_Title	guideline title	character	128
	gl_Year	guideline year of publication	integer	1
	gl_Topic	guideline topic (of disease)	character	32
	gl_Org	guideline organization	character	32
	sec_Title	section title	character	128
	sec_Rec_Number	total number of recommendations in section	integer	1
	sec_Sent_Number	total number of sentences in section	integer	1
	sec_Sent_Sampled	number of sampled sentences in section	integer	1
	sec_Sent_Sampfrac	fraction of sampled sentences in section	float	1
	sec_Excl_Number	number of excluded sentences in section	integer	1
	sec_Incl_Number	number of included sentences in section	integer	1
	sec_Incl_Frac	fraction of inclusion in section	float	1
	rec_No	recommendation identifier	integer	1

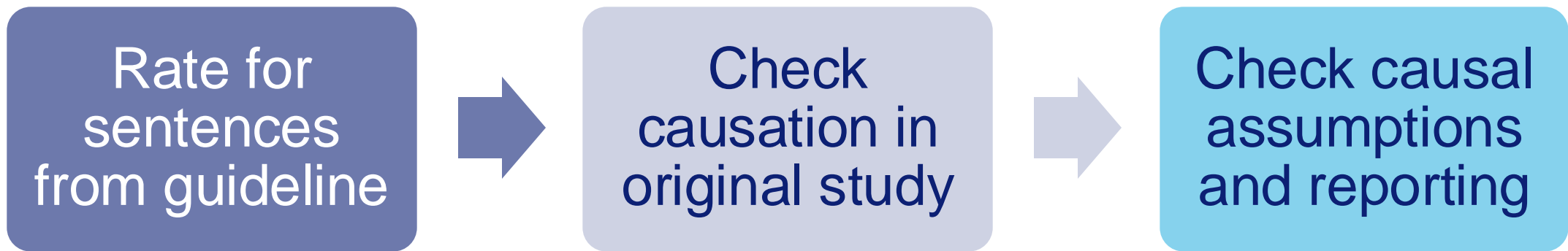| 25 | sent_Link_Phrase | (causal) linking phrase | character | 32 |
26	sent_Link_Phr_Root	(causal linking root word	character	5
27	sent_Causal_Exps	Exposure implied by sentence	character	64
28	sent_Causal_Otcm	Outcome implied by sentence	character	64
29	os_Number	number of corresponding original studies	integer	1
30	os_No	original study identifier	integer	1
31	os_Title	original study title	character	128
32	os_Firstauthor	original study first author	character	32
33	os_Year	original study year of publication	integer	1
34	os_Nation	original study origin of first author	character	16
35	os_Journal	original study journal of publication	character	64
36	os_Cited	original study total cited number	integer	1
37	os_Abs_Concl_cont	conclusive sentence in abstract	character	512
38	os_Abs_Concl_Link_Phr	linking phrase of conclusive sentence in abstract	character	32
39	os_Abs_Concl_Link_Phr_Ro	linking phrase root of conclusive sentence in ab	character	5
40	os_Abs_Concl_Causal_Exps	Exposure implied by conclusive sentence in abs	character	64
41	os_Abs_Concl_Causal_Otcm	Outcome implied by conclusive sentence in abs	character	64

Codebook | glInfo | glSent | recInfo | osInfo | osStatements | osCompon

MATERIAL & METHODS
Data analysis

Rate for sentences from guideline → Check causation in original study → Check causal assumptions and reporting

MATERIAL & METHODS
Data analysis

- Rate for causality

Table 2

Causal Implication Strength Rating Scale for an Analysis of Causal and Associational Language in Observational Health Research

Rating	Linking Sentence	Action Recommendation
N/A		No action recommendation exists.
None	The linking sentence does not imply in any way that a causal relationship was identified.	The action recommendation would be made appropriately in the absence of any causal relationship.
Weak	The linking sentence might imply that a causal relationship was identified, but it is unclear or not possible to come to that conclusion in the absence of any causal inference.	The action recommendation may be made appropriately had a causal relationship been identified, but it is unclear or not possible to come to that recommendation in the absence of any causal inference.
Moderate	The linking sentence mostly implies that a causal relationship was identified, but it is unclear or not possible to come to that conclusion in the absence of any causal inference.	The action recommendation most likely could only be made appropriately had a causal relationship been identified, but it is unclear or not possible to come to that recommendation in the absence of any causal inference.
Strong	The linking sentence clearly implies that causality had been identified.	The action recommendation could only be made appropriately had a causal relationship been identified.

PREVIOUS STUDIES

Haber et al. 2022: rating of causal statements

- Haber et al. (2022). **Causal and Associational Language in Observational Health Research: A Systematic Evaluation**. *Am J Epidemiol* 191(12):2084-97.[3]

- 1,170 articles published in last decade ***screened***.

- ***Degree of causality*** implied in ***abstracts and full text*** for exposure/outcome linking language and action recommendations ***rated***.

- Most common ***linking phrases*** and how strong these words implying causality ***marked***.

- ***Correlation heatmap*** to depict results.

Erasmus MC
Universitair Medisch Centrum Rotterdam

Table 2

Causal Implication Strength Rating Scale for an Analysis of Causal and Associational Language in Observational Health Research
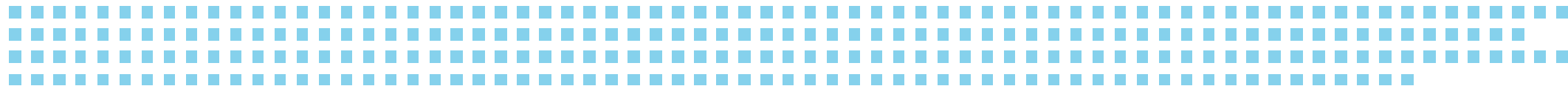
Rating	Linking Sentence	Action Recommendation
N/A		No action recommendation exists.
None	The linking sentence does not imply in any way that a causal relationship was identified.	The action recommendation would be made appropriately in the absence of any causal relationship.
Weak	The linking sentence might imply that a causal relationship was identified, but it is unclear or not possible to come to that conclusion in the absence of any causal inference.	The action recommendation may be made appropriately had a causal relationship been identified, but it is unclear or not possible to come to that recommendation in the absence of any causal inference.
Moderate	The linking sentence mostly implies that a causal relationship was identified, but it is unclear or not possible to come to that conclusion in the absence of any causal inference.	The action recommendation most likely could only be made appropriately had a causal relationship been identified, but it is unclear or not possible to come to that recommendation in the absence of any causal inference.
Strong	The linking sentence clearly implies that causality had been identified.	The action recommendation could only be made appropriately had a causal relationship been identified.

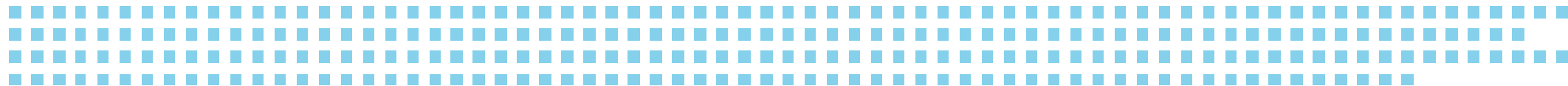# MATERIAL & METHODS
Data analysis

- Check causation in original studies

- Conclusive sentences in abstract and in conclusion section will be checked and rated for.

MATERIAL & METHODS
Data analysis

- Check causal assumptions and reporting.

- For assumptions…., only check (conditional) exchangeability.

MATERIAL & METHODS
Data analysis

- Check causal assumptions and reporting.

- For assumptions…., only check (conditional) exchangeability.
- Check causal reporting quality according to Target Trial Framework.

PREVIOUS STUDIES

Smit et al. 2023: checking causal reporting quality

- Smit JL et al. (2023). **Causal inference using observational intensive care unit data: a scoping review and recommendations for future practice.** *NPJ Digit. Med.* 6:221.[4]

- *(Causal) reporting quality* of studies introducing models for causal inference in ICU evaluated.

- *Target trial components* and *causal assumptions* evaluated.

Table 2. Components of the target trial framework included in the reporting quality assessment with examples for the ICU setting.

Component	Subcomponent	Included for QOR assessment	ICU example
Eligibility criteria	–	✓	Individuals aged 65 years or older admitted to the ICU meeting Sepsis-3 criteria upon admission.
Treatment strategies	–	✓	1. Liberal fluid therapy (administration of intravenous fluid boluses during the first several hours of treatment) 2. Restrictive fluid therapy (Intravenous fluid boluses during ICU stay in only in case of severe hypoperfusion)
Assignment procedures	–		Unblinded, random assignment to one of the treatment strategies.
Follow-up period	Start of follow-up	✓	Time of ICU admission.
	End of follow-up	✓	Death, ICU discharge, or loss to follow-up, whichever occurs first.
	Time resolution	✓	Hourly weights were applied to adjust for the impact of time-varying confounders on the hourly risk of adhering to one of the two treatment strategies.
Outcome	–	✓	All- cause mortality.
Causal contrasts of interest	–		Per-protocol effect.
Analysis plan[a]		✓	Per-protocol effect will be estimated adjusting for pre- and postbaseline confounders by a marginal structural model using IPTW.[b]

[a]The analysis plan component is subdivided in a specific set of subcomponents depending on the modeling strategy used, these are summarized in Supplementary Table 9.
[b]This description would not be considered as sufficient reporting of the analysis plan component, but simply serves as an example.

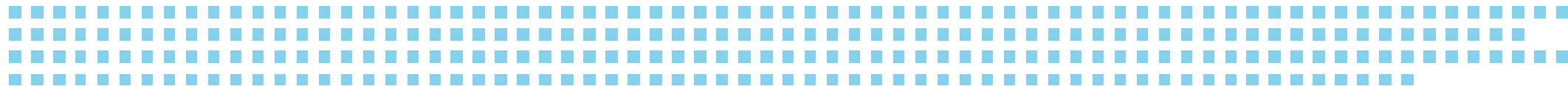## Target trial components framework from Hernán MA et al.[5]
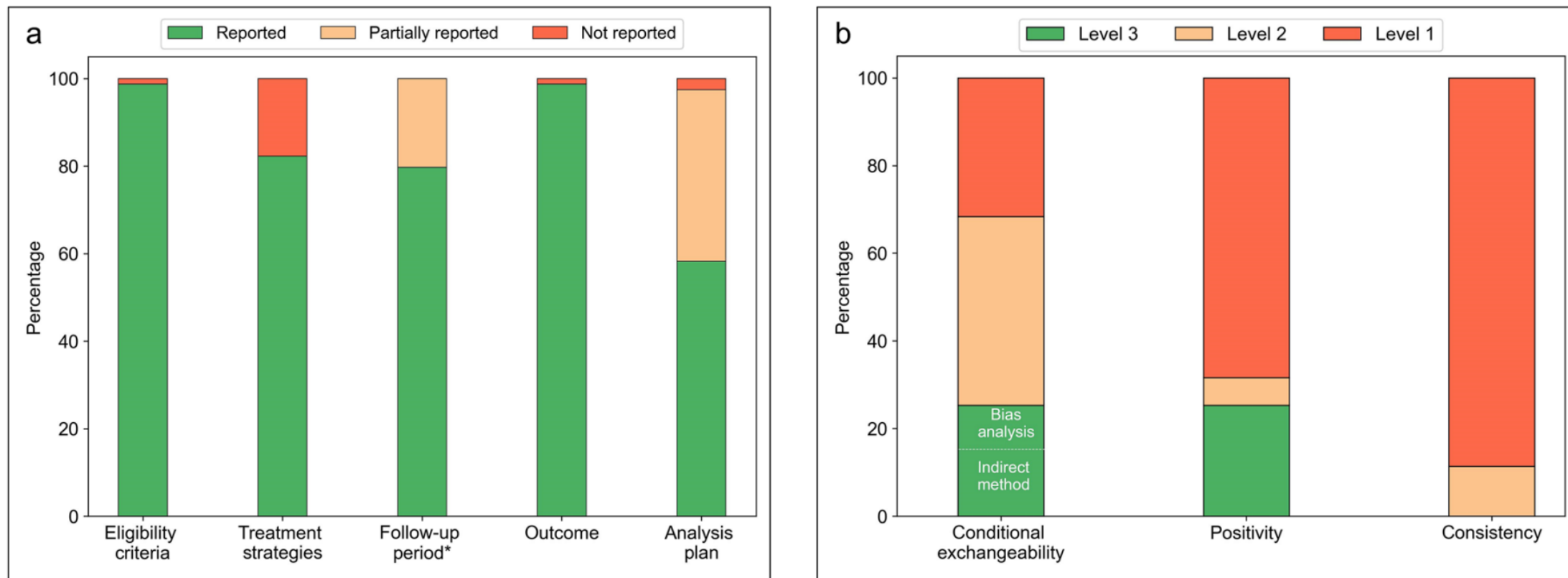
Fig. 3 Quality of Reporting summary plots. a Reporting quality of the target trial components. *For the follow-up component, the studies that used simulated patient data ($n = 5$) are not taken into account. **b** Reporting quality of causal assumptions (level 1 = assumption not mentioned, level 2 = assumption mentioned, level 3 = attempt to check for potential violations of the assumption reported).

MATERIAL & METHODS

Evidence synthesis

- It is estimated that **xx% (95%CI xx, xx)** of the statements in the guidelines are causal or implied causation;

- "Benefit/beneficial" was used in xx% of the causal statements; "prevent" xx%, "reduce" xx%, …

- Causal statements are rated as x.x/4 on average…,

- xx% of the original studies reported full analysis plan…

Erasmus MC
Universitair Medisch Centrum Rotterdam

Study Guid.	No	Weak	Some	Strong
No	86	33	18	3
Weak	-	95	…	…
Some	-	-	…	…
Strong	-	-	-	…

Cohen's $\kappa = .533 \ (95\%CI \ .495, .580)$
Spearman $r_s = .627 \ (95\%CI \ .599, .672)$
$P_s = .0013$

Example

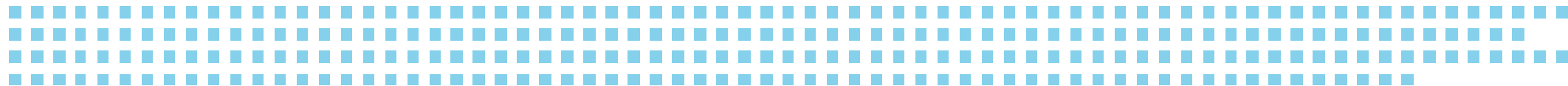| Study R.	No	Weak	Some	Strong
Poor	75	35	27	3
Some	23	24	…	…
Good	…	…	…	…

Spearman $r_s = .627\ (95\%CI\ .599, .672)$
$P_s = .0013$

Example

MATERIAL & METHODS
Evidence synthesis

... And we can run other analyses of correlation/difference if we want.

TIME SCHEDULE

Table 2: **Time schedule**

Time interval	Duration	Progress
Feb - Apr 2024	3 month	Data selection
May - Jul 2024	3 months	Data extraction
Aug - Nov 2024	4 months	Causal statement annotation and rating
Dec 2024 - Feb 2025	3 months	Causal assumption check
Mar 2025	1 month	Data mapping and evidence synthesis
Apr - May 2025	2 months	Manuscript writing and defense preparation
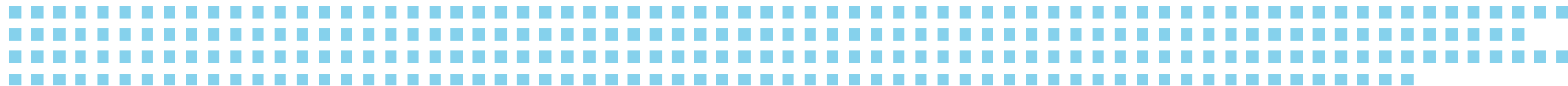
QUESTIONS?

And suggestions?

REFERENCES

(1) Graham R, et al., ed. Clinical Practice Guidelines We Can Trust. Washington DC: National Academies Press; 2011. https://www.ncbi.nlm.nih.gov/books/NBK209538/

(2) ElSayed NA, et al. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2023. *Diabetes Care* 2023;46(Suppl. 1):S41–8. doi: 10.2337/dc23-S003

(3) Haber NA, et al. Causal and Associational Language in Observational Health Research: A Systematic Evaluation. *Am J Epidemiol* 2022; 191(12):2084-97. doi: 10.1093/aje/kwac137

(4) Smit JL, et al. Causal inference using observational intensive care unit data: a scoping review and recommendations for future practice. *NPJ Digit Med* 2023;6:221. doi: 10.1038/s41746-023-00961-1

(5) Hernán MA, et al. Target Trial Emulation: A Framework for Causal Inference From Observational Data. *JAMA* 328(24):2446-2447. doi: 10.1001/jama.2022.21383.

(6) IHME. Global Burden of Disease Study. https://www.healthdata.org/research-analysis/gbd (visited on 01/30/2024).

Erasmus MC
Universitair Medisch Centrum Rotterdam