SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2024 - 10ª EDIZIONE

MODULI SPECIALISTICI - S2

VENERDÌ 12 - SABATO 13 APRILE 2024

NEGRAR DI VALPOLICELLA (VR)

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

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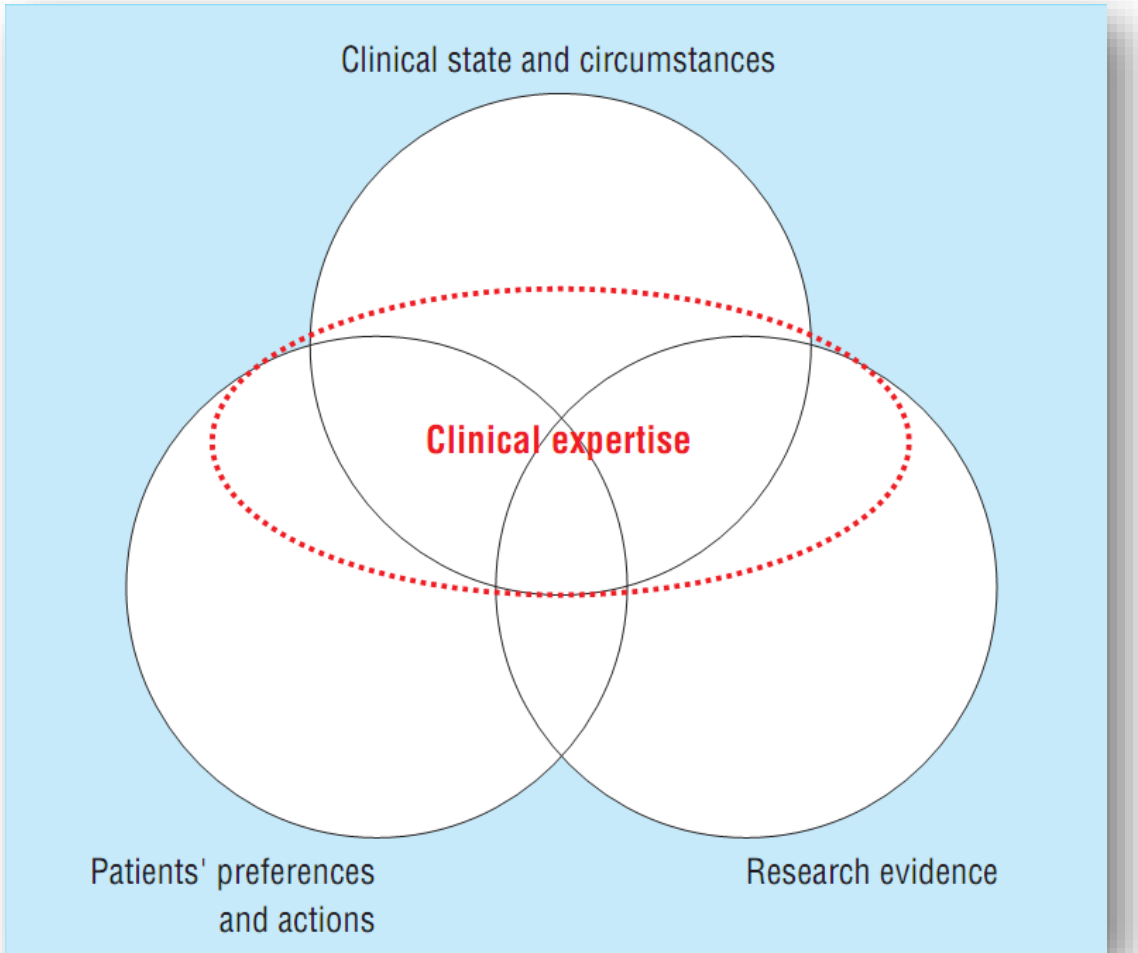
Una Premessa...

Physicians' and patients' choices in evidence based practice

Evidence does not make decisions, people do

R Brian Haynes P J Devereaux Gordon H Guyatt

BMJ 2002;324:1350



Physicians' and patients' choices in evidence based practice

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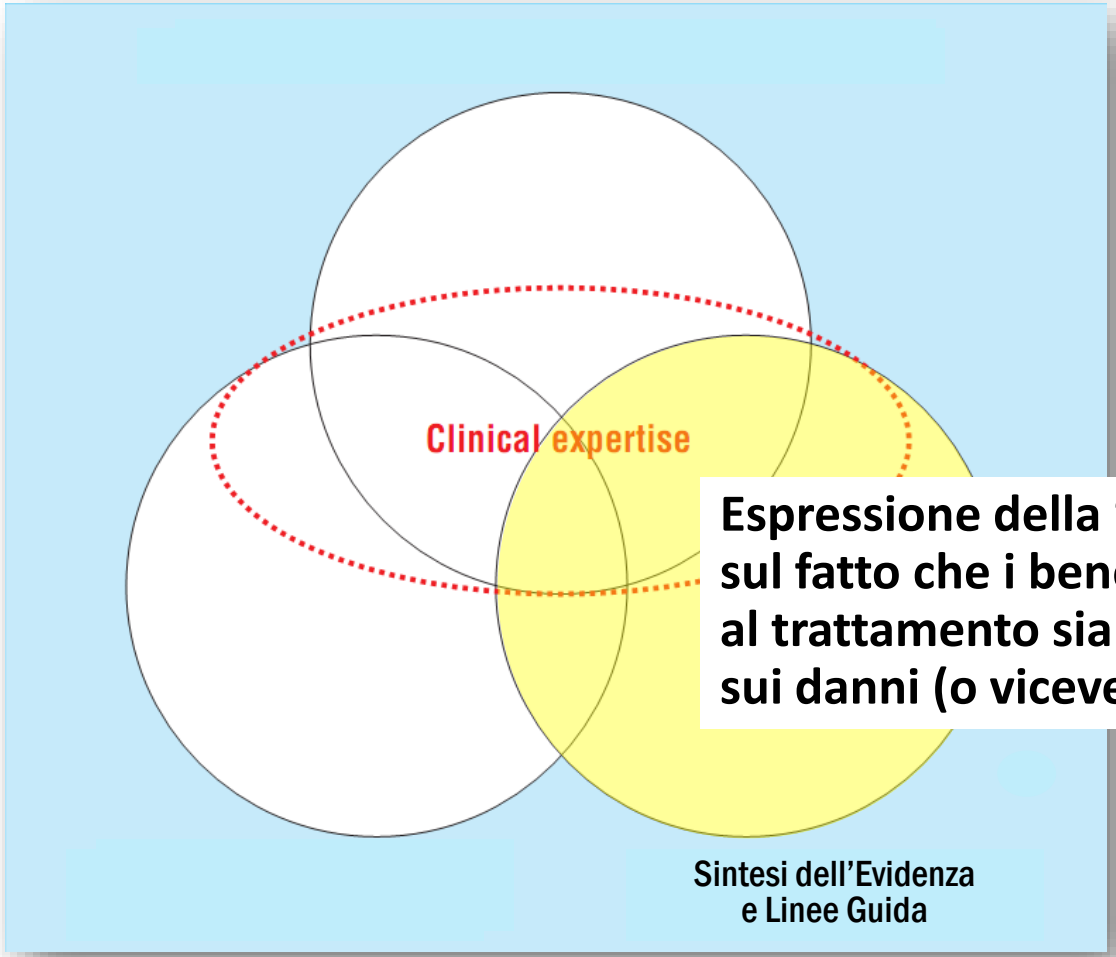


Espressione della "confidenza" sul fatto che i benefici ascrivibili al trattamento siano prevalenti sui danni (o viceversa)

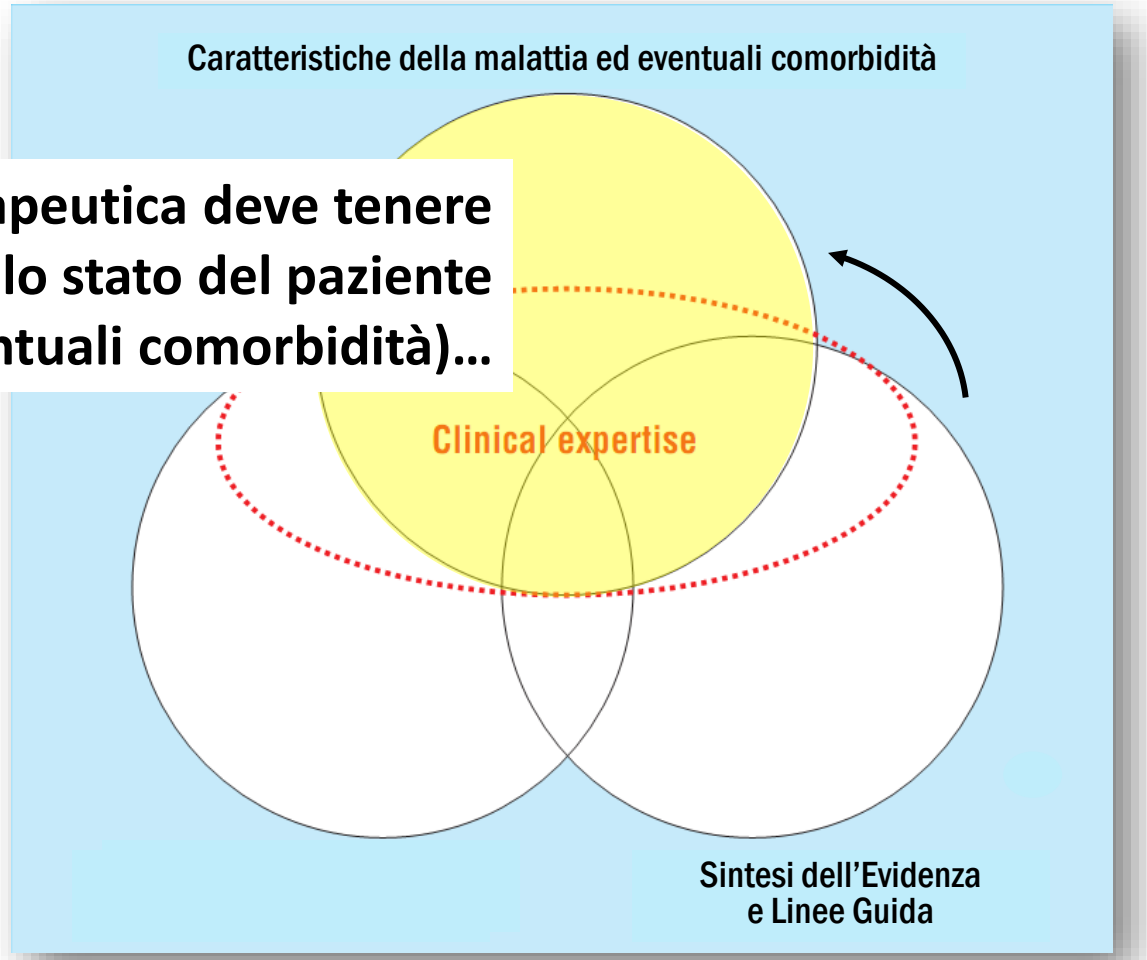
Physicians' and patients' choices in evidence based practice

Evidence does not make decisions, people do

R Brian Haynes P J Devereaux Gordon H Guyatt

BMJ 2002;324:1350

La proposta terapeutica deve tenere conto dello stato del paziente (malattia ed eventuali comorbidità)…



Physicians' and patients' choices in evidence based practice

Evidence does not make decisions, people do

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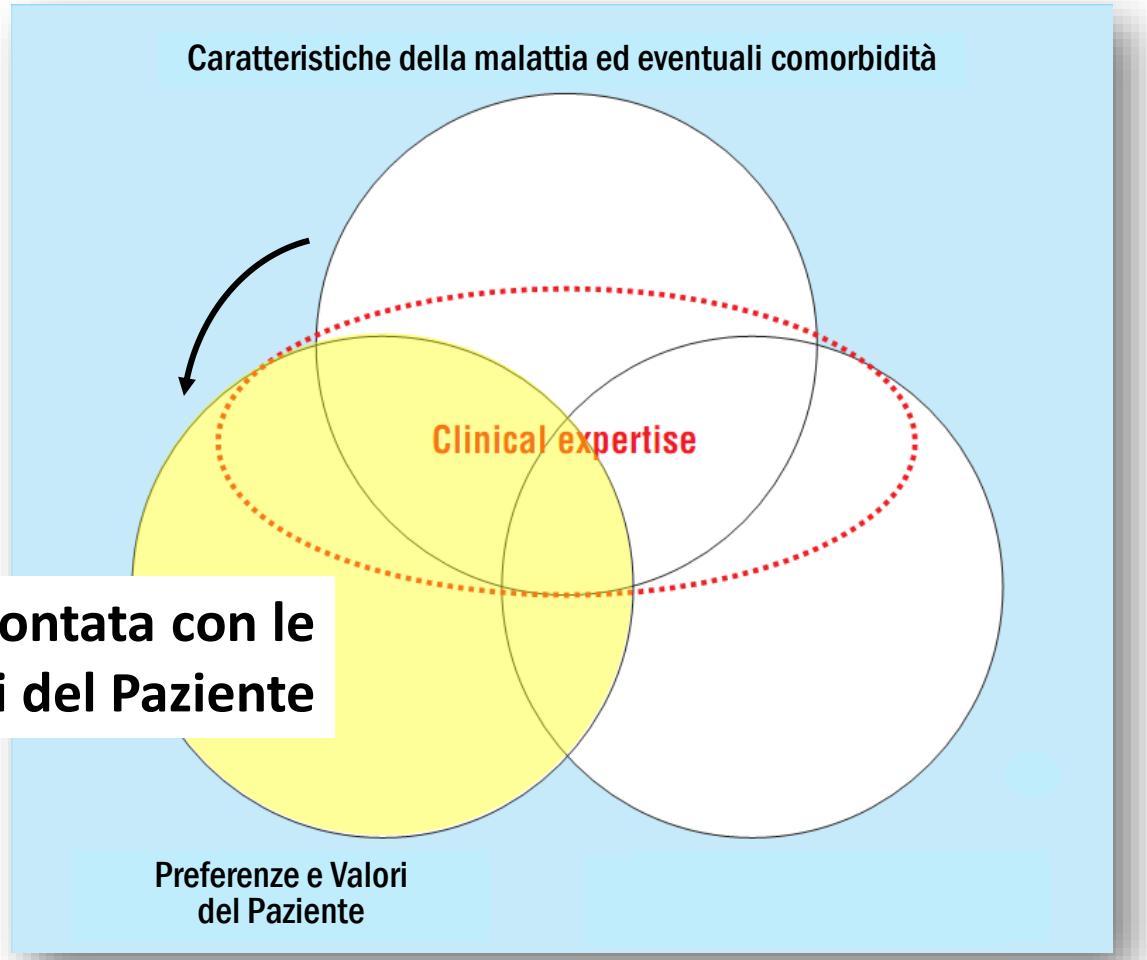

… e deve essere confrontata con le Preferenza e i Valori del Paziente

LEGGE 8 marzo 2017, n. 24

Disposizioni in materia di sicurezza delle cure e della persona assistita, nonche' in materia di responsabilita' professionale degli esercenti le professioni sanitarie. (17G00041) (GU Serie Generale n.64 del 17-03-2017)

Art. 5

Buone pratiche clinico-assistenziali e raccomandazioni previste dalle linee guida

1. Gli esercenti le professioni sanitarie, nell'esecuzione delle prestazioni sanitarie con finalita' preventive, diagnostiche, terapeutiche, palliative, riabilitative e di medicina legale, si attengono, salve le specificita' del caso concreto, alle raccomandazioni previste dalle linee guida pubblicate ai sensi del comma 3 ed elaborate da enti e istituzioni pubblici e privati nonche' dalle societa' scientifiche e dalle associazioni tecnico-scientifiche delle professioni sanitarie iscritte in apposito elenco istituito e regolamentato con decreto del Ministro della salute, da emanare entro novanta giorni dalla data di entrata in vigore della presente legge, e da aggiornare con cadenza biennale. In mancanza delle suddette raccomandazioni, gli esercenti le professioni sanitarie si attengono alle buone pratiche clinico-assistenziali.

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Obiettivo da perseguire:

determinare la "confidenza" sul fatto che i benefici ascrivibili al trattamento siano prevalenti sui danni (o viceversa)

Metodiche di produzione di Linee Guida a confronto

(G.L. Pappagallo)

National Comprehensive Cancer Network

Your Best Resource in the Fight Against Cancer®

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

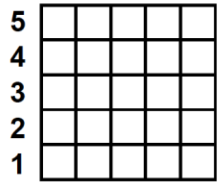
All recommendations are category 2A unless otherwise noted.

- Non revisione sistematica (sufficiente il rimborso delle assicurazioni)
- Non quesito clinico specifico
- Non chiara definizione della certezza delle prove
- Importanza eccessiva del consenso
- Non chiaro riferimento al rapporto tra benefici e danni

G.L. Pappagallo, 2023

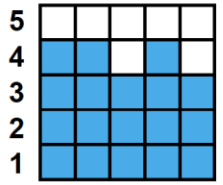
NCCN Evidence Blocks™

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	Survival
4	
3	
2	
1	

Quality of Evidence

5	Study Design
4	
3	
2	
1	

Safety of Regimen/Agent

5	Interference with ADLs
4	
3	
2	
1	

Note: For significant chronic or long-term toxicities, score decreased by 1

Consistency of Evidence

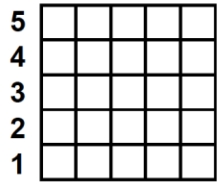
5	Consistency
4	
3	
2	
1	

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	Costs
4	
3	
2	
1	

NCCN Evidence Blocks™

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



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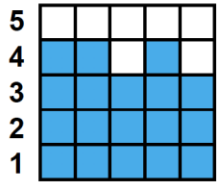
Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)

Level	Therapy/Prevention, Aetiology/Harm
1a	SR (with homogeneity*) of RCTs
1b	Individual RCT (with narrow Confidence Interval‡)
1c	All or none§
2a	SR (with homogeneity*) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	"Outcomes" Research; Ecological studies
3a	SR (with homogeneity*) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies§§)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

- Prevista revisione sistematica
- Certezza delle prove chiaramente definita (rischio di bias, imprecisione, eterogeneità)
- Non riferimento al rapporto tra benefici e danni
- Raccomandazioni espresse in base alla sola certezza delle prove (possibili equivoci)

G.L. Pappagallo, 2022

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

ESMO-MCBS

SINGAPORE 2016 ESMO ASIA

GUIDELINES INCLUDING GRADING OF NOVEL DRUGS WITH ESMO-MCBS

George Pentheroudakis

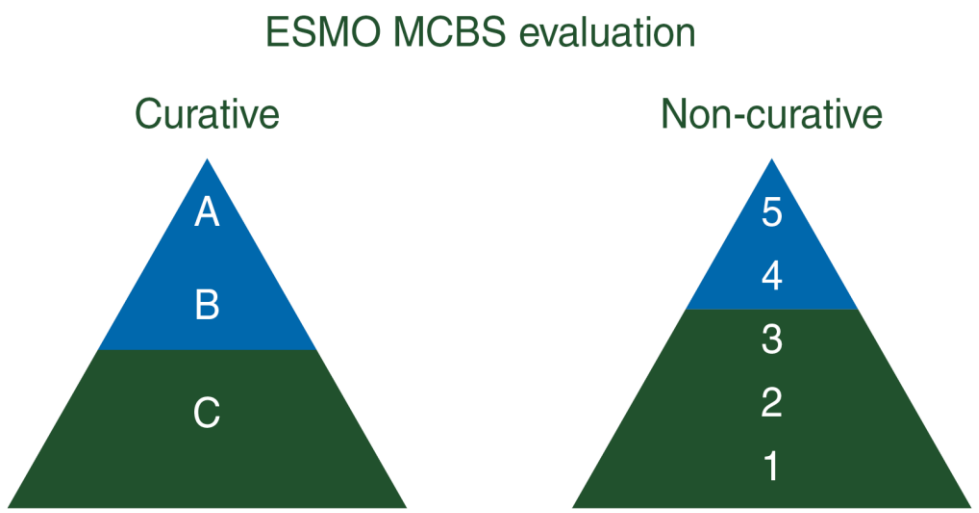
Chair, ESMO Guidelines Committee

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

Annals of Oncology 26: 1547–1573, 2015

This tool uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment.



Visualisation of ESMO-MCB scores for curative and non-curative setting. A & B and 5 and 4 represent the grades with substantial improvement.

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

Annals of Oncology 26: 1547–1573, 2015

Table 1. Potential benefits of a new treatment

Living longer
Improved OS
Improved surrogate of OS
DFS (when OS data are immature in adjuvant setting)
Improved PFS
Living better
Improved quality of life
Improved surrogate of quality of life
Improved PFS
Reduced toxicity

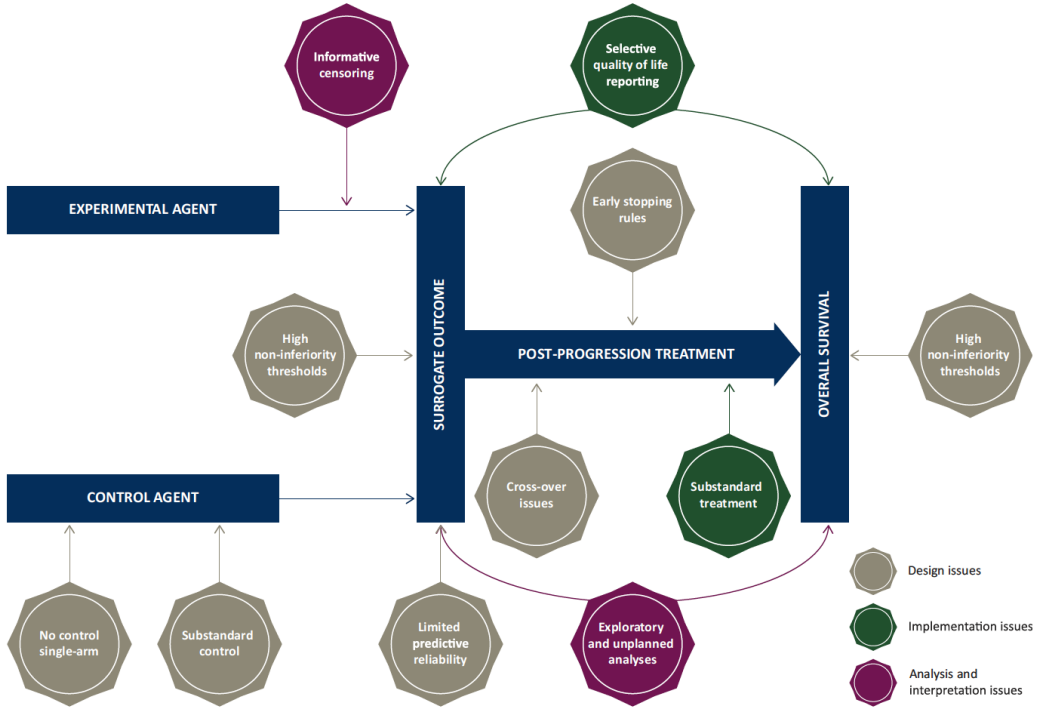
- Beneficio riferito al braccio di controllo dello studio e NON allo *standard of care*
- Entità del beneficio valutata in termini di HR anche in assenza di *proportional hazard*
- Prevalenza della statistica (*P-value*) sulla clinica (*absolute benefit*)

G.L. Pappagallo, 2022

Biases in study design, implementation, and data analysis that distort the appraisal of clinical benefit and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring

B. Gyawali[1,2,3*], E. G. E. de Vries[4], U. Dafni[5,6], T. Amaral[7], J. Barriuso[8], J. Bogaerts[9], A. Calles[10], G. Curigliano[11,12], C. Gomez-Roca[13], B. Kiesewetter[14], S. Oosting[4], A. Passaro[15], G. Pentheroudakis[16], M. Piccart[17], F. Roitberg[18,19], J. Tabernero[20], N. Tarazona[21], D. Trapani[12], R. Wester[22], G. Zarkavelis[23], C. Zielinski[24], P. Zygoura[6] & N. I. Cherny[25]

https://doi.org/10.1016/j.esmoop.2021.100117



Conclusion: Interpretation of the ESMO-MCBS scores requires critical appraisal of trials to understand caveats in trial design, implementation, and data analysis that may have biased results and conclusions. These will be addressed in future iterations of the ESMO-MCBS.

American Urological Association

American Urological Association Clinical Practice Guidelines Development

[2015]

Strength of Evidence

Grade A *- high quality evidence: well-conducted randomized clinical trials (RCTs); exceptionally strong observational studies*

Grade B *- moderate quality evidence: RCTs with some weaknesses; generally strong observational studies*

Grade C *- low quality evidence: observational studies that provide conflicting information or design problems (such as very small sample size)*

American Urological Association

Guidelines Statement Classification			
	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence

Table 4. EAU Guideline's levels of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Table 5. EAU Guideline's grades of recommendation

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

European Association of Urology

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

From 2018 onwards, the EAU Guidelines have been using a **modified GRADE approach** for the grading of recommendations.

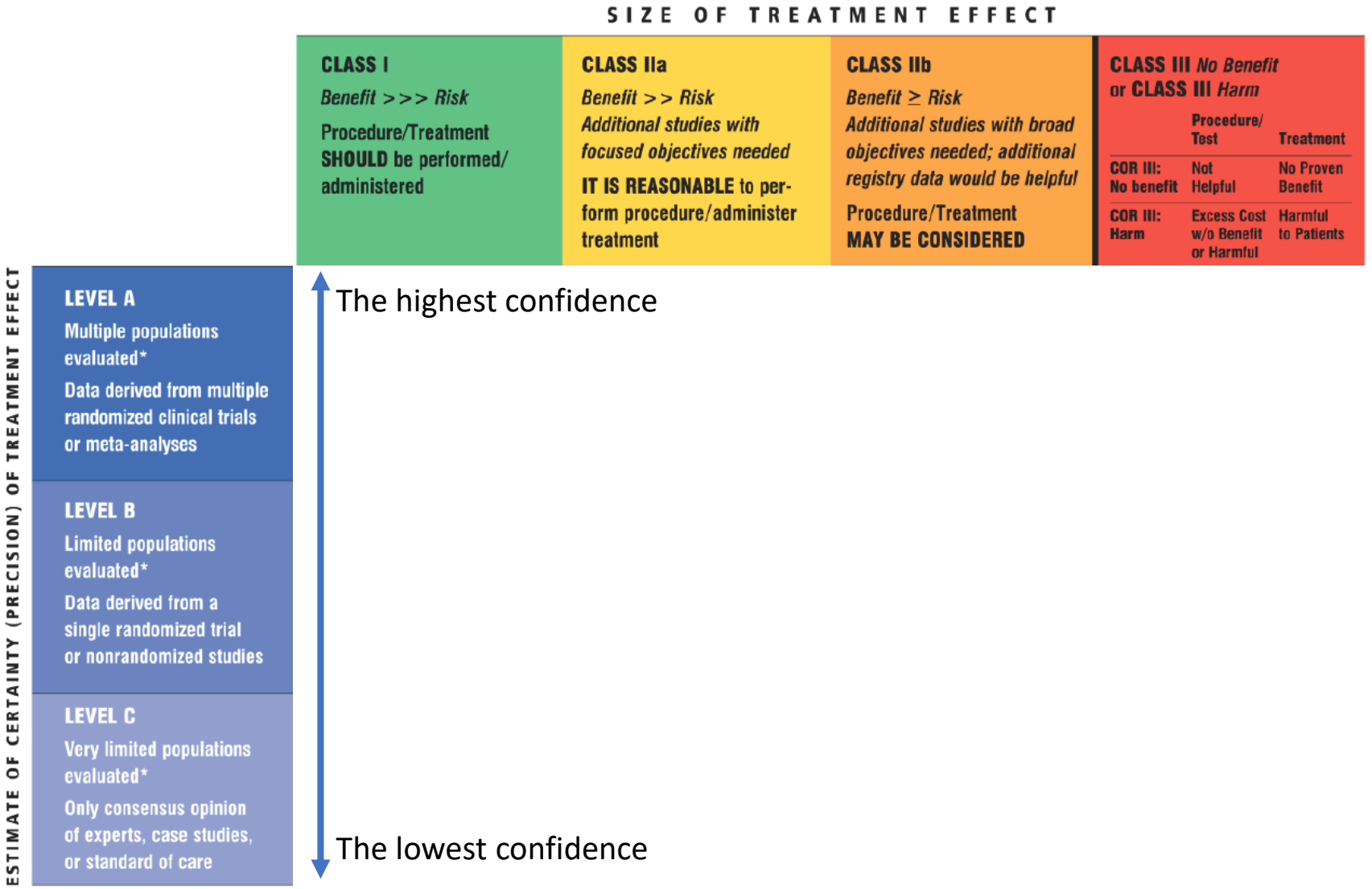
The strength of each recommendation is represented by the words 'strong' or 'weak'.

European Association of Urology. Guidelines Office development handbook. Arnhem, The Netherlands; EAU; 2022. https://uroweb.org/eau-guidelines/methodology-policies.

- Quesito clinico P.I.C.O?
- Revisione sistematica?
- Certezza delle prove chiaramente definita (*v. Oxford CEBM*)
- Riferimento al rapporto tra benefici e danni?
- *Summary of Evidence* (SOE) *tables* non disponibili

G.L. Pappagallo, 2023

2013 ACC/AHA Cardiovascular Risk Guideline



2013 ACC/AHA Cardiovascular Risk Guideline

SIZE OF TREATMENT EFFECT

CLASS I	CLASS IIa	CLASS IIb	CLASS III *No Benefit* or CLASS III *Harm*
Benefit >>> Risk	*Benefit >> Risk*	*Benefit ≥ Risk*	
Procedure/Treatment **SHOULD** be performed/ administered	*Additional studies with focused objectives needed*	*Additional studies with broad objectives needed; additional registry data would be helpful*	
	IT IS REASONABLE to perform procedure/administer treatment	Procedure/Treatment **MAY BE CONSIDERED**	

	Procedure/ Test	Treatment
COR III: No benefit	Not Helpful	No Proven Benefit
COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients

Benefit outweights harm

Harm outweights benefit

2013 ACC/AHA Cardiovascular Risk Guideline

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group

David Atkins[1], Martin Eccles[2], Signe Flottorp[3], Gordon H Guyatt[4], David Henry[5], Suzanne Hill[5], Alessandro Liberati[6], Dianne O'Connell[7], Andrew D Oxman[3], Bob Phillips[8], Holger Schünemann[4,9], Tessa Tan-Torres Edejer[10], Gunn E Vist*[3], John W Williams Jr[11] and The GRADE Working Group[3]

BMC Health Services Research 2004, **4**:38

Table 1: Summary of assessments of the sensibility of six approaches to rating levels of evidence and strength of recommendation

Criteria[1]	ACCP			ANHMRC[2]			USTFCPS			OCEBM			SIGN			USPSTF[3]		
	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes	No		Yes
1. Applicable to different questions:																		
Effectiveness			12		2	8		1	11			12	1		11		2	9
Harm		1	11		5	5	1	7	4		1	11	1	3	8	2	2	7
Diagnosis	7	3	2	4	4	2	9	3				12	5	2	5	2	2	7
Prognosis	6	3	3	2	5	3	9	2	1			11	4	3	5	3	3	5
2. Can be used by:																		
Professionals		1	11	1	5	3		7	4	1	6	5		5	7		3	8
Policy makers	1	5	6	1	5	3	1	2	9	3	7	2	2	6	4	1	4	6
Patients	4	5	3	5	5		6	3	3	9	3		7	5		4	6	1
3. Clear and simple	1	5	6	2	6	1	2	8	2	2	4	5	1	5	6	1	4	7
4. Information not available		8	4	1	5	3	1	6	5		4	8	1	7	4	1	9	2
5. Subjective decisions	2	10		5	2	2	5	5	2		7	5	5	7		2	9	
6. Inappropriate dimensions	1	3	8		1	6	2	4	6		1	10	1	2	8	1	4	6
7. Missing dimensions	1	6	5	2	2	4	5	4	3	9	3	1	5	4	3	2	5	4
Aggregation of dimensions:																		
8. Clear and simple	1	5	6	4	1	2	2	2	7	3	4	4		6	6	2	7	2
9. Appropriate		6	5	3	1	1	3	4	4	2	5	4	1	4	6	1	5	5
10. Sufficient categories	1	4	6	4	2	1		5	7	2	2	7	1	2	9		1	10
11. Likely to discriminate		7	5	2	5	1	1	9	2	2	4	6		5	7		4	7
12. Assessments reproducible	1	8	3	4	4		2	7	2		7	4	1	8	2		10	

Based on discussions of the strengths and limitations of current approaches to grading levels of evidence and the strength of recommendations, we agreed to develop an approach that addresses the major limitations that we identified.

World Health Organization

GRADE

Working Group

Grades of **R**ecommendation **A**ssessment, **D**evelopment and **E**valuation

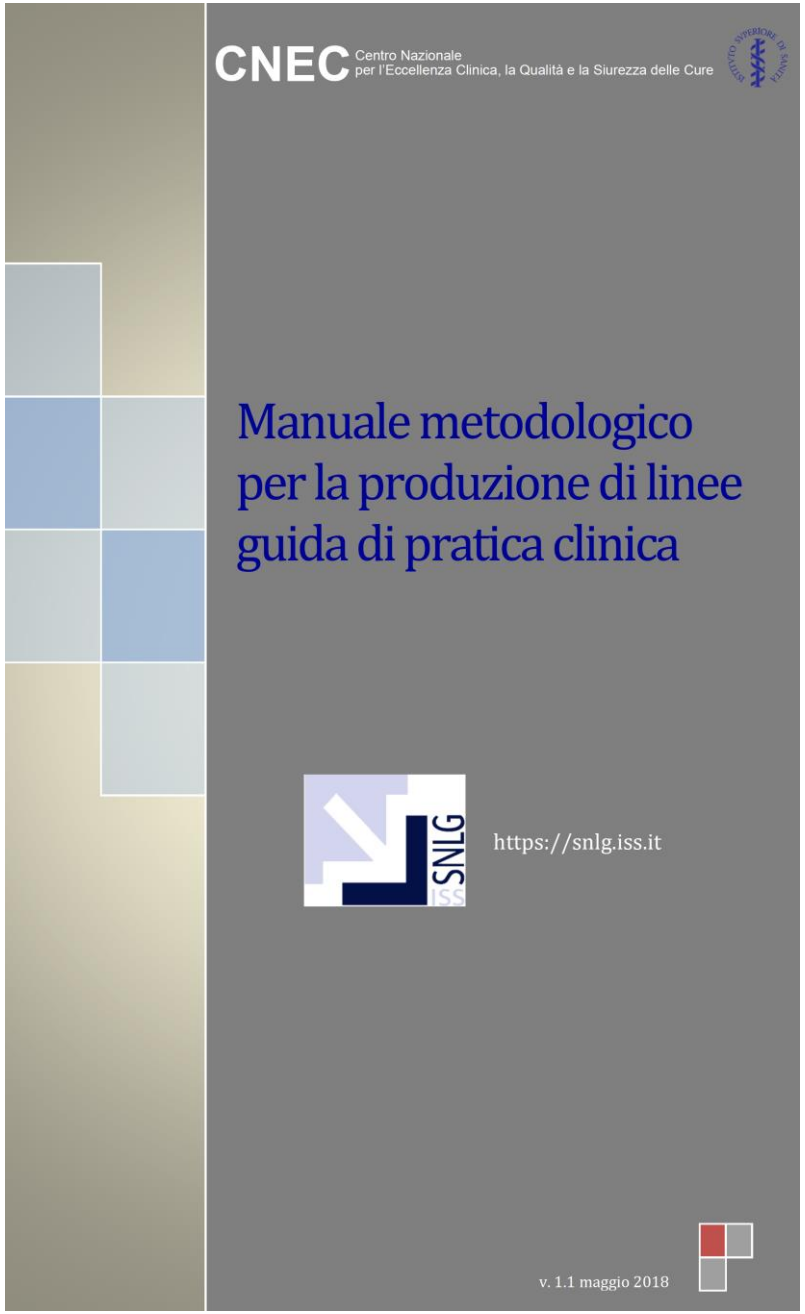
McMaster University
Inspiring Innovation and Discovery

- Aim: to develop a common, transparent and sensible system for grading the quality of evidence and the strength of recommendations (over 100 systems)
- International group of guideline developers, methodologists & clinicians from around the world (>200 contributors) – since 2000
- International group: WHO, ACCP, AHRQ, Australian NMRC, BMJ Clinical Evidence, CC, CDC, McMaster, NICE, Oxford CEBM, SIGN, UpToDate, USPSTF

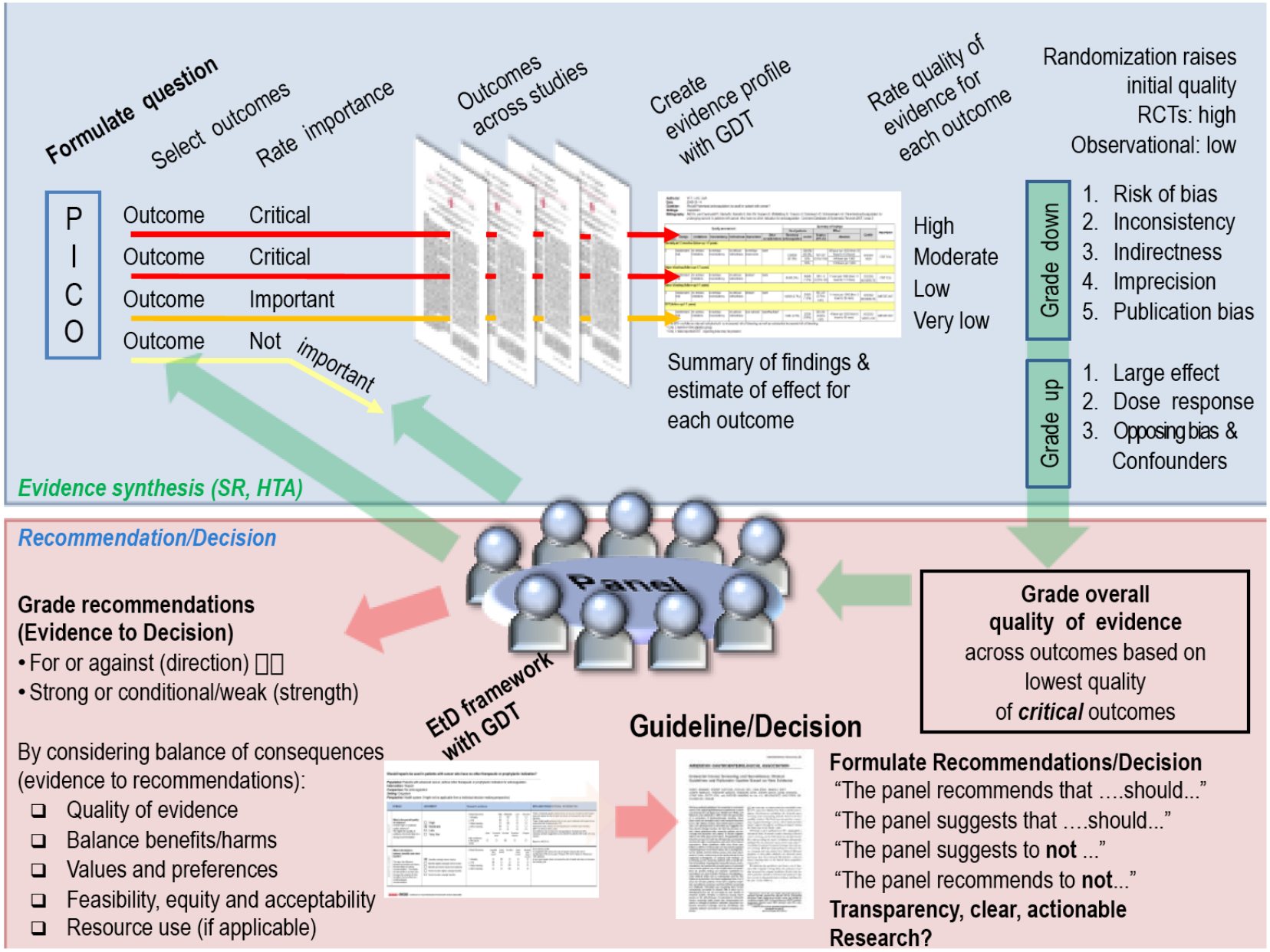
CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005, AJRCCM 2006, Chest 2006, BMJ 2008

The GRADE approach

- Considers
  - all factors to determine how confident we are in the results – quality of evidence
  - the evidence for each outcome in the review separately
  - magnitude of the effect
- Ensures
  - systematic process
  - transparency



Il metodo GRADE propone una valutazione della qualità delle prove più ampia e articolata di quella proposta da tutti gli altri sistemi di grading e rappresenta *lo standard metodologico di riferimento per la produzione di linee guida adottato sempre più diffusamente a livello internazionale.*


Formulate question
Select outcomes
Rate importance
Outcomes across studies
Create evidence profile with GDT
Rate quality of evidence for each outcome
Randomization raises initial quality
RCTs: high
Observational: low
P
I
C
O
Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important
Summary of findings & estimate of effect for each outcome
High
Moderate
Low
Very low
Grade down
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias
Grade up
1. Large effect
2. Dose response
3. Opposing bias & Confounders
Evidence synthesis (SR, HTA)
Recommendation/Decision
Panel
Grade overall quality of evidence across outcomes based on lowest quality of critical outcomes
Grade recommendations (Evidence to Decision)
• For or against (direction)
• Strong or conditional/weak (strength)
By considering balance of consequences (evidence to recommendations):
Quality of evidence
Balance benefits/harms
Values and preferences
Feasibility, equity and acceptability
Resource use (if applicable)
EtD framework with GDT
Guideline/Decision
Formulate Recommendations/Decision
"The panel recommends that ….should..."
"The panel suggests that ….should..."
"The panel suggests to not ..."
"The panel recommends to not..."
Transparency, clear, actionable
Research?

SACRO CUORE DON CALABRIA I R C C S

ECI CANCER CENTRE

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2024 - 10ª EDIZIONE

MODULI SPECIALISTICI - S2

VENERDÌ 12 - SABATO 13 APRILE 2024

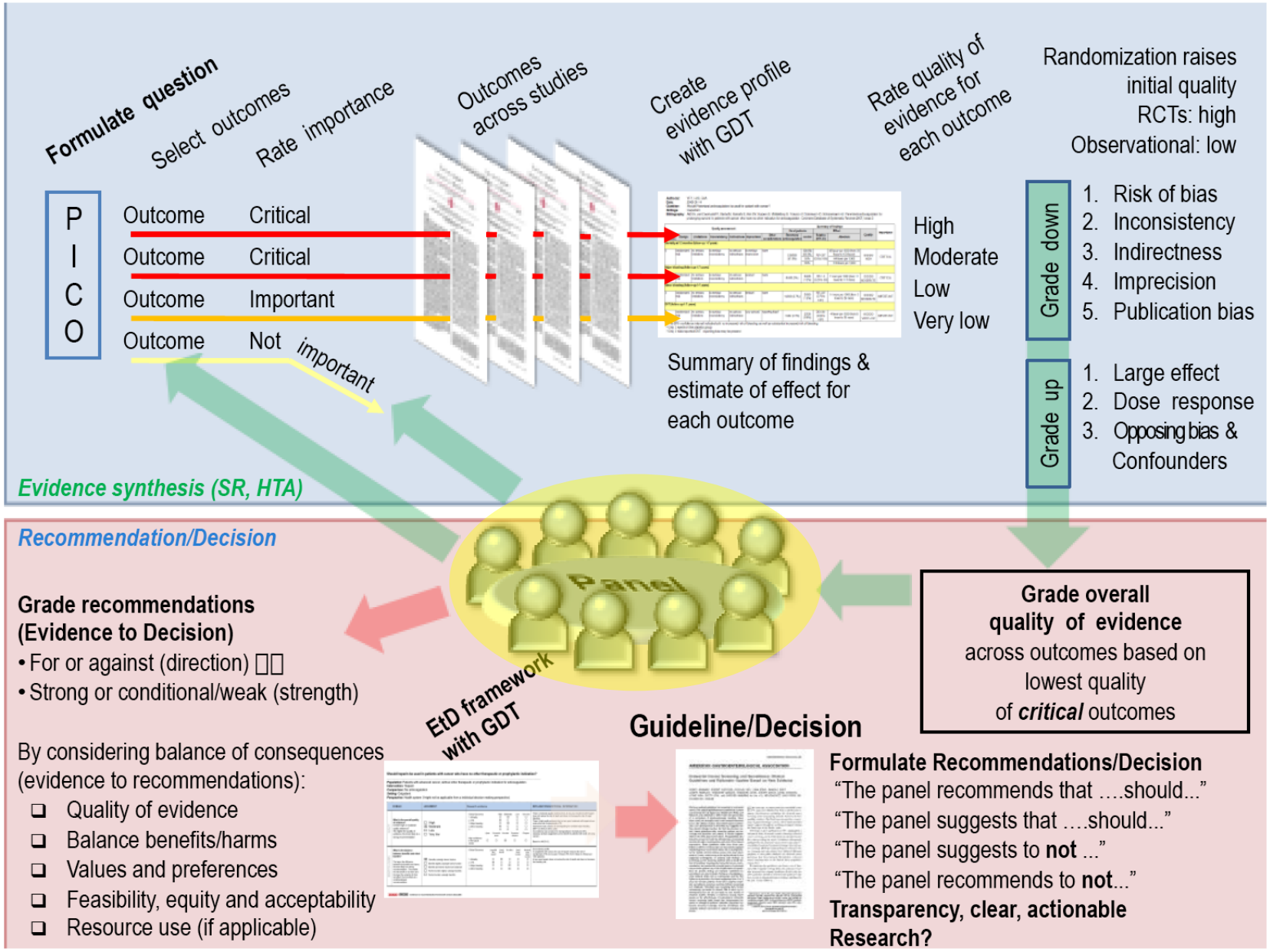
NEGRAR DI VALPOLICELLA (VR)

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

GRADE

Dal quesito clinico alla raccolta sistematica delle prove

(Giovanni Pappagallo)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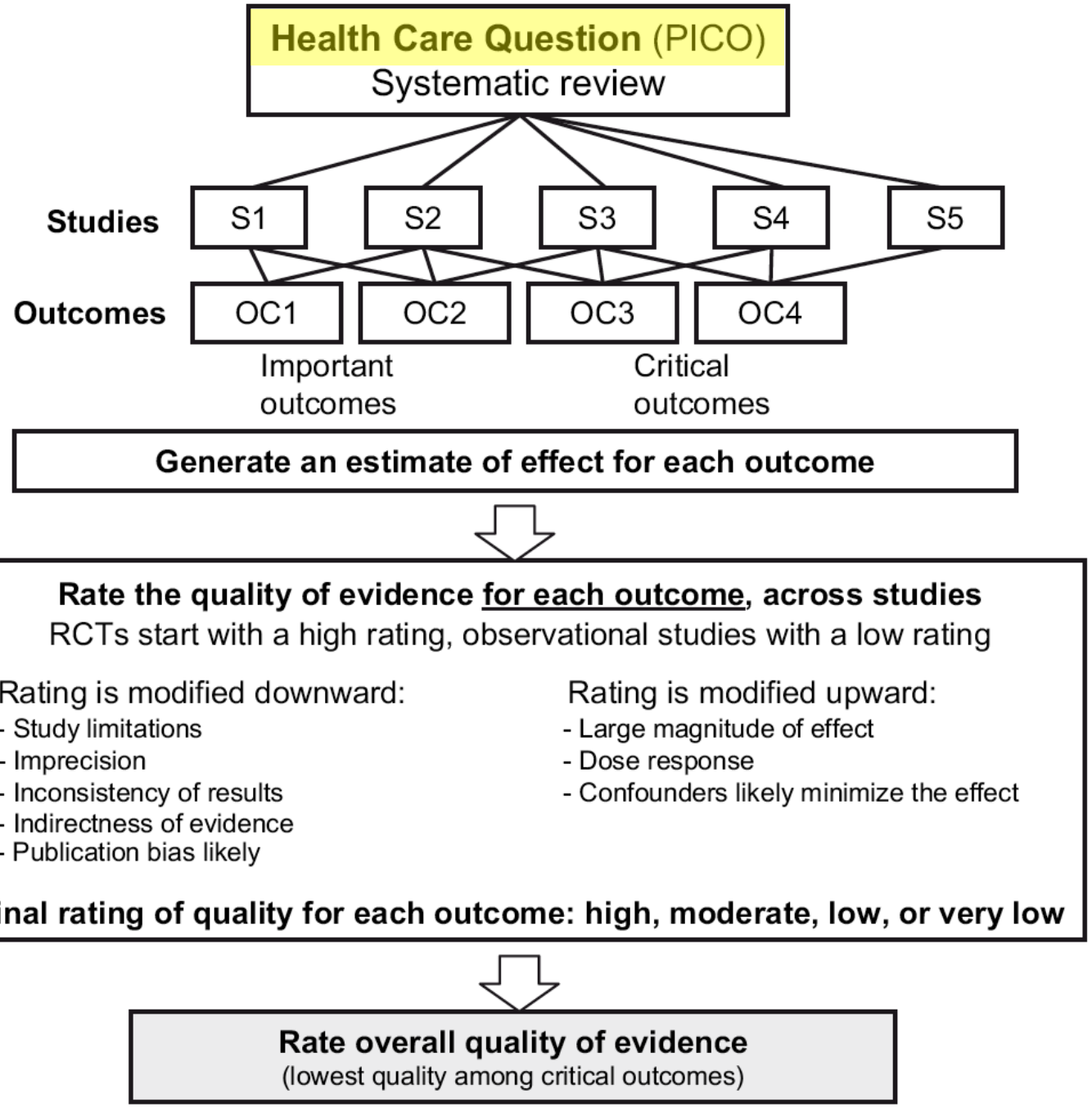
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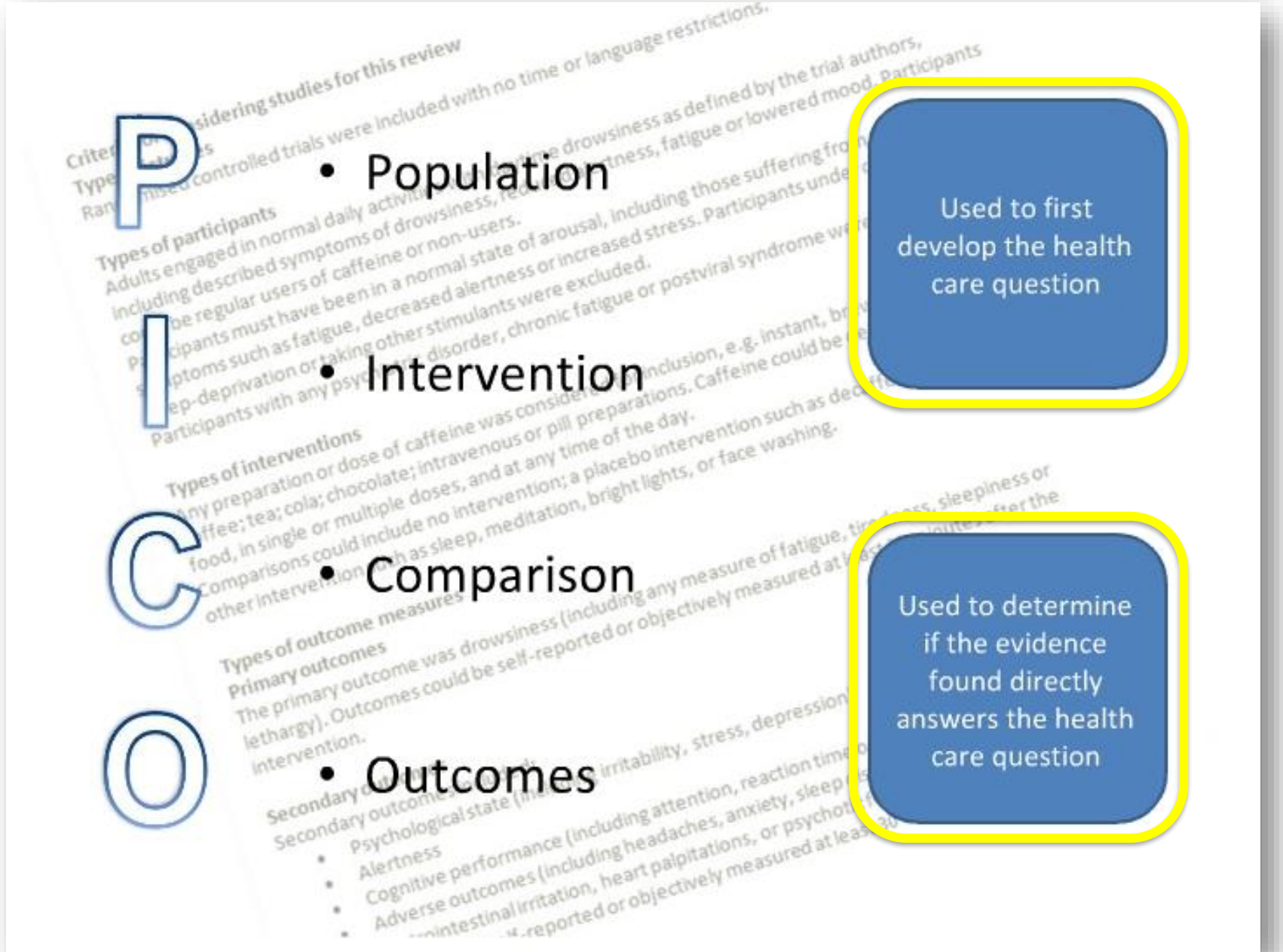
Important Questions

Should be
from practice
NOT
evidence driven



- **P** Population
- **I** Intervention
- **C** Comparison
- **O** Outcomes

Used to first develop the health care question

Used to determine if the evidence found directly answers the health care question

GRADE

Strutturazione del Quesito Clinico sec. modello P.I.C.O.

P	Nei **P**azienti con…	Specifiche caratteristiche di malattia (stadio, classe di rischio, ecc.)
I	l'**I**ntervento…	Intervento terapeutico oggetto del quesito clinico
C	(è suscettibile di impiego) in **C**onfronto con…	Trattamento altrimenti considerabile in alternativa all'intervento in esame
O	riguardo agli **O**utcome di beneficio/danno…	Parametri clinico-laboratoristici ritenuti essenziali per la proposta terapeutica

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Outcomes

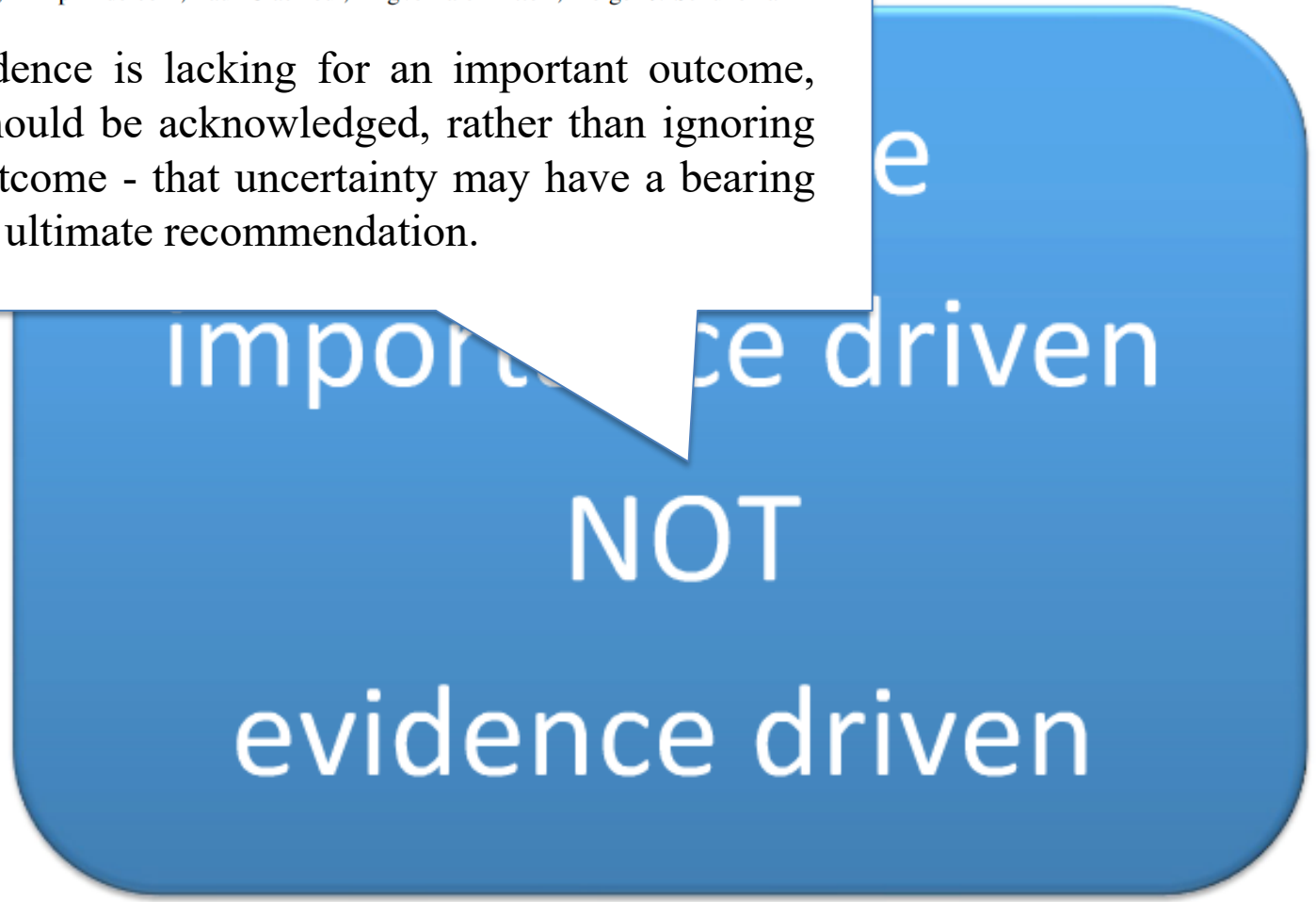
Should be
importance driven
NOT
evidence driven

Journal of Clinical Epidemiology 64 (2011) 395–400

GRADE guidelines: 2. Framing the question and deciding on important outcomes

Gordon H. Guyatt[a,*], Andrew D. Oxman[b], Regina Kunz[c], David Atkins[d], Jan Brozek[a], Gunn Vist[b], Philip Alderson[e], Paul Glasziou[f], Yngve Falck-Ytter[g], Holger J. Schünemann[a]

If evidence is lacking for an important outcome, this should be acknowledged, rather than ignoring the outcome - that uncertainty may have a bearing on the ultimate recommendation.



Choosing outcomes

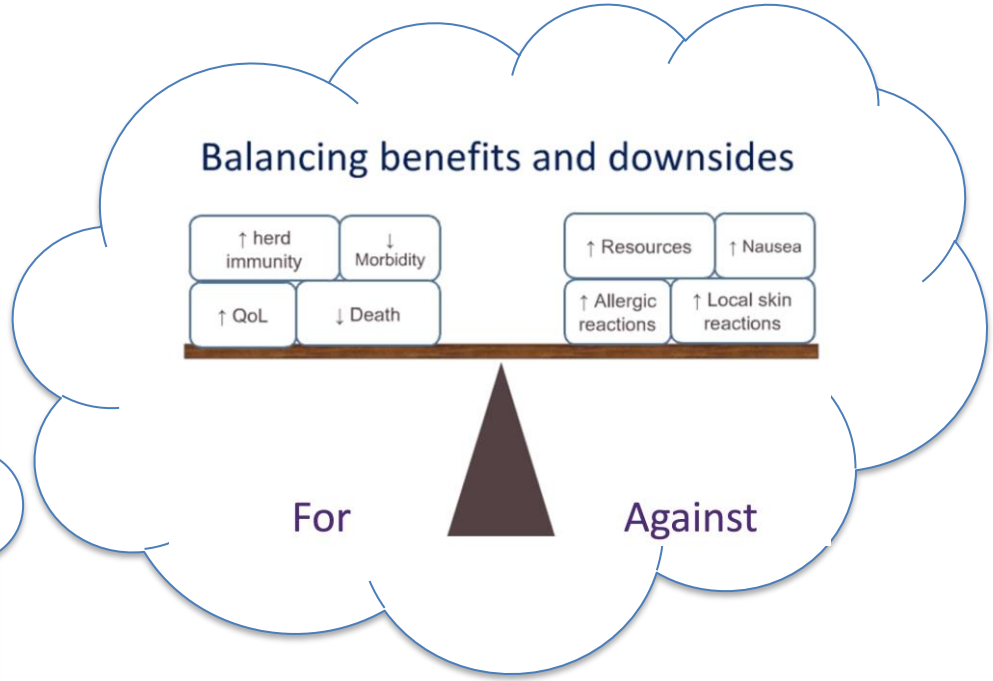
Desirable outcomes

- lower mortality
- reduced hospital stay
- reduced duration of disease
- reduced resource expenditure

Undesirable outcomes

- adverse reactions
- the development of resistance
- costs of treatment

Recommendations must consider desirable and undesirable outcomes

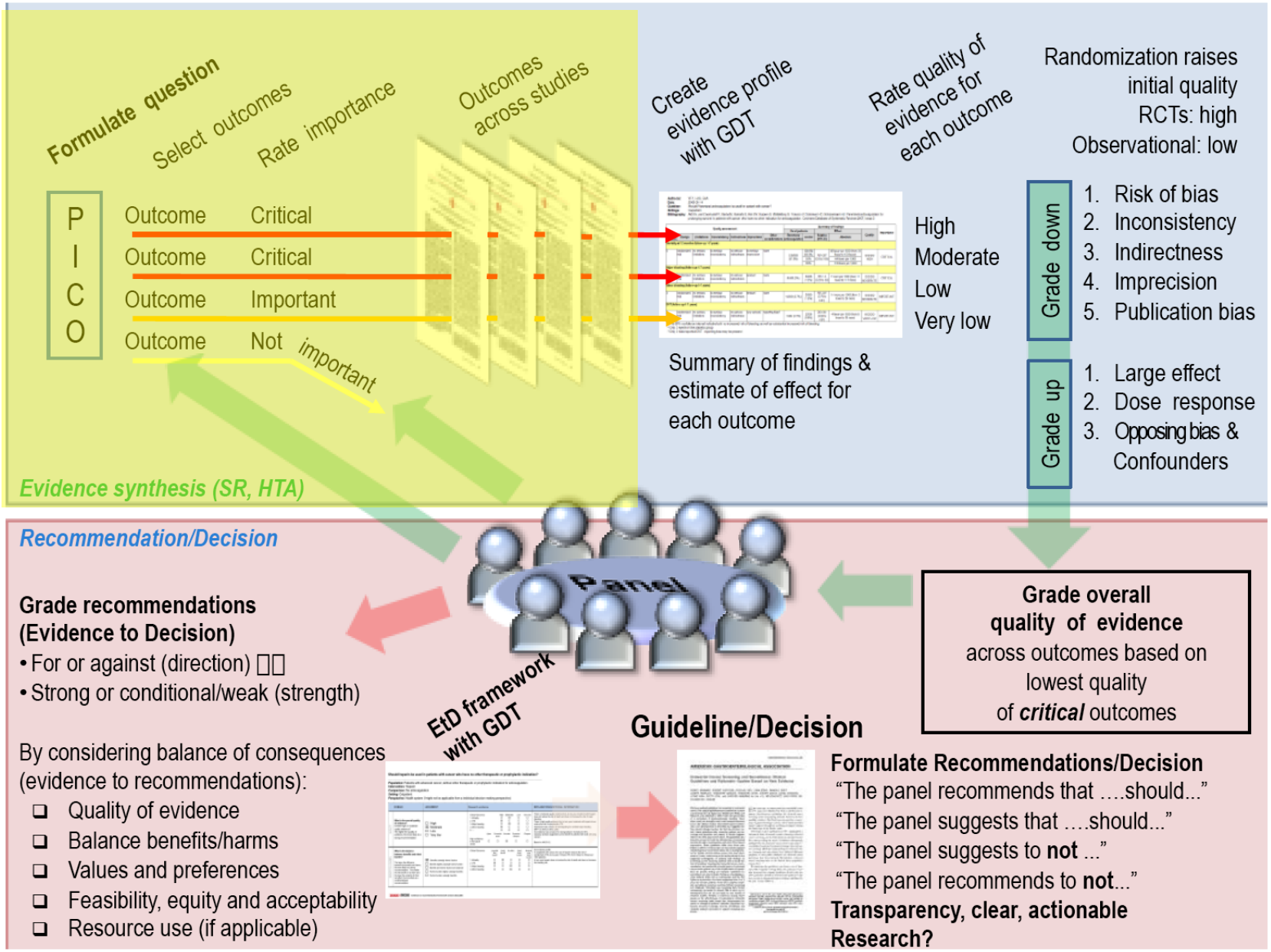


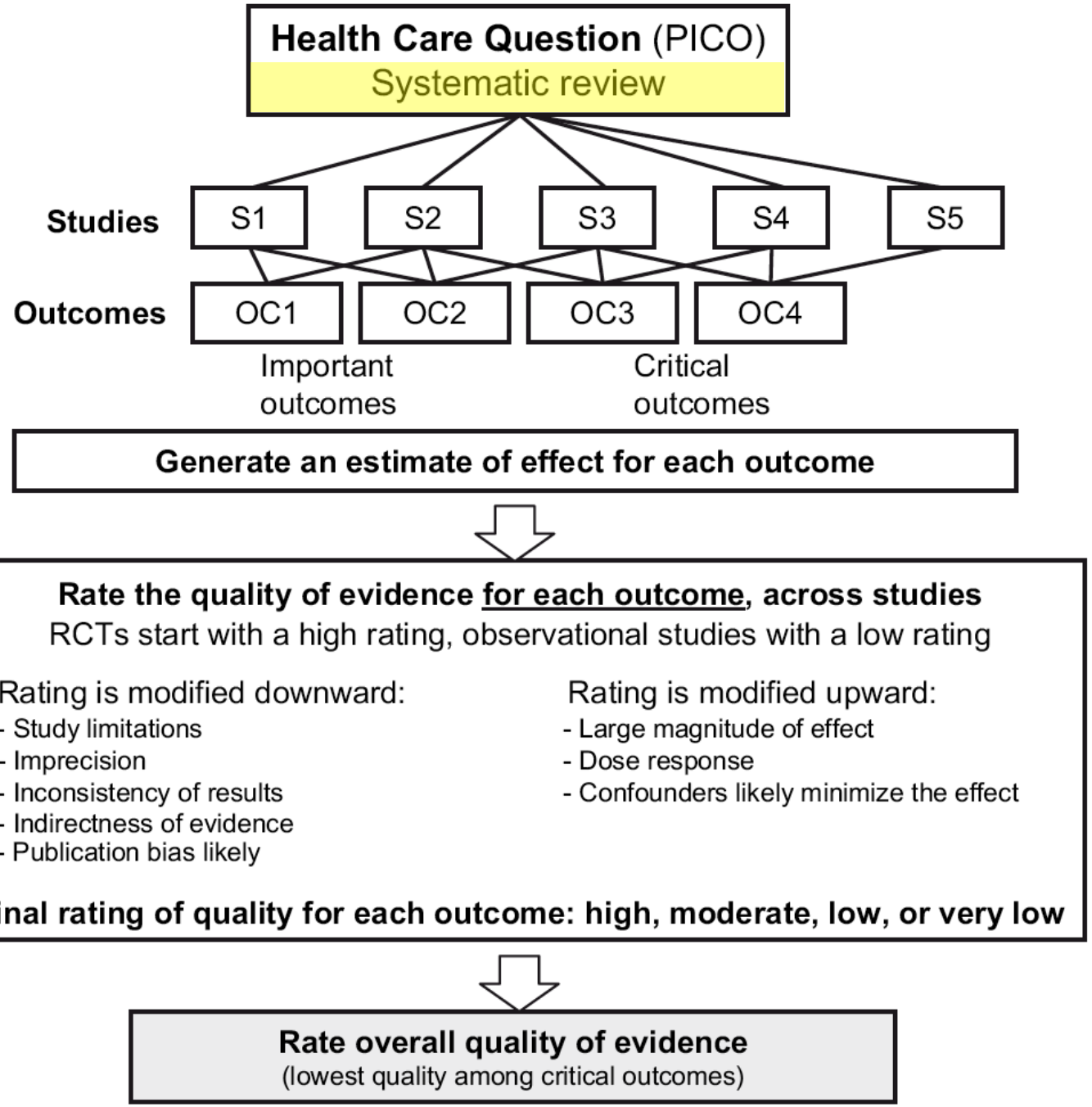
Valutazione dell'importanza degli *outcome* mediante votazione individuale dei panelisti, utilizzando una scala a 9 punti e assegnando l'outcome a una delle tre categorie sulla base del punteggio mediano ottenuto.

Classificazione degli *outcome* proposta dal metodo GRADE

Rating **(mediana del voto)**	**Importanza**	**Incluso in**
7 8 9	*outcome* importanti ed essenziali	tabelle sulla qualità delle prove: SÌ raccomandazione: SÌ
4 5 6	*outcome* importanti ma non essenziali	tabelle sulla qualità delle prove: SÌ raccomandazione: NO
1 2 3	*outcome* non importanti	tabelle sulla qualità delle prove: NO raccomandazione: NO

The GRADE process in developing guidelines

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Rating is modified upward:
- Large magnitude of effect
- Dose response
- Confounders likely minimize the effect
Final rating of quality for each outcome: high, moderate, low, or very low
Rate overall quality of evidence
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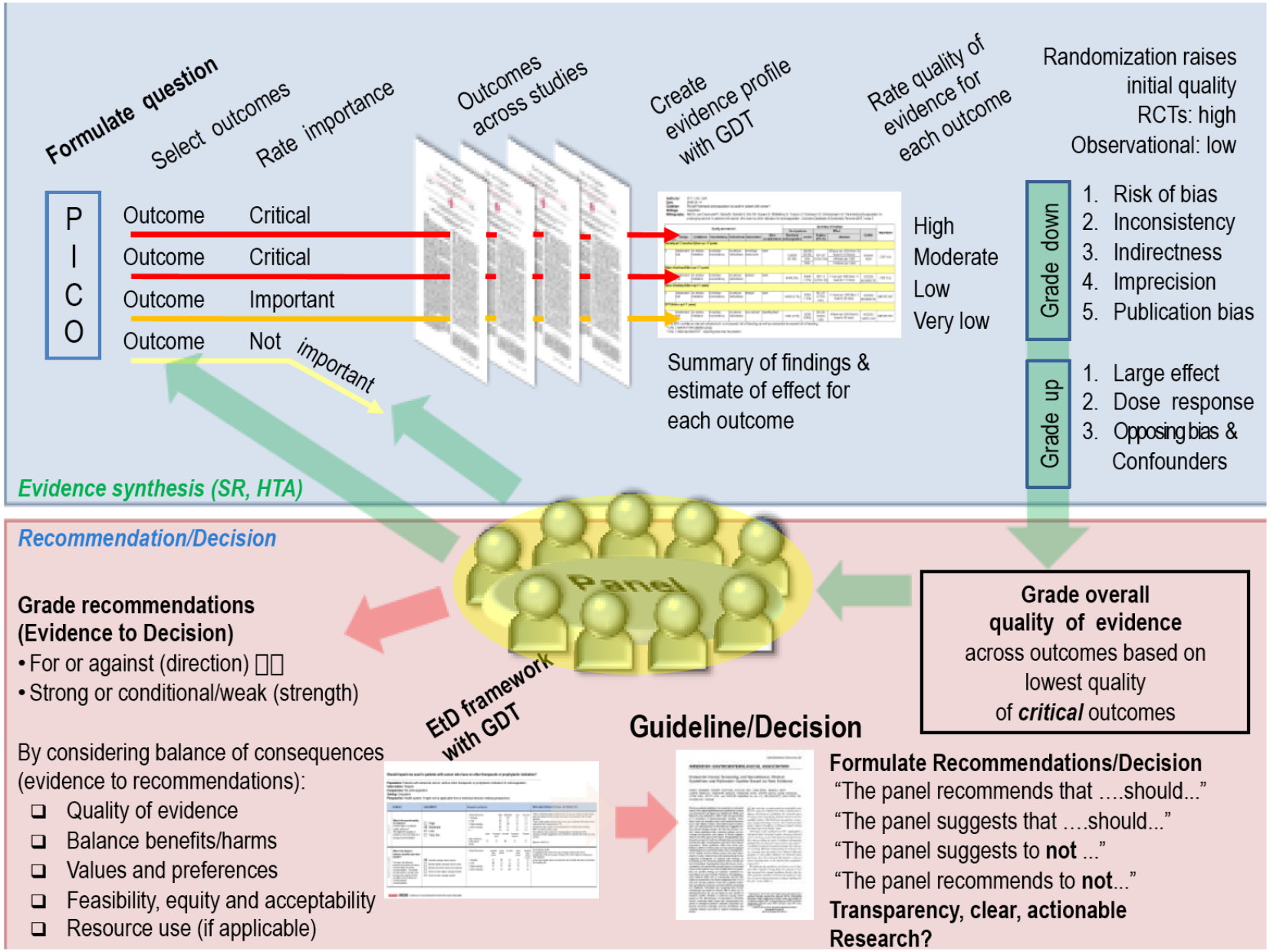
Revisione Sistematica

Metodo esplicito e trasparente per identificare, valutare e riassumere i risultati di singoli studi sugli effetti di un intervento sanitario.

The GRADE process in developing guidelines



Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation

BMJ 2015;349:g7647

OPEN ACCESS

Larissa Shamseer[1], David Moher[1], Mike Clarke[2], Davina Ghersi[3], Alessandro Liberati (deceased)[4], Mark Petticrew[5], Paul Shekelle[6], Lesley A Stewart[7], the PRISMA-P Group

[1]Ottawa Hospital Research Institute and University of Ottawa, Canada; [2]Queen's University Belfast, Ireland; [3]National Health and Medical Research Council, Australia; [4]University of Modena, Italy; [5]London School of Hygiene and Tropical Medicine, UK; [6]Southern California Evidence-based Practice Center, USA; [7]Centre for Reviews and Dissemination, University of York, UK

An international group of experts has created a guideline to improve the transparency, accuracy, completeness, and frequency of documented systematic review and meta-analysis protocols—PRISMA-P (for protocols) 2015.

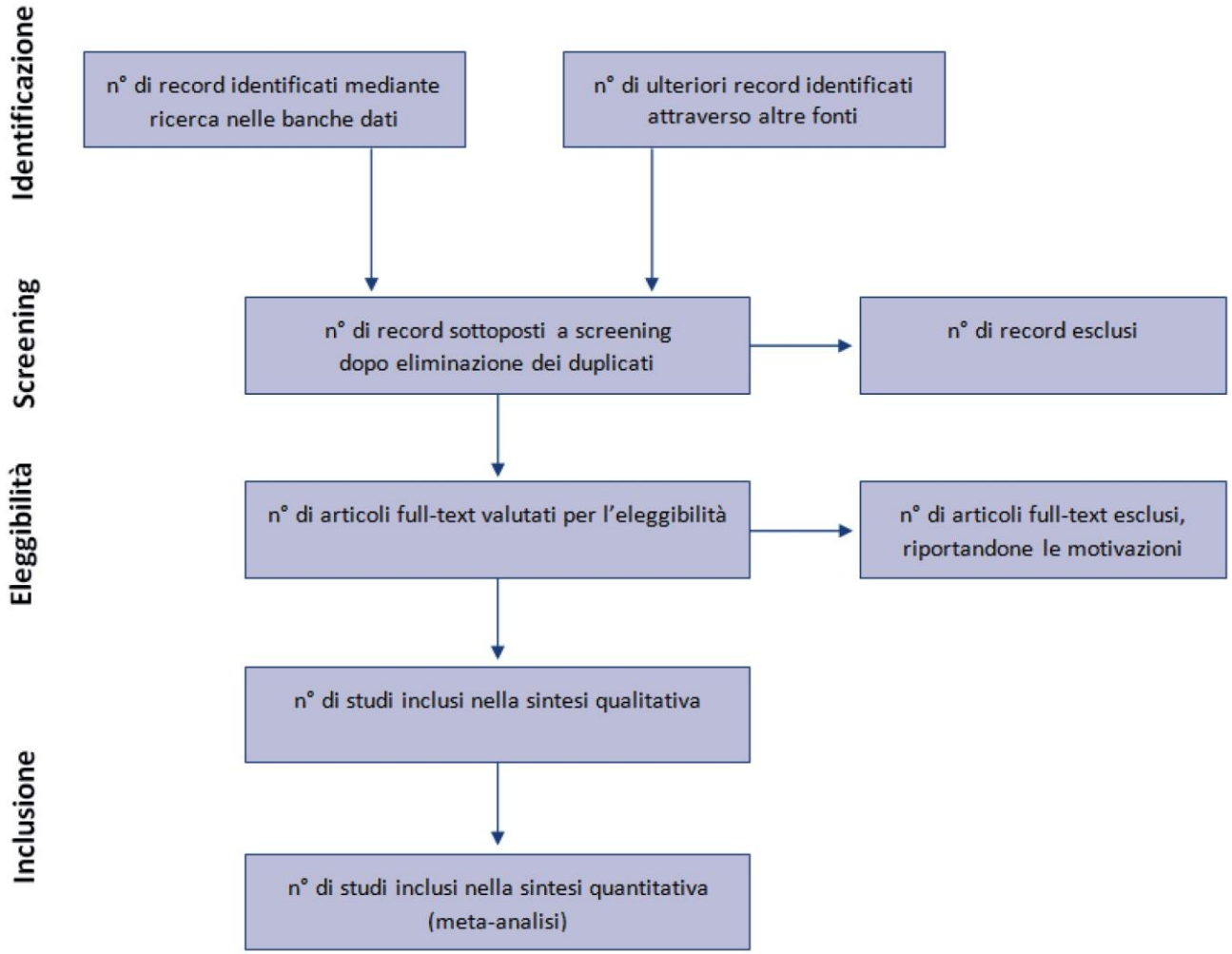
The PRISMA-P checklist contains 17 items considered to be essential and minimum components of a systematic review or meta-analysis protocol.

This PRISMA-P 2015 Explanation and Elaboration paper provides readers with a full understanding of and evidence about the necessity of each item as well as a model example from an existing published protocol.

Linee guida per il reporting di revisioni sistematiche e meta-analisi: il PRISMA Statement

David Moher[1,2*], Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[6]

Evidence 2015;7(6): e1000114



GRADE Adolopment

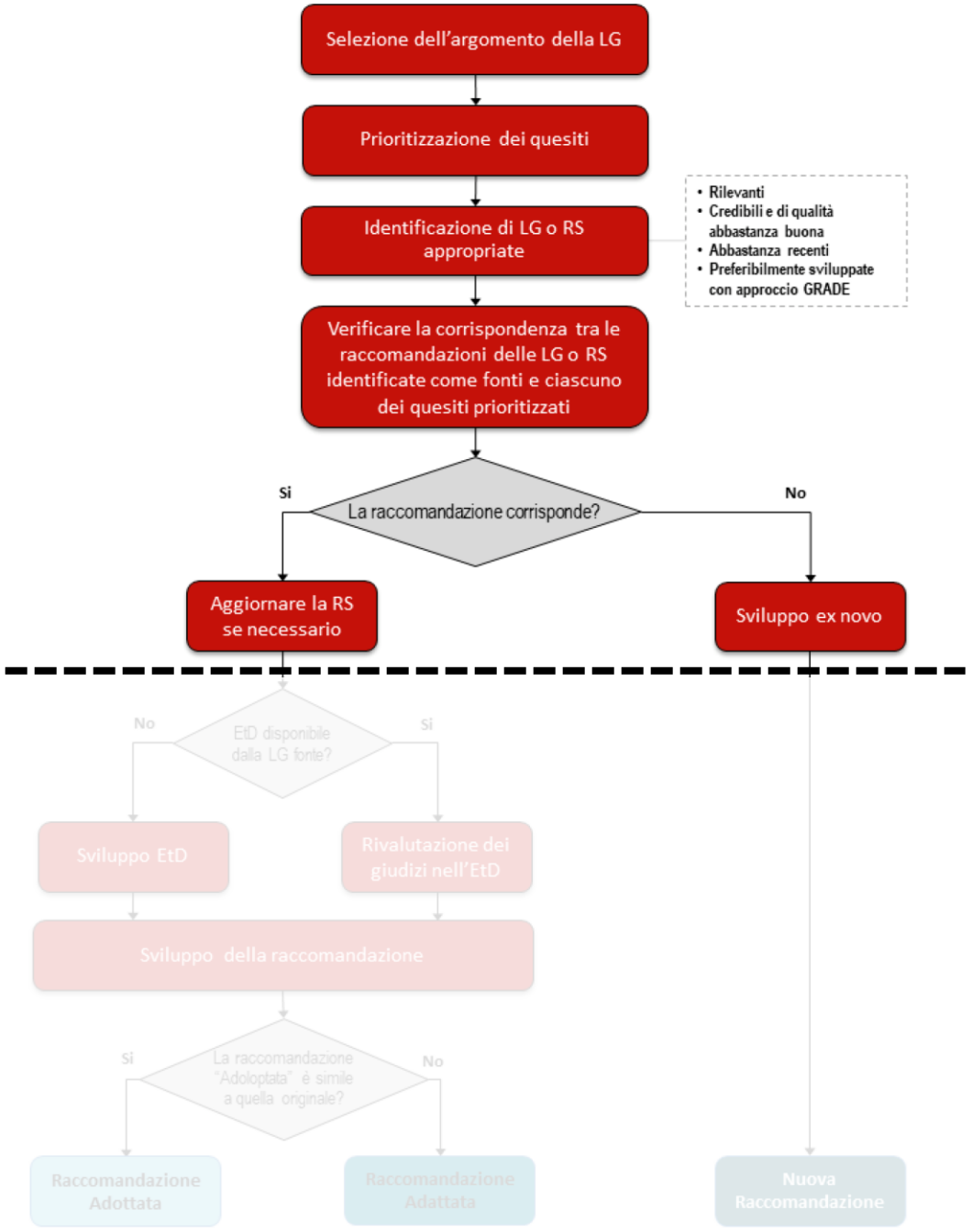
Evoluzione del metodo GRADE che consente di valutare se è opportuno produrre una LG *ex novo* ovvero è sufficiente un adattamento al contesto o l'adozione di raccomandazioni esistenti per rispondere a determinati quesiti PICO.

Decisione sulla base di requisiti di **credibilità**, **stato di aggiornamento**, **accettabilità** e **applicabilità** al contesto culturale e organizzativo.

Journal of Clinical Epidemiology 81 (2017) 101–110

GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT

Holger J. Schünemann[a,b,*], Wojtek Wiercioch[a], Jan Brozek[a,b], Itziar Etxeandia-Ikobaltzeta[a], Reem A. Mustafa[a,c,d], Veena Manja[e,f], Romina Brignardello-Petersen[g,h], Ignacio Neumann[a,i], Maicon Falavigna[j,k], Waleed Alhazzani[a,b], Nancy Santesso[a], Yuan Zhang[a], Jörg J. Meerpohl[l,m], Rebecca L. Morgan[a], Bram Rochwerg[a], Andrea Darzi[d], Maria Ximenas Rojas[n], Alonso Carrasco-Labra[a,i], Yaser Adi[o], Zulfa AlRayees[p], John Riva[a,q], Claudia Bollig[l], Ainsley Moore[a,q], Juan José Yepes-Nuñez[a], Carlos Cuello[a,r], Reem Waziry[s,t], Elie A. Akl[a,s]



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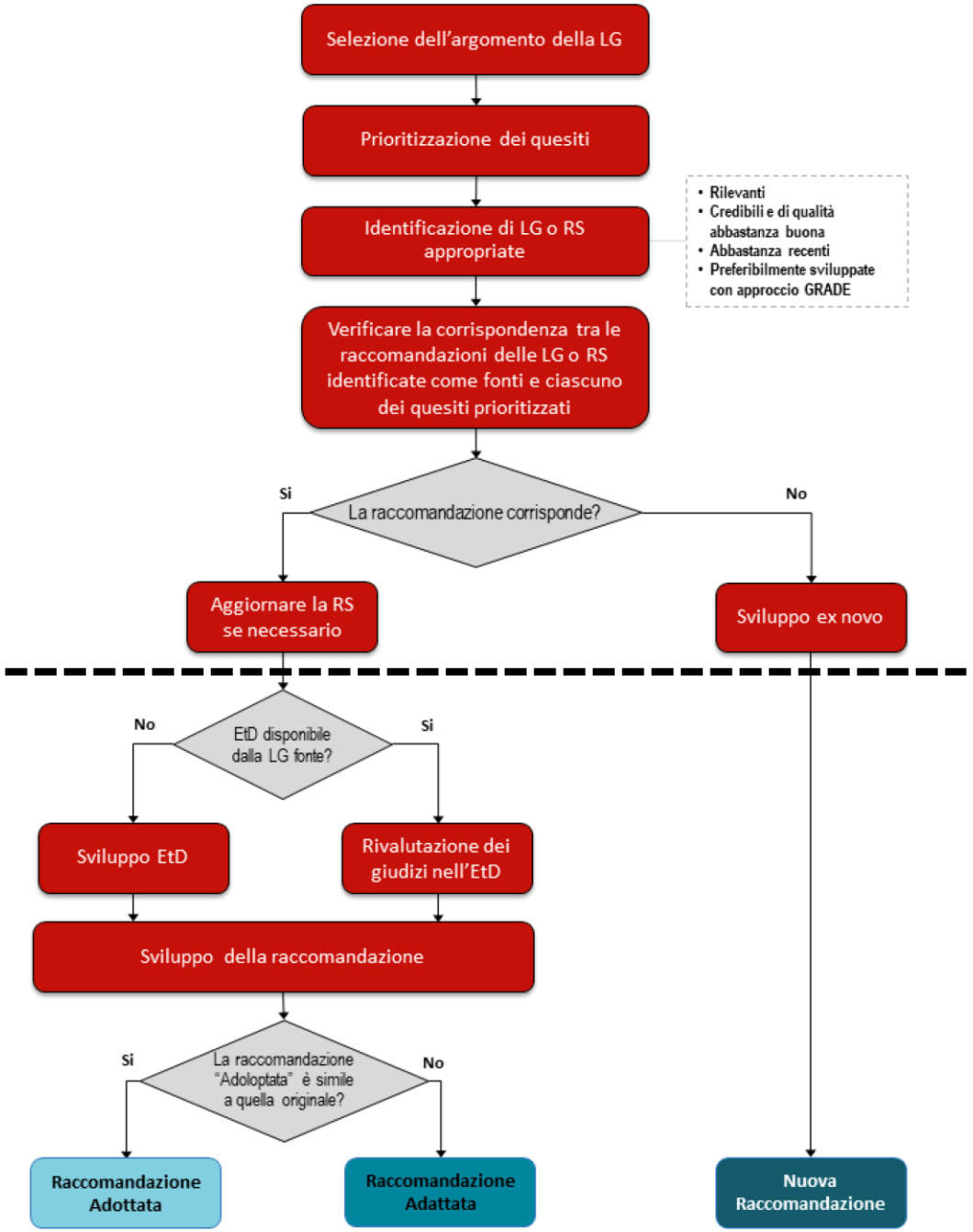

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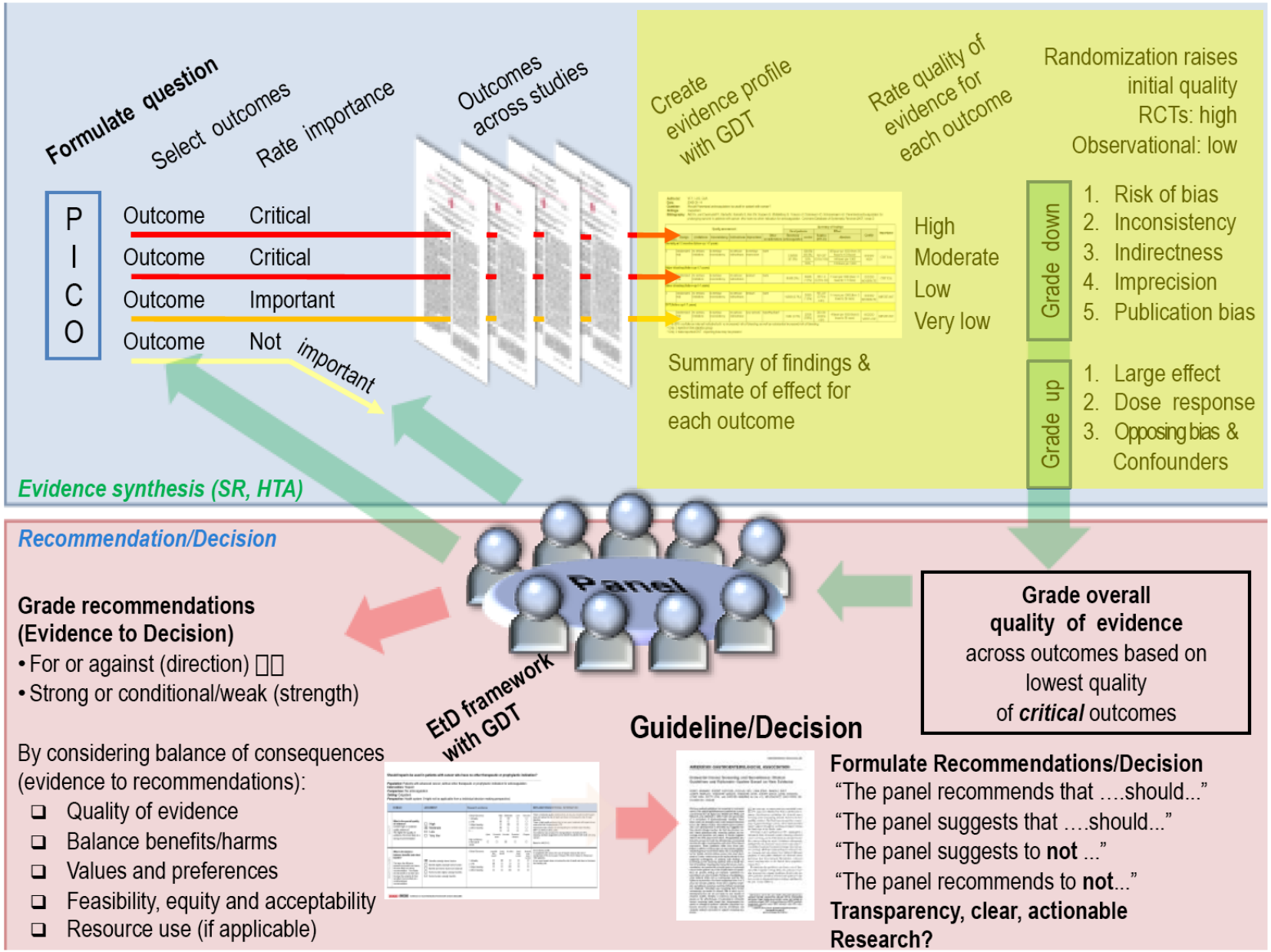

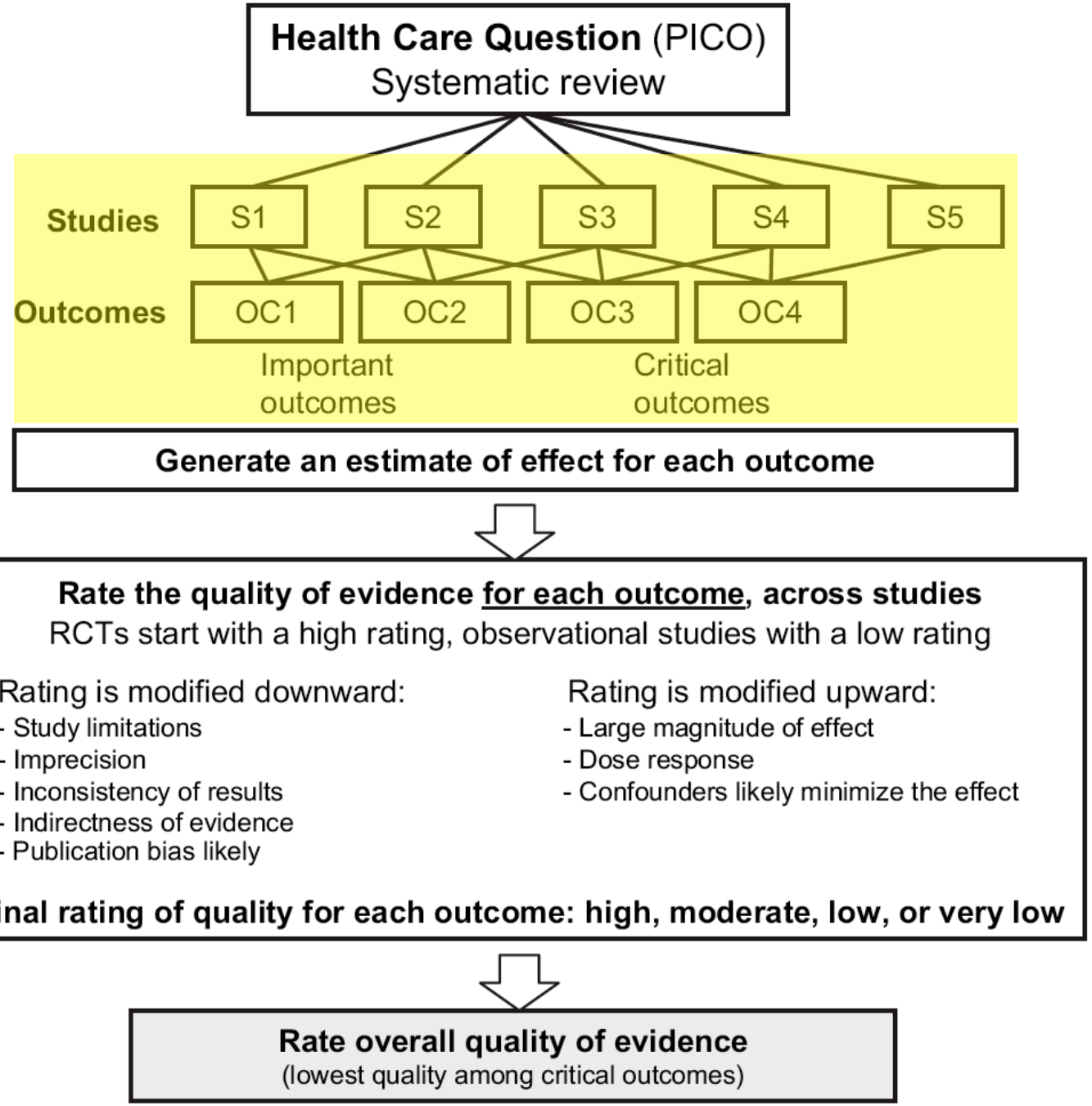
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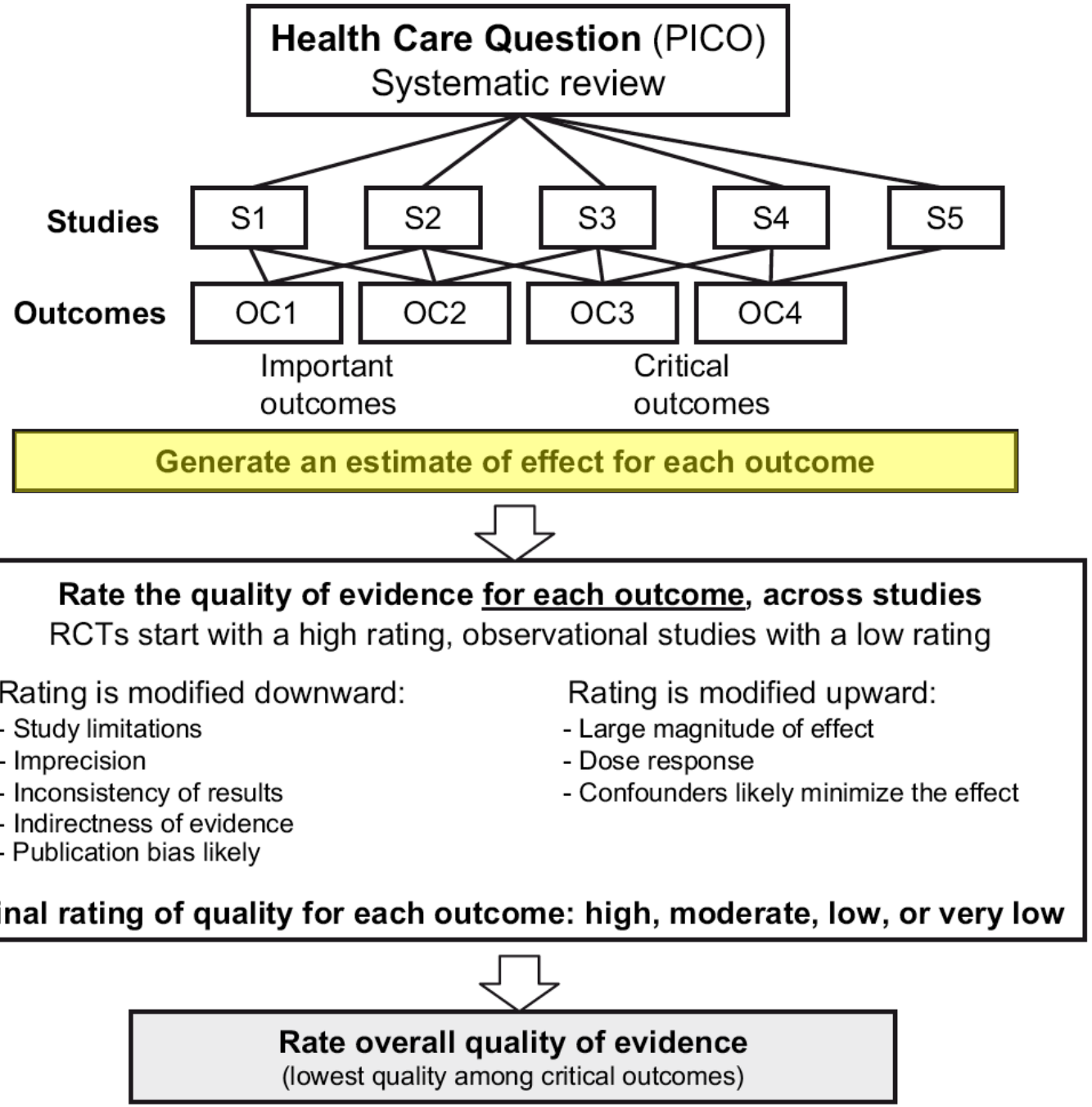
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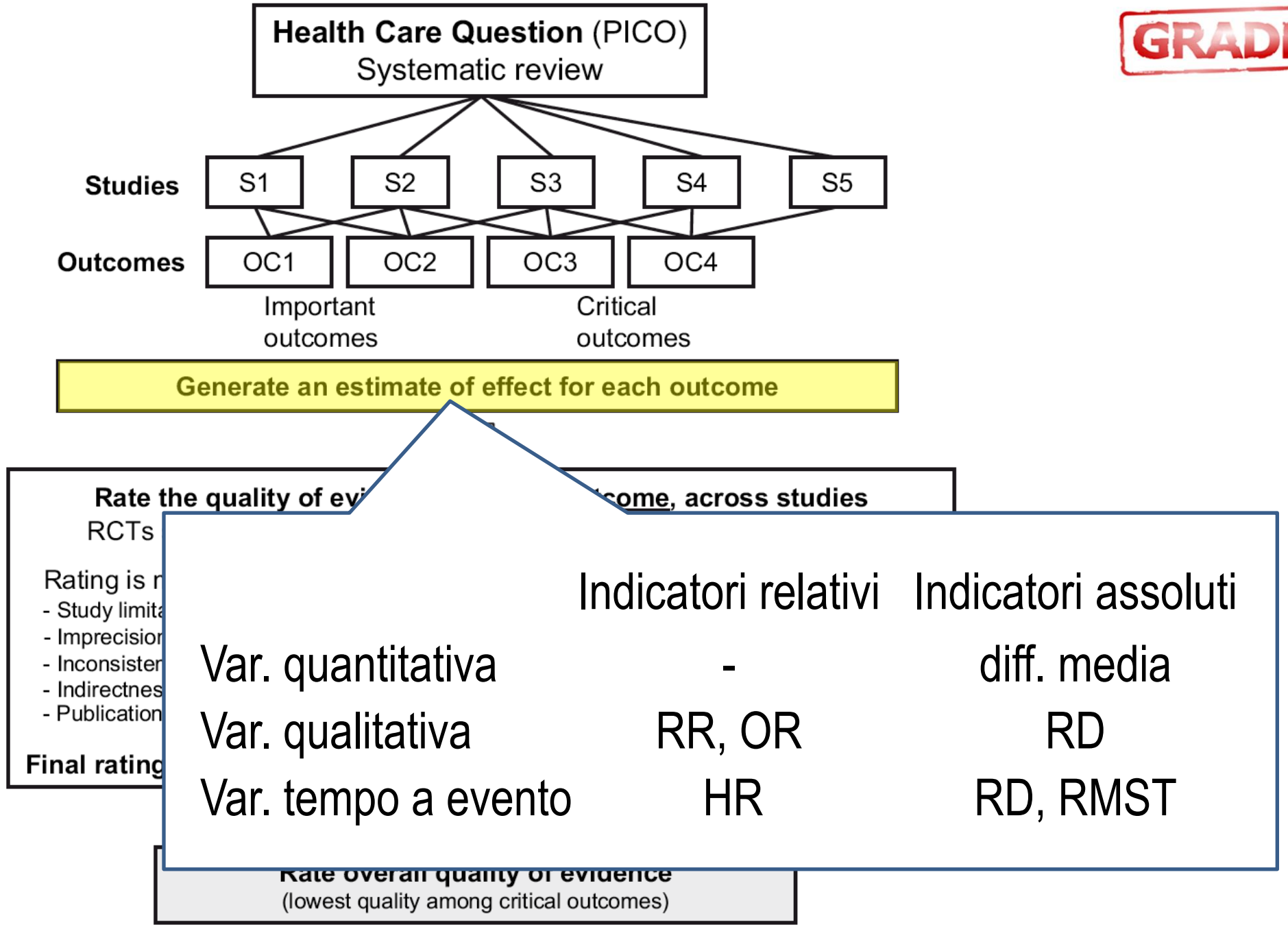
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Indicatori assoluti
Var. quantitativa
-
diff. media
Var. qualitativa
RR, OR
RD
Var. tempo a evento
HR
RD, RMST

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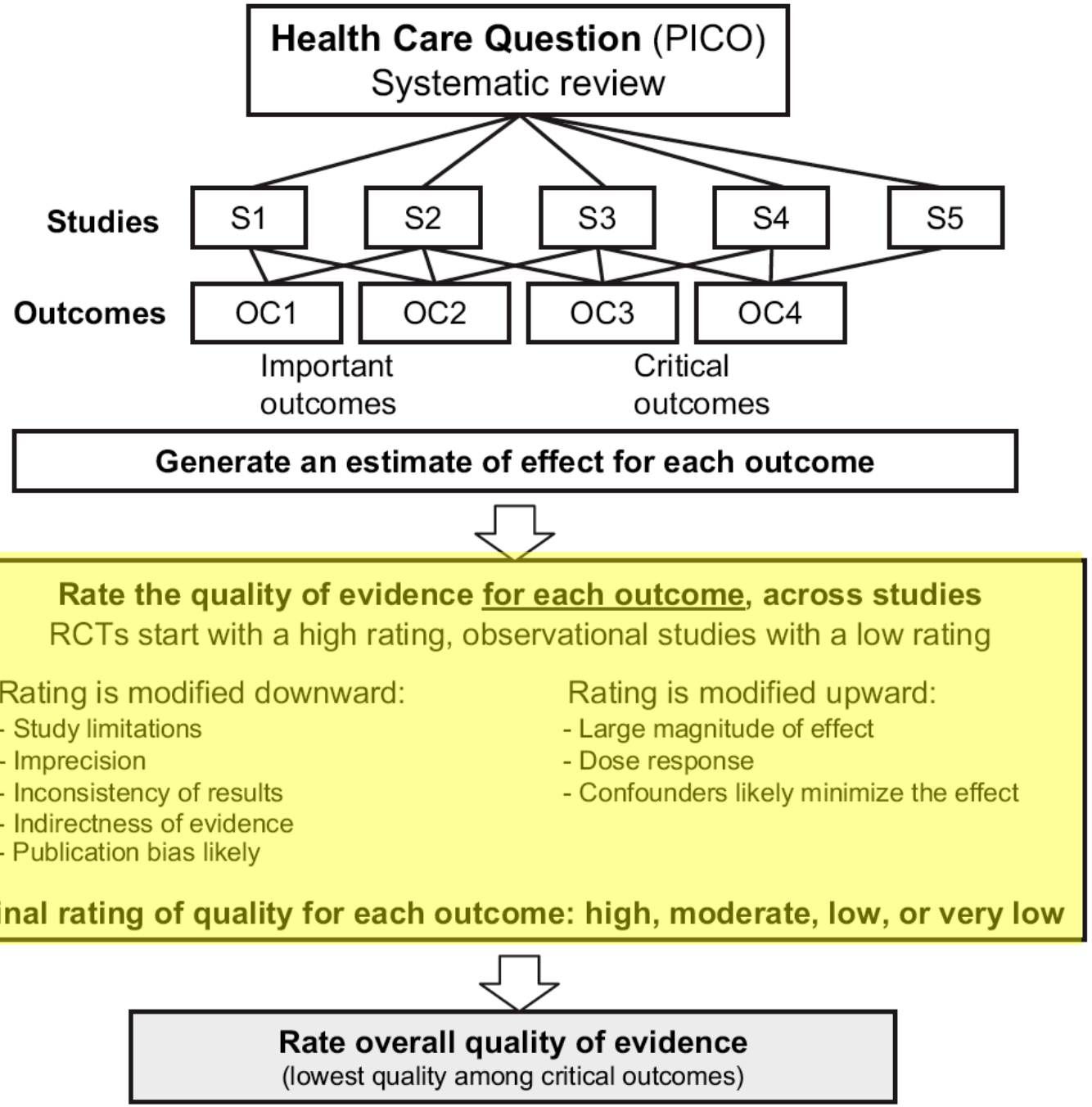
Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

GRADE

La valutazione della qualità delle prove (1): *risk of bias*

(Michela Cinquini)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GRADE Quality of Evidence

In the context of making recommendations:

- The quality of evidence reflects the extent of our confidence that the estimates of an effect are adequate to support a particular decision or recommendation.

Quality of the body of evidence

Four levels

⨁⨁⨁⨁ High	We are very confident that the true effect lies close to that of the estimate of the effect
⨁⨁⨁◯ Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁◯◯ Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁◯◯◯ Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Tabella 5- Criteri* per l'aumento (*upgrading*) o la diminuzione (*downgrading*) del giudizio di qualità (alta, moderata, bassa, molto bassa) delle prove

Tipo di prove	Studio controllato e randomizzato = alta Studio osservazionale = bassa Qualsiasi altro tipo di informazione = molto basso
A. Diminuzione della categoria di attribuzione (es. da "alta" a "moderata")	1. Limiti gravi (-1 livello) o molto gravi (-2 livelli) nella qualità di conduzione dello studio 2. Incoerenza nei risultati tra studi diversi sullo stesso quesito (-1 o -2 livelli) 3. Alcune (-1 livello) o importanti (-2 livelli) incertezze circa la diretta trasferibilità dei risultati (directness) 4. Imprecisione o dati insufficienti (*sparse data*) (-1 o -2 livelli) 5. Possibilità di pubblicazione selettiva dei dati (*publication* e *reporting bias*) (-1 o-2 livelli)
B. Aumento della categoria di attribuzione (es. da "bassa" a "moderata")	1. Associazione intervento-outcome forte, ovvero con rischio relativo >2 (<0,5), sulla base di prove concordanti provenienti da due o più studi osservazionali, senza alcun fattore di confondimento plausibile (+1 livello) 2. Associazione intervento-outcome molto forte, ovvero con rischio relativo >5 (<0,2) (+2 livelli) 3. Presenza di un gradiente dose-risposta (+1 livello) 4. Aver considerato tutti i possibili fattori di confondimento che avrebbero potuto alterare le stime di effetto (+1 livello)

* non sono da considerarsi un algoritmo

Tabella 5- Criteri* per l'aumento (*upgrading*) o la diminuzione (*downgrading*) del giudizio di qualità (alta, moderata, bassa, molto bassa) delle prove

Tipo di prove	Studio controllato e randomizzato = alta Studio osservazionale = bassa Qualsiasi altro tipo di informazione = molto basso
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* non sono da considerarsi un algoritmo

Tabella 5- Criteri* per l'aumento (*upgrading*) o la diminuzione (*downgrading*) del giudizio di qualità (alta, moderata, bassa, molto bassa) delle prove

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* non sono da considerarsi un algoritmo

- **RCTs ⊕⊕⊕⊕**
- **observational studies ⊕⊕◯◯**
- **5 factors that can lower quality**
  1. limitations in study design, execution and reporting *(risk of bias criteria)*
  2. Inconsistency *(or heterogeneity)*
  3. Indirectness *(PICO and applicability)*
  4. Imprecision
  5. Publication bias
- **3 factors can increase quality**
  1. large magnitude of effect
  2. opposing plausible residual bias or confounding
  3. dose-response gradient

ELSEVIER

Journal of Clinical Epidemiology 64 (2011) 407–415

Journal of Clinical Epidemiology

GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias)

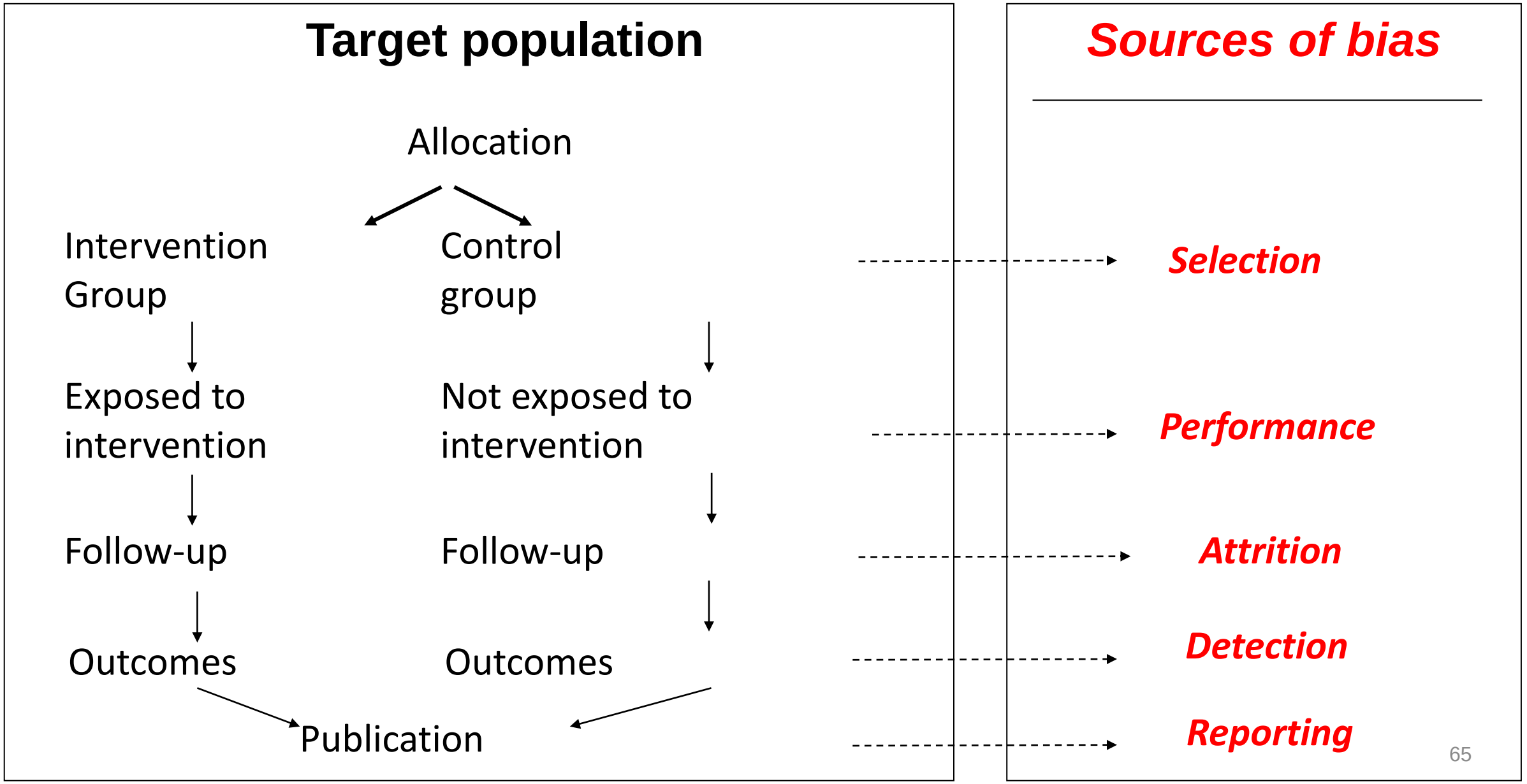
Gordon H. Guyatt[a,*], Andrew D. Oxman[b], Gunn Vist[b], Regina Kunz[c], Jan Brozek[a], Pablo Alonso-Coello[d], Victor Montori[e], Elie A. Akl[f], Ben Djulbegovic[g,h,i], Yngve Falck-Ytter[j], Susan L. Norris[k], John W. Williams Jr.[l], David Atkins[m], Joerg Meerpohl[n,o], Holger J. Schünemann[a]

Bias

Systematic distortion of the estimated intervention effect away from the truth, caused by **inadequacies** in the **design**, **conduct**, or **analysis** of a trial , or in the **publication of its results**. In other words, in a biased trial, the results observed reflect other factors in addition to (or, in extreme cases, instead of) the effect of the tested therapeutic procedure alone.

Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663–94

Trial as a flow



Selection bias: due componenti

Generazione lista di randomizzazione

- **Basso rischio di bias**. Uso di metodi realmente casuali come ad esempio: tavole di numeri random, sistemi computerizzati, lancio di una moneta o di un dado, sorteggio.
- **Alto rischio di bias.** Uso di metodi **NON** realmente casuali come ad esempio: giorno di nascita o di ammissione in ospedale, giudizio del medico, preferenze del paziente, risultati di test di laboratorio, disponibilità del trattamento, alternanza
- **Rischio incerto**. Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Nascondimento della sequenza di randomizzazione*

- **Basso rischio di bias**. Sperimentatori che arruolano i pazienti non possono prevedere in quale gruppo verrà inserito il paziente perché si usa uno dei seguenti metodi: randomizzazione centralizzata (telefonica, via web, o gestita da personale esterno alla sperimentazione - farmacista, statistico); buste chiuse e opache.
- **Alto rischio di bias.** Sperimentatori che arruolano i pazienti possono prevedere in quale gruppo verrà inserito il paziente perché si usa uno dei seguenti metodi: liste di randomizzazione, buste aperte o non opache, alternanza, data di nascita, numero di cartella, ect.
- **Rischio incerto**. Non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

*allocation concealment

Esempio 1

To prevent the introduction of bias, randomisation will be via an online system, accessed via http://www.ctu.co.uk, hosted by the Clinical Trials Unit (CTU), King's College London (KCL). Eligible participants will be randomised to either the nilvadipine or placebo treatment group. The

***Generazione della sequenza**: basso rischio*

***Allocation concealment:** basso rischio*

Esempio 2

Eligible patients with even-number hospital records were assigned to treatment (5000 U twice daily), those with odd-number records served as controls

***Generazione della sequenza**: alto rischio*

***Allocation concealment:** alto rischio*

Esempio 3

Subjects were assigned at random in a 2:1 ratio to naltrexone or control (Cornish 1977)

***Sequence generation**: rischio incerto*

***Allocation concealment:** rischio incerto*

Esempio 4

Patients were randomly assigned in a 1:1:1 ratio to one of three treatment groups: ledipasvir–sofosbuvir for 8 weeks, ledipasvir–sofosbuvir plus ribavirin for 8 weeks, or ledipasvir–sofosbuvir for 12 weeks. Randomization was stratified according to HCV genotype (1a or 1b).

***Generazione della sequenza**: rischio incerto*

***Allocation concealment:** rischio incerto*

Blinding

- Sperimentatori e partecipanti non conoscono gruppo di allocazione (*performance bias*)

- Valutatori degli esiti non conoscono gruppo di allocazione (*detection bias*)

Singolo cieco
i pazienti inclusi nello studio non conoscono il gruppo al quale sono stati assegnati

Doppio cieco
i pazienti e gli sperimentatori non conoscono il gruppo al quale (i pazienti) sono stati assegnati

Triplo cieco
i pazienti, gli sperimentatori e i valutatori degli esiti non conoscono il gruppo di allocazione

…

Non sempre il significato è questo … è sempre bene valutare chi è davvero in cieco!

Performance bias

Si verifica quando i partecipanti allo studio (sperimentatori o pazienti) modificano i loro comportamenti perché sanno a quale gruppo è assegnato un dato paziente

Esempi:

Lo sperimentatore controlla la presenza di effetti avversi più frequentemente nei pazienti assegnati al gruppo di trattamento.

Un paziente nel gruppo placebo assume altri farmaci, fa più (o meno) visite di controllo.

Detection bias

Si verifica quando la valutazione degli esiti dello studio viene influenzata dalla conoscenza del gruppo al quale è assegnato un dato paziente

Esempi:

Interpretazione di esiti radiologici, risoluzione dei sintomi, valutazione delle ricadute di malattia diversa nei pazienti assegnati al trattamento e al controllo

Performance bias

Cecità di pazienti e sperimentatori

- **Basso rischio di bias.** Pazienti e sperimentatori non conoscono l'assegnazione dei pazienti al gruppo di controllo o di trattamento oppure è poco probabile che la mancanza di cecità influenzi la performance di pazienti e sperimentatori
- **Alto rischio di bias.** Pazienti e sperimentatori conoscono l'assegnazione dei pazienti o, durante lo studio, diventa chiaro a quale gruppo di trattamento sono allocati (rottura del cieco). Studi definiti come "open label"
- **Rischio incerto**. Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Detection bias

Cecità del valutatore degli esiti dello studio (outcome)

- **Basso rischio di bias.** L'esito dello studio è valutato senza conoscere l'assegnazione dei pazienti al gruppo di controllo o di intervento; oppure è poco probabile che la mancanza di cecità influenzi la valutazione
- **Alto rischio di bias.** L'esito dello studio è valutato conoscendo l'assegnazione dei pazienti al gruppo di controllo o di intervento ed è probabile che la mancanza di cecità influenzi la valutazione
- **Rischio incerto**. Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

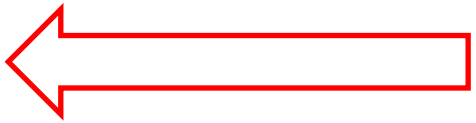
Performance and detection bias

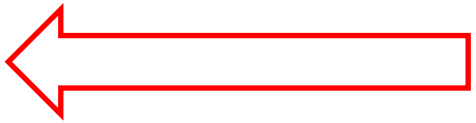
- Impatto diverso su outcome **soggettivi** e **oggettivi** (quindi la valutazione va fatta separatamente)
- Se studio su **farmaco in doppio cieco** e dice che tutti gli operatori erano all'oscuro dell'assegnazione è probabile che sia in cieco anche l'outcome assessor, anche se non espressamente detto
- Se studio su **interventi che non possono essere in doppio cieco** (psicosociali, educativi, chirurgici, riabilitativi) importante che sia in cieco l'outcome assessor e deve essere specificato
  - Performance: high risk per outcomes soggettivi sempre
  - Detection: low risk se c'è blinding of outcome assessor anche per outcomes soggettivi

Esempio 1

Eligible participants will be randomised to either the nilvadipine or placebo treatment group. The nilvadipine capsules and placebo capsules will be packaged and labelled identically. Randomisation will be at the level of the individual patient, using block randomisation with randomly varying block sizes and stratified by country site. Once the patient has been randomised, the online system will automatically recognise which treatment packs are located in each study pharmacy at the recruiting study site and will randomly select a pack in the appropriate trial arm to be dispensed to the patient. All study staff at all sites will be blinded to treatment allocation and will remain blind until the end of the trial.

The primary outcome measure is the change from baseline to week 78 in cognitive function, as assessed by the ADAS-Cog 12.





Performance bias: *basso rischio*

Detection bias: *basso rischio*

Esempio 2

PROCEDURES

After providing written informed consent, all trial participants were randomly assigned to receive one of two doses of dabigatran, or to receive warfarin, by means of a central, interactive, automated telephone system. Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered, in an unblinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an international normalized ratio (INR) of 2.0 to 3.0, with the INR measured at least monthly. The time that the INR was with-

.....

group and were centrally blinded. Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments.

Performance bias: *alto rischio*

Detection bias: *basso rischio*

Esempio 3

Study medications were prepared by a research pharmacist, who had no direct contact with participants. Buprenorphine mono tablets (containing only buprenorphine) and placebo tablets that appeared identical were provided by the manufacturer. Naltrexone was purchased for the study: tablets were crushed, and the study pharmacist placed naltrexone or placebo inside capsules that appeared identical. To mask slight taste differences between active and placebo buprenorphine tablets, participants gargled with a mentholated antiseptic mouthwash before taking the sublingual tablets (Schottenfeld 2008)

Performance bias: basso rischio

Detection bias: basso rischio

Attrition bias

- Quando non tutti i soggetti randomizzati completano lo studio
- i soggetti non escono a caso dallo studio: è possibile che quelli che escono siano sistematicamente diversi da quelli che non escono: i gruppi non sono più randomizzati
- **Validità esterna** : es: escono tutti i più giovani, o i meno gravi, o i maschi: posso trarre conclusioni solo su quelli che rimangono
- **Validità interna (Bias):** se la probabilità di uscire dallo studio è legata all'intervento o all'outcome, cioè se quelli che escono hanno sistematicamente probabilità più alte o più basse di avere l'outcome di quelli che restano

Attrition bias

Low risk of bias

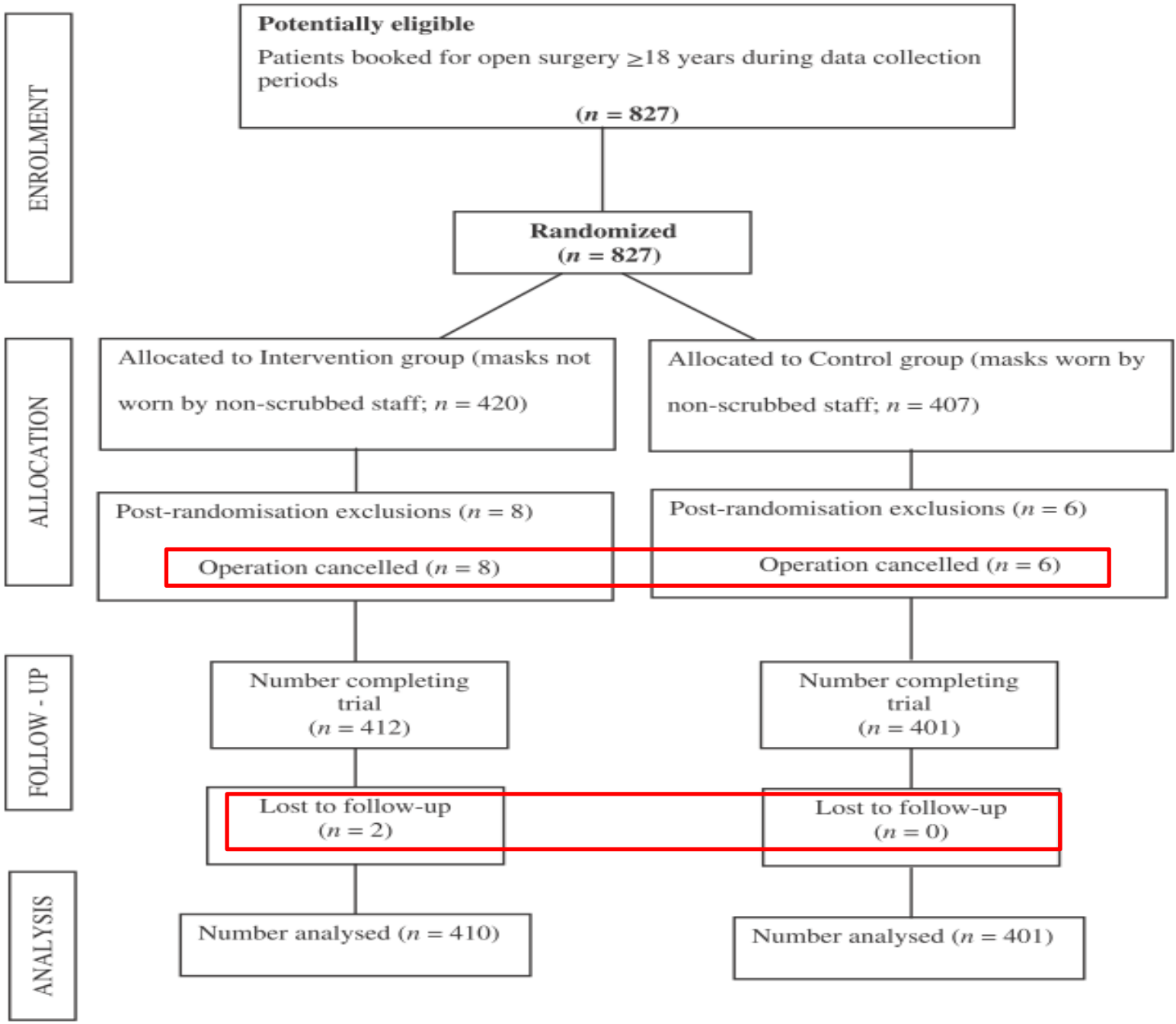
- No missing outcome data;
- the proportion of missing outcomes compared with observed event risk not enough to have a relevant impact on the intervention effect;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons across groups;
- Missing data imputed using appropriate methods
- All patients analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)

High risk of bias:

- the proportion of missing outcomes compared with observed event risk enough to induce relevant bias in intervention effect estimate
- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;

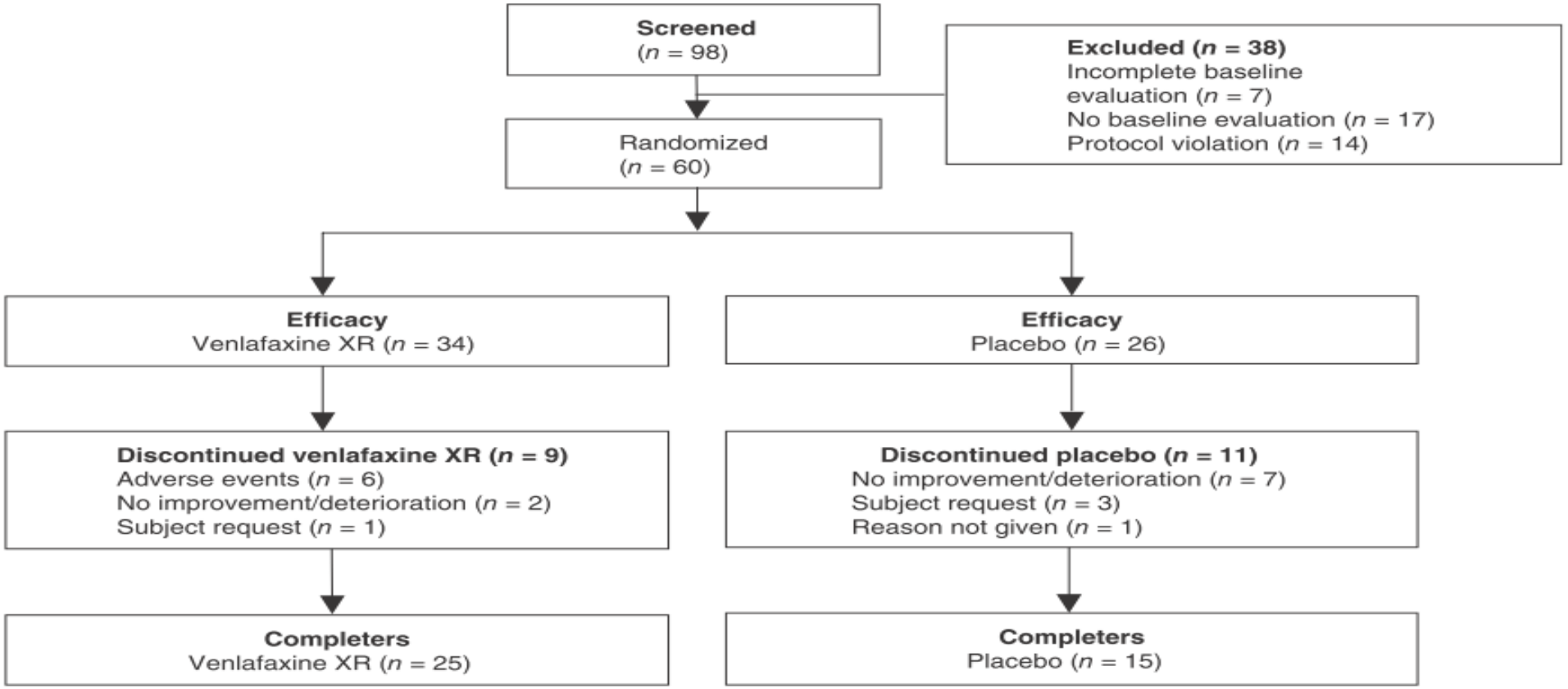
Esempio 1

A tota
enrolled and 811 (98.1%) patients complete
group and 410 No Mask group (Fig. 1).



Attrition bias:
basso rischio

Esempio 2



Totale:
33%
(20 su 60)

Intervento: 26%
(9 su 34)

Placebo: 42%
(11 su 26)

Attrition bias: *alto rischio*

Esempio 3

L’informazione nella sezione risultati

A total of 1395 (91.3%) randomized patients completed the doubleblind treatment phase. There were no patterns or trends suggesting any differences in discontinuation rates or the reasons for discontinuation between the treatment groups (Figure 1). (Bays 2004)

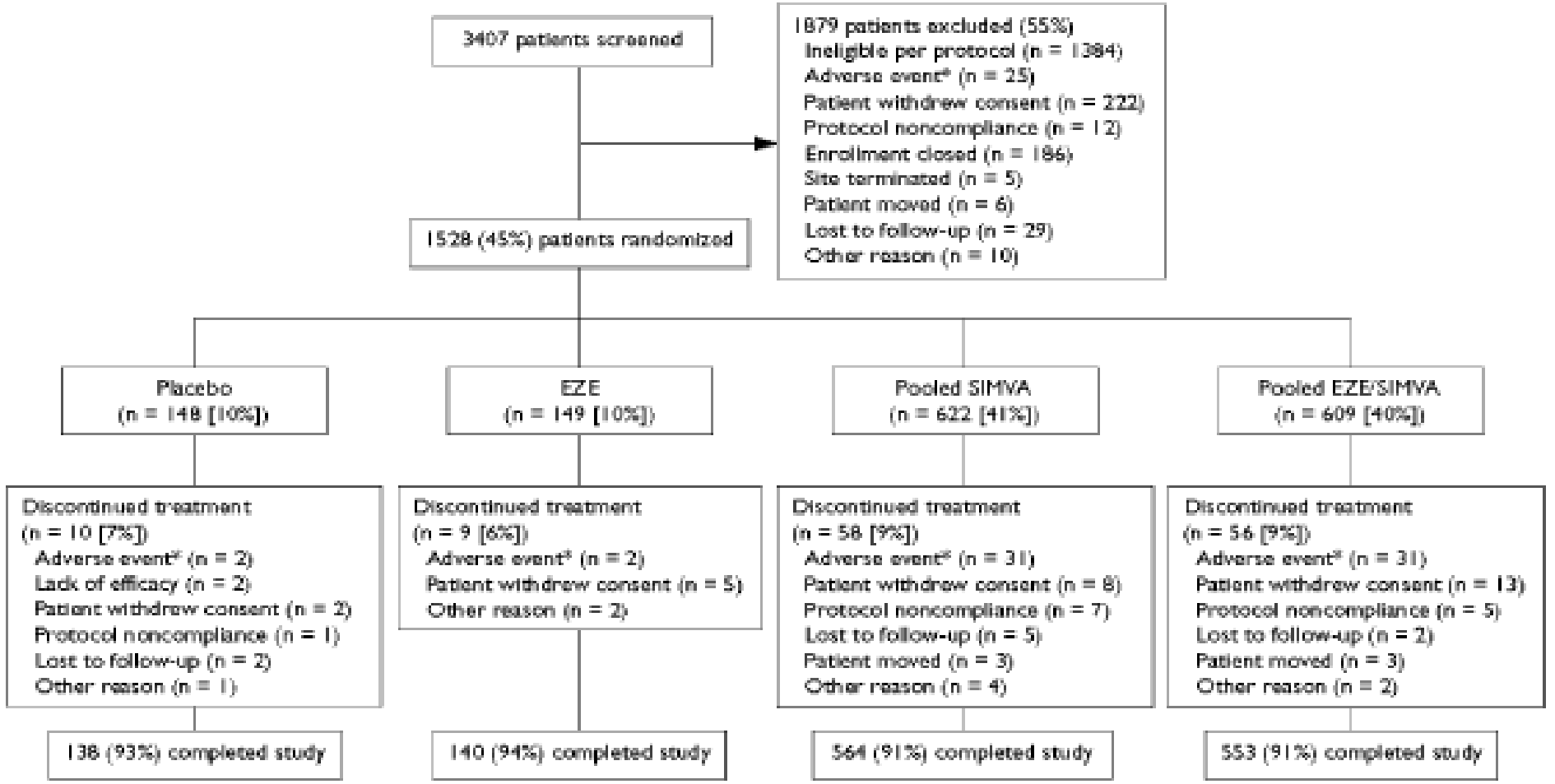


Figure 1. Disposition of patients in the study. Number of patients who were randomized, discontinued prematurely, and completed the study are shown for the placebo, ezetimibe monotherapy (EZE), pooled simvastatin monotherapy (pooled SIMVA), and pooled ezetimibe/simvastatin tablet (pooled EZE/SIMVA) groups. *Number of patients with clinical and laboratory adverse events.

Attrition bias: *basso rischio*

Reporting bias is selection bias

- Reporting bias is perhaps the greatest source of selection bias
- Originally defined as the publication or non-publication of studies depending on the direction and statistical significance of the results
- Is a complex phenomenon

Full — n and effect size, plus precision / *p*-value for continuous data

Partial — Effect size or precision (± n or *p*-value)

Qualitative — *p*-value

Unreported

Incompletely reported outcomes

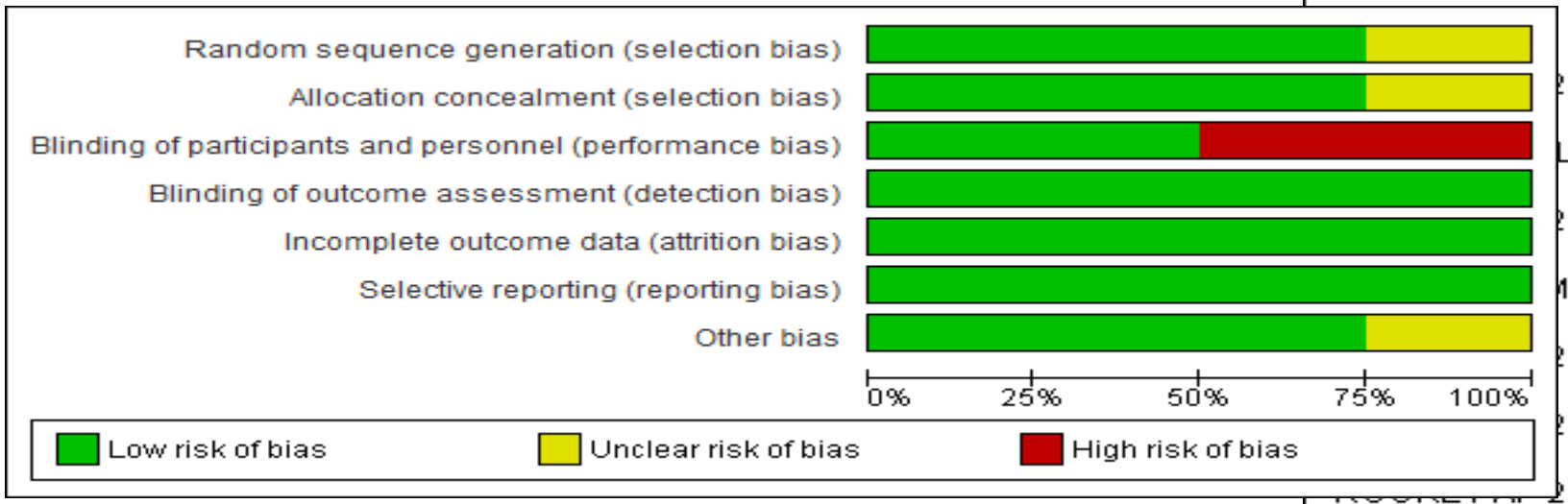
(Chan, 2004)

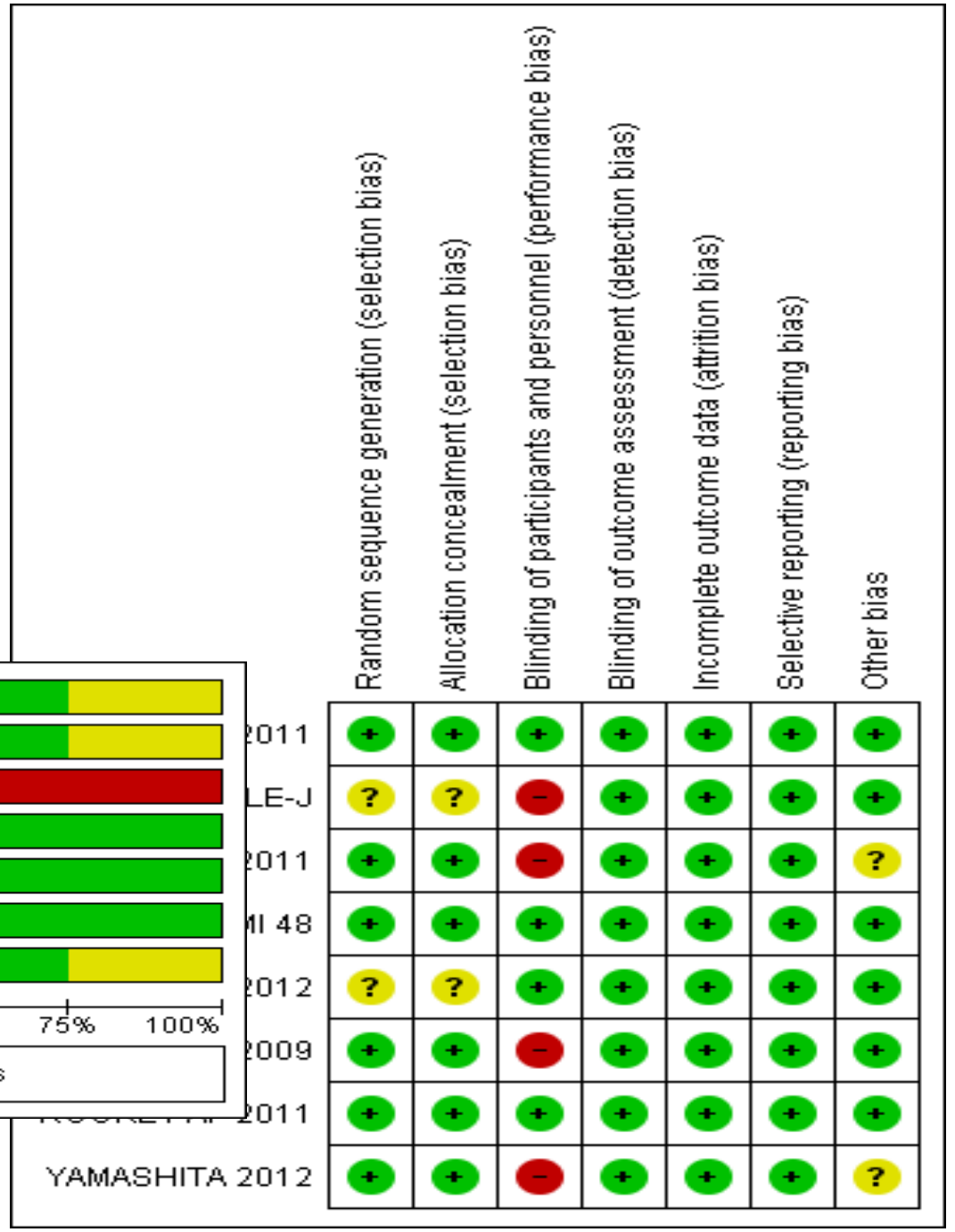
Risk of bias in one study

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias)	High risk	open label
Blinding of outcome assessment (detection bias)	Low risk	An independent blinded endpoint committee adjudicated all reported bleeding and efficacy events
Incomplete outcome data (attrition bias)	Low risk	ITT. all patients followed up
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Risk of bias across studies/domains





Dal Risk of bias al GRADE

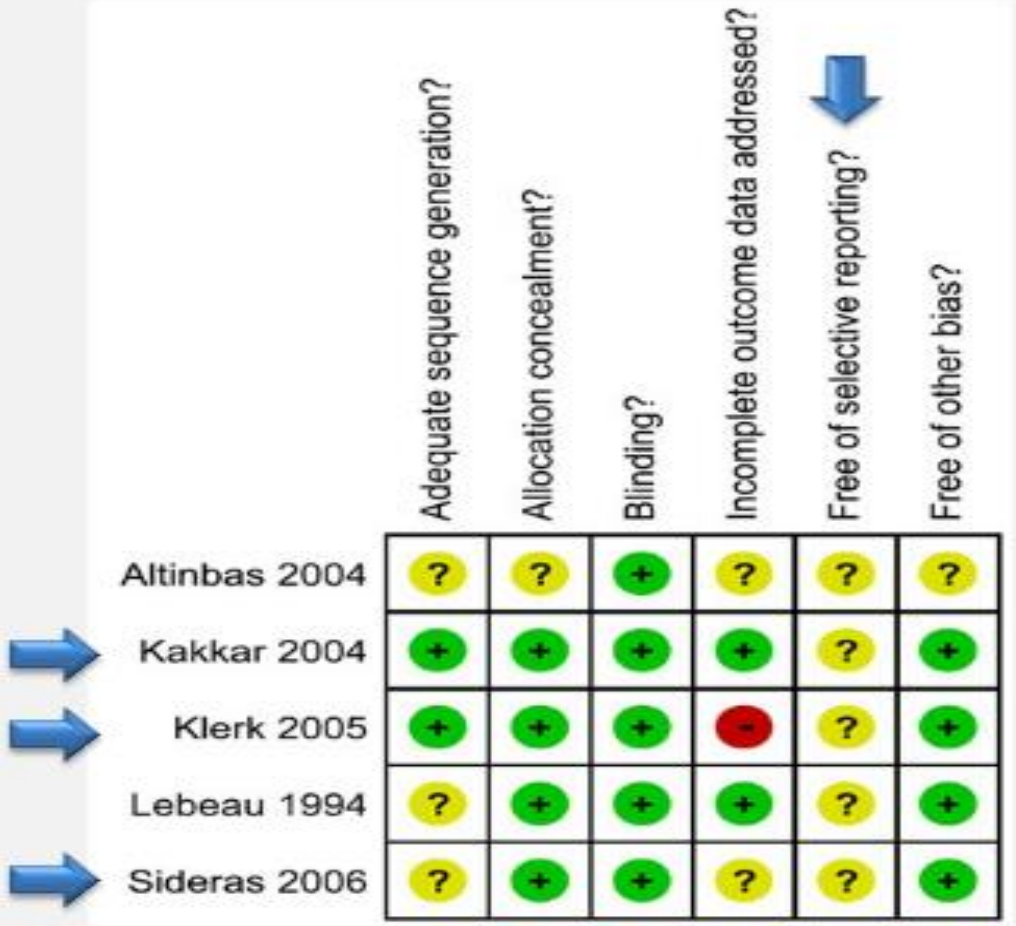
- La fiducia nelle prove complessiva, riferita ad un **singolo outcome**, può essere abbassata se si ritiene che esista un **importante rischio di bias** negli studi che contribuiscono a quelle evidenze

- Fiducia (certainty) minore nell'affidabilità dei risultati

- **APPROCCIO GRADE**
  - Se non si sospettano bias importanti, non si abbassa «not serious» (no change in quality)
  - Se si sospettano bias importanti, si abbassa di 1 livello «serious» (downgrade quality of evidence 1 level)
  - Se si sospettano bias molto importanti, si abbassa di 2 livelli «very serious» (downgrade quality of evidence 2 level)

Example: Major Bleeding with anticoagulation

Population: *people with cancer*
Intervention: *anti-coagulants, such as heparin*
Outcome: *major bleeding*



Alkl et al, CDSR 2008

Concern maggiore su selective reporting of outcome
Solo tre studi riportano l'outcome major bleeding

!!! Do not count number of green, yellow, red spots!!!

Would you downgrade for risk of bias?

☐ No, there are no serious limitations

☒ Yes, there are serious limitations

Most people would agree that selective reporting of outcome is concern

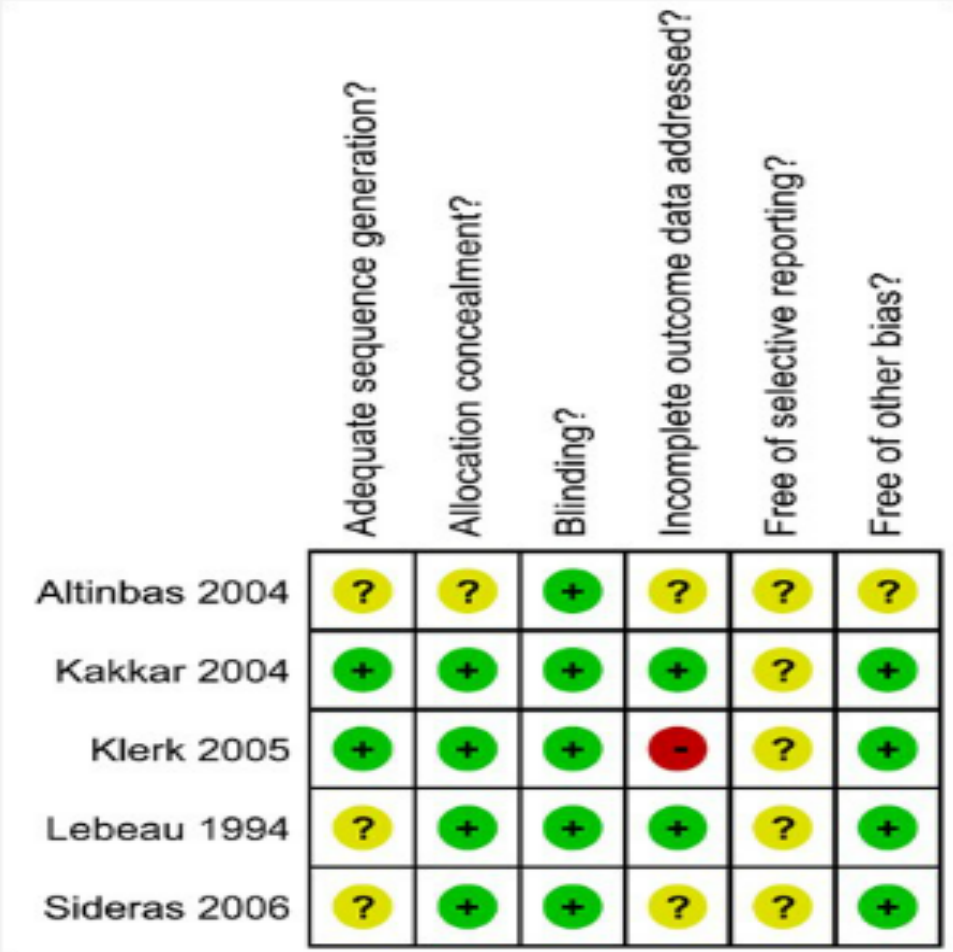
☐ Yes, there are very serious limitations

Example: Major Bleeding with anticoagulation

Population: *people with cancer*
Intervention: *anti-coagulants, such as heparin*
Outcome: *major bleeding*

Limitations likely to reduce confidence in effect
Downgrade 1 level

Footnotes
[1] Only 3 of 5 studies reported major bleeding, selective reporting likely



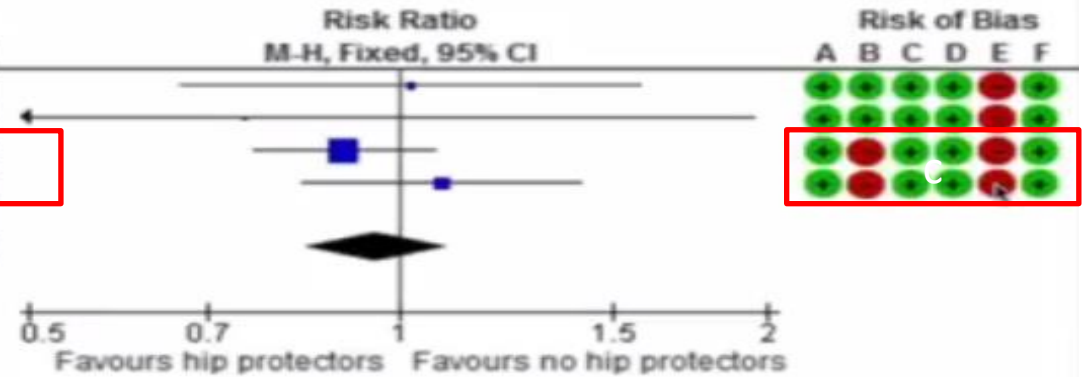
Alkl et al, CDSR 2008

Mortality (dichotomous outcome)

Mortality

Study or Subgroup	Hip protectors Events	Total	No hip protectors Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cameron 2001	28	86	28	88	9.5%	1.02 [0.66, 1.58]
Jantti 1996	6	36	8	36	2.7%	0.75 [0.29, 1.94]
Meyer 2003	157	459	183	483	61.1%	0.90 [0.76, 1.07]
Van Schoor 2003	83	276	79	285	26.6%	1.08 [0.84, 1.41]
Total (95% CI)		**857**		**892**	**100.0%**	**0.96 [0.84, 1.10]**
Total events	274		298			

Heterogeneity: Chi² = 1.69, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)



A: random sequence generation
B: allocation concealment
C: Blinding of participants and personnel
D: Blinding of outcome assessor
E: Incomplete outcome data
F: selective outcome reporting

Would you downgrade for risk of bias?

☐ No, there are no serious limitations

☒ Yes, there are serious limitations

Some concerns with allocation concealment and high losses to follow up

☐ Yes, there are very serious limitations

Dal Risk of bias al GRADE

- Non fare medie, non contare i domini a rischio o quelli adeguati
- Tutto si basa su giudizi, spesso soggettivi
- Calarsi nel contesto clinico e metodologico
- Trasparenza nelle decisioni (soprattutto nelle situazioni intermedie)
- Focus sugli studi a basso rischio di bias
- Focus sugli studi che portano un maggiore contributo informativo (peso nella meta-analisi)
- Siate conservativi
- Rischio di bias nel contesto delle altre dimensioni della qualità

SCUOLA DI METODOLOGIA
DELLA RICERCA CLINICA

2024 - 10ª EDIZIONE

MODULI SPECIALISTICI - S2

VENERDÌ 12 - SABATO 13 APRILE 2024

NEGRAR DI VALPOLICELLA (VR)

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

GRADE

La valutazione della qualità delle prove (2): *imprecision*

(Michela Cinquini)

GRADE re-clarification of the construct of certainty of evidence

Journal of Clinical Epidemiology 87 (2017) 4–13

Journal of Clinical Epidemiology

GRADE UPDATE OF PAPERS

The GRADE Working Group clarifies the construct of certainty of evidence

Monica Hultcrantz[a,b,*], David Rind[c,d], Elie A. Akl[e,f], Shaun Treweek[g], Reem A. Mustafa[e,h], Alfonso Iorio[e,i], Brian S. Alper[j,k], Joerg J. Meerpohl[l,m], M Hassan Murad[n], Mohammed T. Ansari[o], Srinivasa Vittal Katikireddi[p], Pernilla Östlund[a,q], Sofia Tranæus[a,q,r], Robin Christensen[s], Gerald Gartlehner[t,u], Jan Brozek[e,i], Ariel Izcovich[v], Holger Schünemann[e,i], Gordon Guyatt[e,i]

Journal of Clinical Epidemiology 137 (2021) 163–175

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings

Linan Zeng[a,b,*], Romina Brignardello-Petersen[b], Monica Hultcrantz[c], Reed A.C. Siemieniuk[b], Nancy Santesso[b], Gregory Traversy[d], Ariel Izcovich[e], Behnam Sadeghirad[b,f], Paul E. Alexander[b], Tahira Devji[b], Bram Rochwerg[b,g], Mohammad H. Murad[h], Rebecca Morgan[b], Robin Christensen[i,j], Holger J. Schünemann[b,g], Gordon H. Guyatt[b,g]

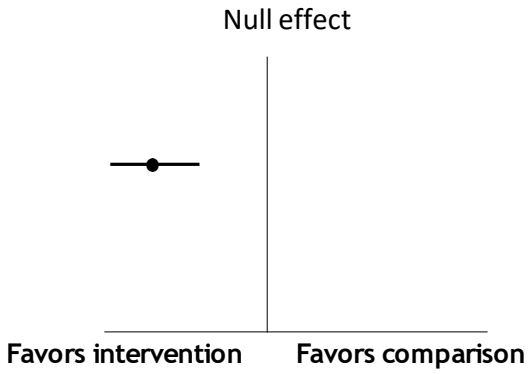
In either guidelines or systematic reviews, when we rate the certainty of evidence, we are assessing our confidence where the point effects lies relative to particular threshold(s) of interest.

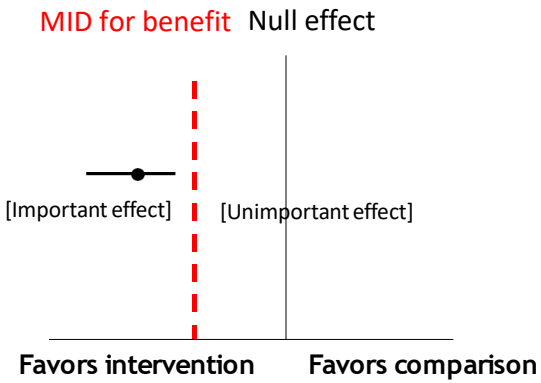
Additional insights regarding imprecision rating

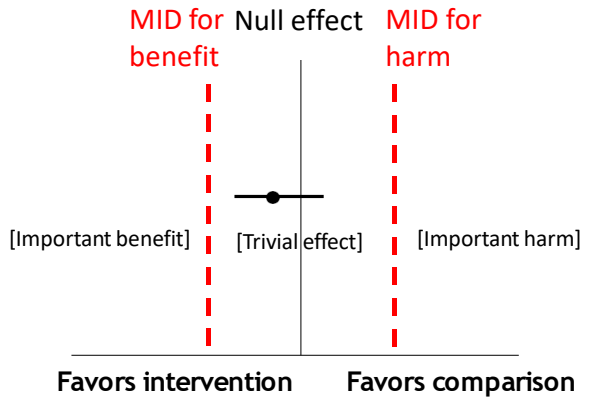
1) In systematic reviews, we are much more likely to use the approach that relies on thresholds and CIs (hereafter that “CI approach”) than optimal information size (OIS) to judge imprecision.
2) We should consider rating down more than one level when the CI appreciably crosses the threshold(s) of interest.

Threshold of interest, target of certainty of evidence rating in minimally contextualized approach

Threshold of interest	(a) Null effect	(b) Minimally important difference (MID)	(c) Range of trivial or no effect
Target of certainty rating	An effect is truly present or not.	An important effect is truly present or not.	A trivial or no effect is truly present or not.







Example 1

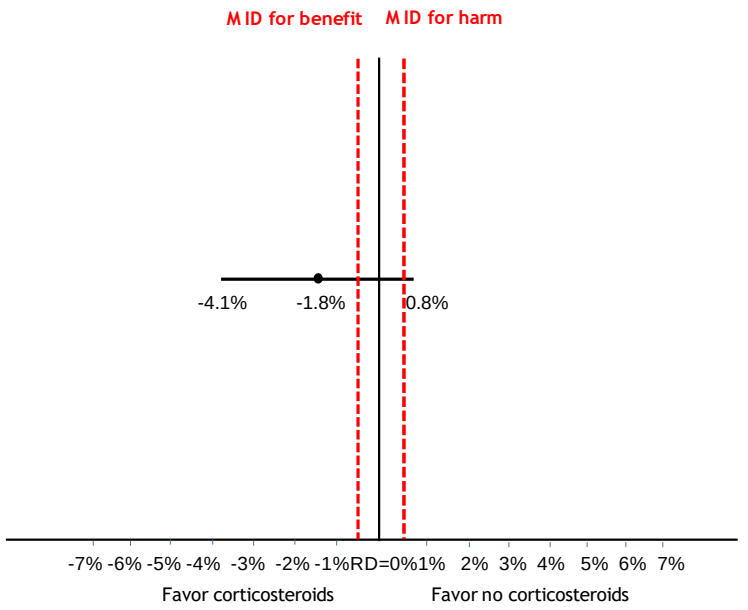
P: patients with sepsis
I/C: corticosteroids versus no corticosteroids
O: death (short- term)

Threshold of interest:
MID for benefit at a reduction of 0.5%

Target of certainty rating:
Corticosteroids have an important reduction in death.

Imprecision judgment:
As the CI includes important harm (i.e. an important increase in death), the authors should likely consider rating down two levels for imprecision.

Plain language summary:
Corticosteroids "probably" have an important benefit (Rating down one)
Corticosteroids "may" have an important benefit (Rating down two)



Circumstances when one should consider rating down two levels for imprecision based on CI approach

1) When rating the certainty that there is a true important benefit, the point estimate reflects **an important benefit**, and the boundary of the CI least favorable to the intervention includes the possibility of harm, particularly **important harm**. (Example 1)

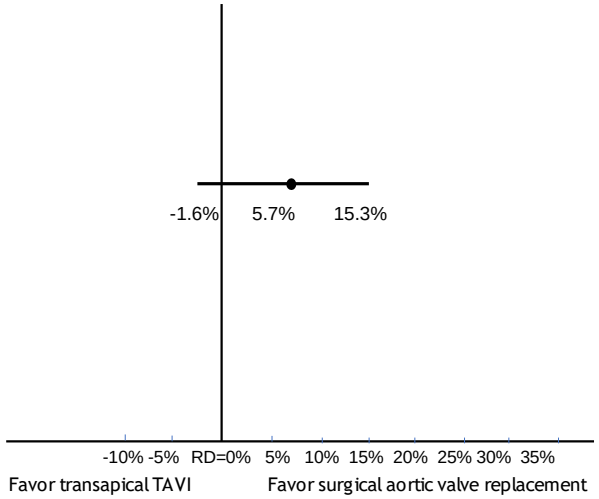
Example 2

P: patients with severe aortic stenosis at low and intermediate risk of intra- or perioperative death
I/C: transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement
O: death

Target of certainty rating:
Transapical TAVI has an important increase in death.

Imprecision judgment:
As the CI includes an important benefits, the authors should likely consider rating down two levels for imprecision.

Plain language summary:
Transapical TAVI "may" have an important harm.



Circumstances when one should consider rating down two levels for imprecision based on CI approach

2) When rating the certainty that there is a true important harm, the point estimate reflects **an important harm**, and the boundary of the CI most favorable to the intervention includes benefit, particularly **important benefit**. (Example 2)

Example 3

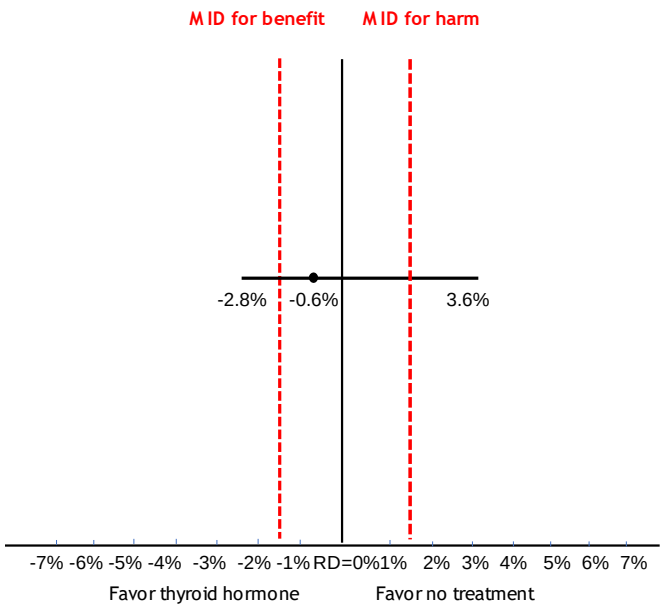
P: patients with subclinical hypothyroidism
I/C: thyroid hormone versus no treatment
O: cardiovascular events

Threshold of interest:
MID for benefit at a reduction of 1.5%

Target of certainty rating:
Thyroid hormone has a trivial or no effect on cardiovascular events.

Imprecision judgment:
As the CI includes both important benefits and important harm, the authors should likely consider rating down two levels for imprecision.

Plain language summary:
Thyroid hormone "may" have trivial or no effect on benefit and harm.



Circumstances when one should consider rating down two levels for imprecision based on CI approach

3) When rating the certainty that the true effect is trivial or no benefit or harm, the point estimate is consistent with **a trivial effect** and the CI includes both **important benefit and important harm**. (Example 3)

Example 4

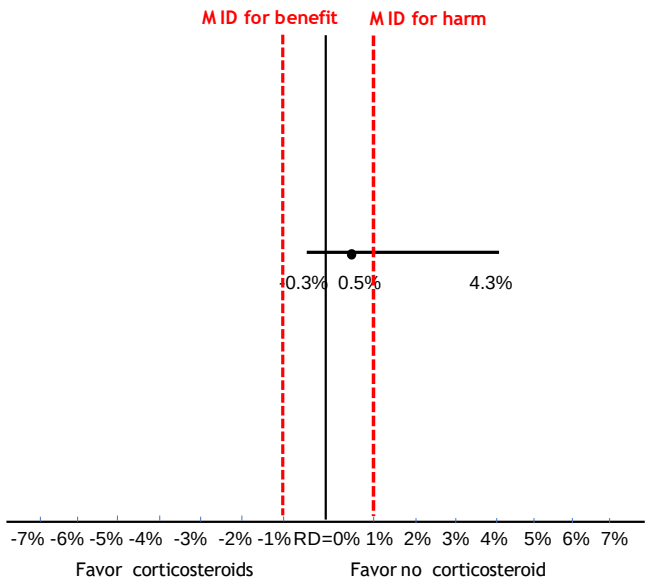
P: patients with sepsis
I/C: corticosteroids versus no corticosteroids
O: strokes

Threshold of interest:
MID for benefit at a reduction of 1.0%

Target of certainty rating:
Corticosteroids have trivial or no effect on stroke.

Imprecision judgment:
As the CI includes an important harm, the more important of the outcome/ the larger the magnitude of effect, the more likely the authors would rating down two levels for imprecision.

Plain language summary:
Corticosteroids "may" have trivial or no effect on benefit



Circumstances when one should consider rating down two levels for imprecision based on CI approach

4) When rating the certainty that the true effect is trivial or no benefit or harm, the point estimate is consistent with **a trivial effect**, and the CI includes substantial (possibly large) **important harm**. (Example 4)

Example 5

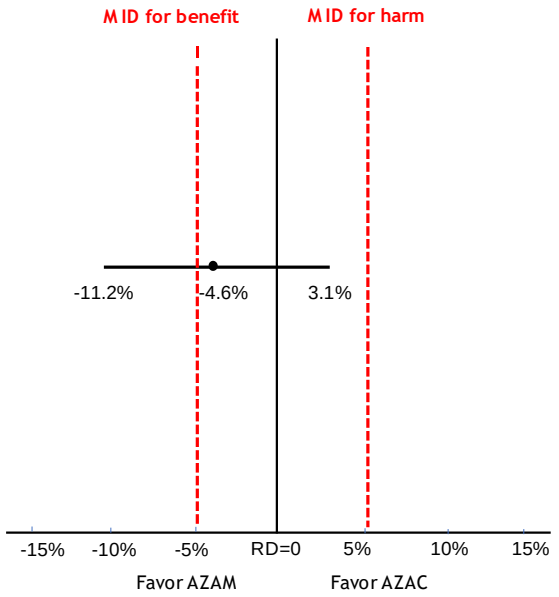
P: patients with acute myeloid leukemia (AML)
I/C: azacitidine monotherapy (AZAM) versus azacytidine combination (AZAC)
O: thrombocytopenia

Threshold of interest:
MID for benefit at a reduction of 5%

Target of certainty rating:
AZAM has a trivial or no effect on thrombocytopenia.

Imprecision judgment:
As the CI includes important benefit, the more important of the outcome/the larger the magnitude of effect, the more likely authors would rate down two for imprecision.

Plain language summary:
Corticosteroids "may" have trivial or no effect on benefit (Rating down two)



Circumstances when one should consider rating down two levels for imprecision based on CI approach

5) When rating the certainty that the true effect is a trivial or no benefit or harm, the point estimate is consistent with a **trivial effect**, and the CI includes substantial (possibly large) **important benefit**. (Example 5)

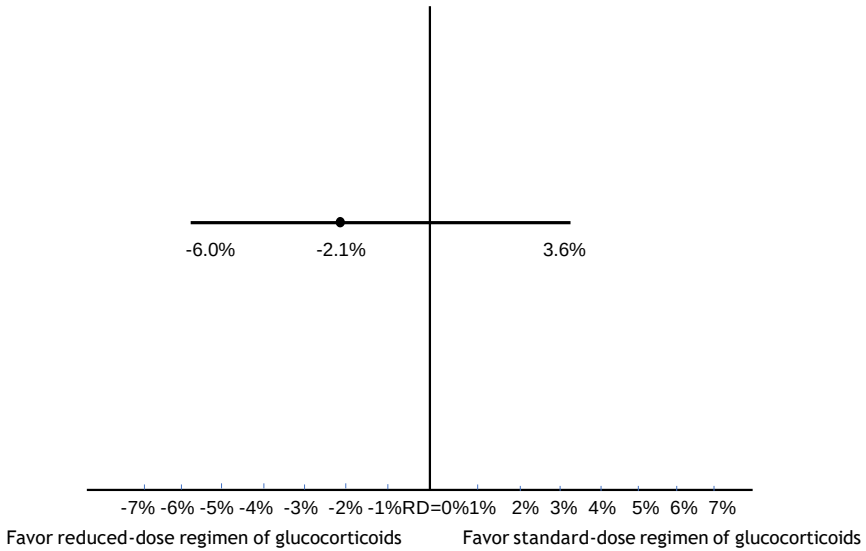
Example 6

P: patients with vasculitis
I/C: reduced-dose regimen of glucocorticoids versus standard-dose regimen of glucocorticoids
O: mortality

Target of certainty rating:
The reduced-dose regimen of glucocorticoids reduces mortality.

Imprecision judgment:
Although the point estimate suggests a benefit, an important harm remains plausible.

Plain language summary:
The reduced-dose regimen of glucocorticoids "may" have a benefit in reducing mortality.



Circumstances when one should consider rating down two levels for imprecision based on CI approach

6) When rating the certainty of non-zero benefit, the point estimate suggests **benefit**, and the CI includes **important harm**. (Example 6)

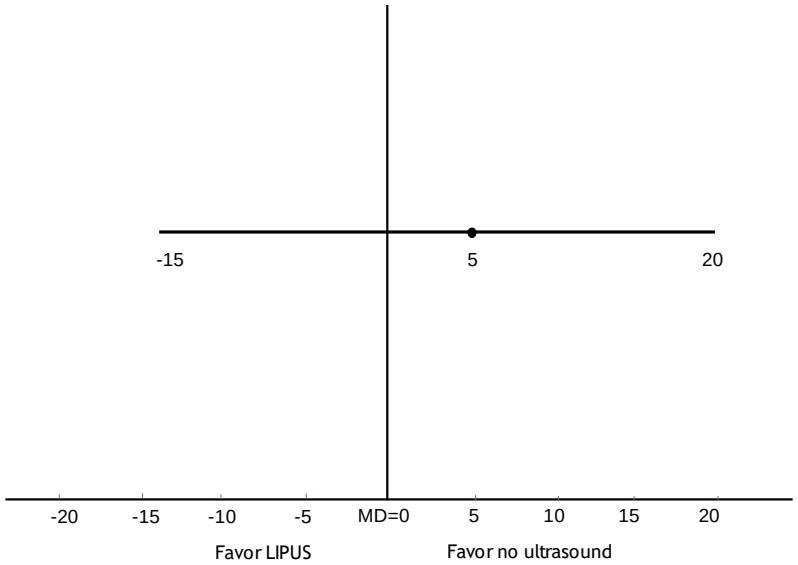
Example 7

P: patients with any type of fracture
I/C: low intensity pulsed ultrasound (LIPUS) versus no ultrasound
O: return back to work

Target of certainty rating:
LIPUS increases the days off required before returning to work.

Imprecision judgment:
CI includes an important benefit.

Plain language summary:
LIPUS "may" increases the days off required before returning to work.



Circumstances when one should consider rating down two levels for imprecision based on CI approach

7) When rating the certainty of non-zero harm, the point estimate suggests **harm**, and the CI includes **important benefit**. (Example 7)

Circumstances when one should consider rating down two levels for imprecision based on CI approach

1)When rating the certainty that there is a true important benefit, the point estimate reflects an important benefit, and the boundary of the CI least favorable to the intervention includes the possibility of harm, particularly important harm. (Example 1)

2)When rating the certainty that there is a true important harm, the point estimate reflects an important harm, and the boundary of the CI most favorable to the intervention includes the possibility of benefit, particularly important benefit. (Example 2)

3)When rating the certainty that the true effect is trivial or no benefit or harm, the point estimate is consistent with a trivial effect and the CI includes the possibility of both important benefit and important harm. (Example 3)

4)When rating the certainty that the true effect is trivial or no benefit or harm, the point estimate is consistent with a trivial effect, and the CI includes the possibility of substantial (possibly large) important harm. (Example 4)

5)When rating the certainty that the true effect is trivial or no benefit or harm, the point estimate is consistent with a trivial effect, and the CI includes the possibility of substantial (possibly large) important benefit. (Example 5)

6)When rating the certainty of non-zero benefit, the point estimate suggests benefit, and the CI includes the possibility of important harm. (Example 6)

7) When rating the certainty of non-zero harm, the point estimate suggests harm, and the CI includes the possibility of important benefit. (Example 7)

When one should check optimal information size (OIS)

- When the CI does not cross threshold(s) of interest and the effect is large (RRR over 30%) and implausible, GRADE suggests considering whether the OIS is met

- When GRADE suggests rating down two levels for imprecision based on OIS calculation ?

- Note: OIS approach focuses on the relative estimate of effect.

Circumstances when one should consider rating down two levels for imprecision based on OIS calculation

1) For dichotomous outcomes, when the ratio of the upper to the lower boundary of the CI is more than 2.5 for odds ratio (odds ratio, OR) or 3 for risk ratio (risk ratio, RR).

ELSEVIER

Journal of Clinical Epidemiology
Volume 139, November 2021, Pages 49-56

Original article

GRADE guidelines 33: Addressing imprecision in a network meta-analysis

Romina Brignardello-Petersen [a], Gordon H. Guyatt [a], Reem A. Mustafa [a, b], Derek K. Chu [a], Monica Hultcrantz [c], Holger J. Schünemann [a, d], George Tomlinson [e]

Example 8

P: patients with chronic suppurative otitis media (1 RCT, 40 patients)
I: topical antibiotics (15/20, 75%)
C: no treatment (8/20, 40%)
O: resolution of ear discharge

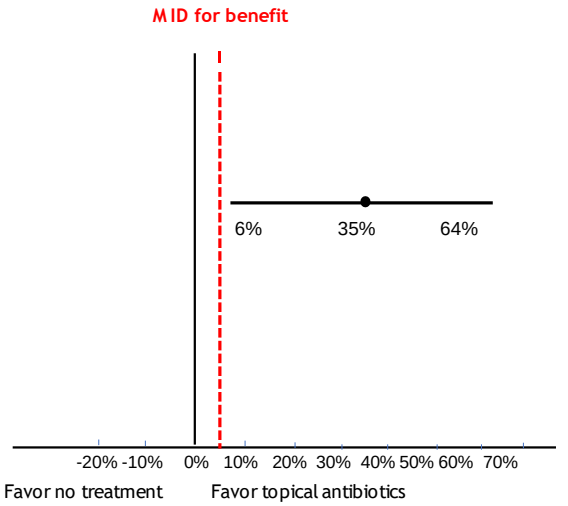
Relative effect: 88% increase (RR 1.88, 95% 1.04 to 3.39)

Threshold of interest:
MID for benefit at a reduction of 5%.

Target of certainty rating:
Topical antibiotics have an important benefit.

Ratio of the upper to the lower boundary of CI around RR:
3.26 (3.39/1.04) > 3

Imprecision judgement: rating down two levels



Circumstances when one should consider rating down two levels for imprecision based on OIS calculation

2) When total sample size of a meta-analysis is smaller than 30%-50% of OIS (i.e. smaller than 30%-50% of 800).

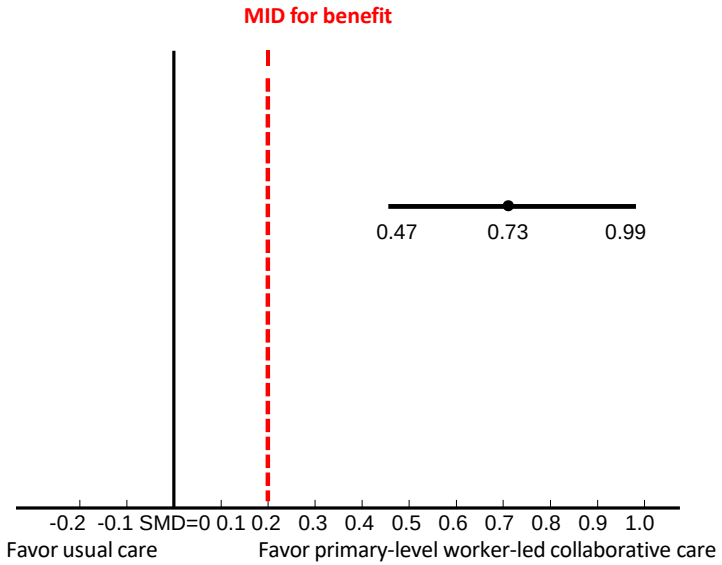
Example 9

P: people living with mental disorders and distress (2 RCTs, 249 patients)
I: primary-level worker interventions versus usual care
O: quality of life

Threshold of interest:
MID for benefit at a reduction of 0.2 standard deviations

Target of certainty rating:
Primary-level worker interventions had an important increase in the quality of life.

Check if OIS is met:
More conservative: Sample size < 50% of OIS (249 vs. 400)
Less conservative: Sample size > 30% of OIS (249 vs. 240)



Circumstances when one should consider rating down two levels for imprecision based on OIS calculation using a minimally contextualized approach

- For dichotomous outcomes, when the ratio of the upper to the lower boundary of the CI is more than 2.5 for odds ratio (odds ratio, OR) or 3 for risk ratio (risk ratio, RR). (Example 8)
- For continuous outcomes, when the total sample size of a meta-analysis is smaller than 30%-50% of the OIS. (Example 9)

An exception: when the baseline risk is low, GRADE suggests being more conservative in rating down for imprecision

- When the baseline risk is very low (rare event), any changes (even big change) in the relative estimates of effect would result in small changes in absolute estimates of effect.
- Focusing on the CI around absolute effect would lead one to reject rating down more than one level for imprecision.
- What a very low baseline risk is depends on the importance of outcome.

Example 10

P: patients with intermittent claudication (2 RCTs, 300 patients)
I: cilostazol (16/150, 10.6%)
C: placebo (7/150, 4.6%)
O: abnormal stools (adverse event)

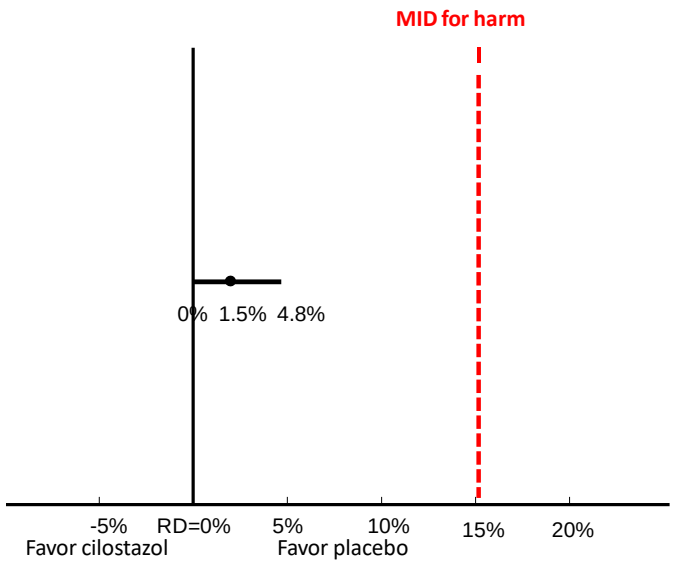
Relative effect: OR:2.44, 95% CI 0.97 to 6.11; RR 2.29, 95% CI 0.97 to 5.40

If baseline risk: 1%, RD: 1.5%, 95%CI 0% to 4.8%

Threshold of interest:
MID for harm at an increase of 15%

Target of certainty rating:
Cilostazol had a trivial effect on abnormal stools.

Ratio of the upper to the lower boundary of CI around OR:
6.3 (6.11/0.97) > 2.5



Simulations of estimated risk differences with the change of odds ratio at three different baseline risks

Cilostazol group		Control group		OR (95% CI)	RD when BS is 1% (95% CI)	RD when BS is 3% (95% CI)	RD when BS is 5% (95% CI)
No. of patients experiencing event	No. of patients not experiencing event	No. of patients experiencing event	No. of patients not experiencing event				
16	134	7	143	2.44 (0.97, 6.11)	1.5% (-0.026%, 4.8%)	4.0% (-0.078%, 1.3%)	6.3% (-0.12%, 19%)
16	134	6	144	2.87 (1.09, 7.53)	1.8% (0.088%, 6.1%)	5.1% (0.26%, 15%)	8.1% (0.42%, 23%)
16	134	5	145	3.46 (1.23, 9.71)	2.4% (0.23%, 7.9%)	6.7% (0.67%, 20%)	10% (1.1%, 28%)
16	134	4	146	4.36 (1.42, 13.36)	3.2% (0.41%, 10%)	8.9% (1.2%, 26%)	14% (1.9%, 36%)

BS: baseline risk; CI: confidence interval; RD: risk difference; OR: odds ratio

When GRADE suggests rating down three levels for imprecision

- Authors might consider rating down three levels for imprecision using a minimally contextualized approach.

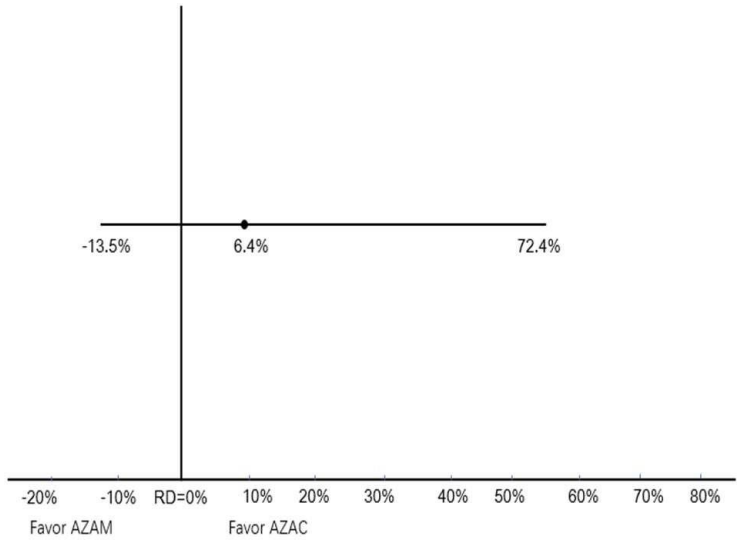
Example 11

P: patients with acute myeloid leukemia (AML)
I: azacitidine monotherapy (AZAM)
C: azacitidine combination (AZAC)
O: septic shock

Threshold of interest:
Null effect threshold (i.e. RD = 0%)

Imprecision: Rating down three levels

Target of certainty rating: no need to decide



Summary

- Inform systematic review and guideline authors who choose to use the CI approach to rating imprecision within a minimally contextualized framework.
- Emphasize the usefulness of the CI approach, reserving OIS calculation to situations of implausibly large treatment effects.
- Focus on the circumstances in which GRADE users will seriously consider rating down two levels for imprecision.

SCUOLA DI METODOLOGIA
DELLA RICERCA CLINICA

2024 - 10ª EDIZIONE

MODULI SPECIALISTICI - S2

VENERDÌ 12 - SABATO 13 APRILE 2024

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Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

GRADE

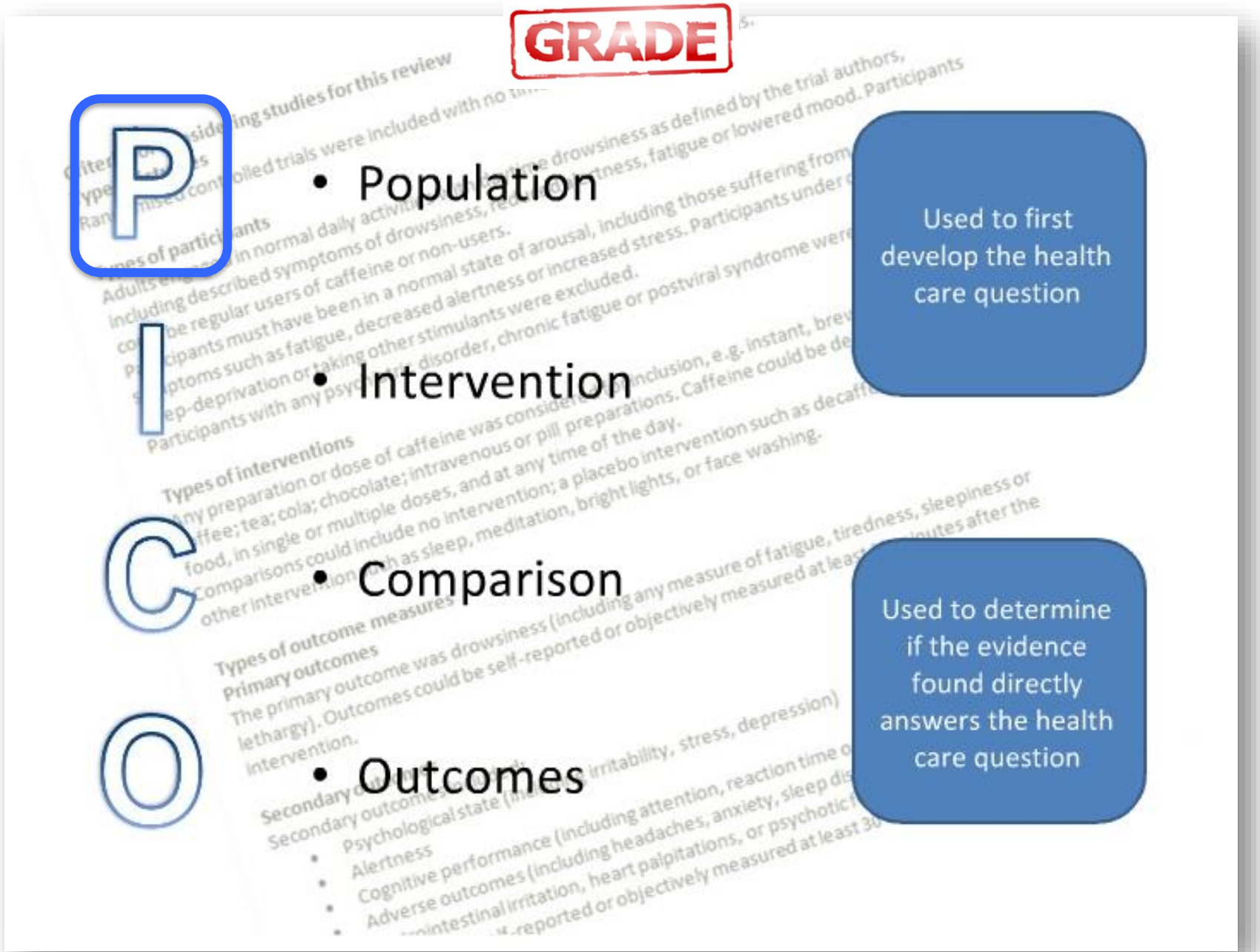
La valutazione della qualità delle prove (3): *indirectness*

(Giovanni Pappagallo)

Direct evidence…

…comes from research that:

- is conducted in the **Population** that we are providing answers for;
- includes the **Intervention** that we are interested in…
- …and compares these interventions with the appropriate **Alternatives**;
- measures the **Outcomes** in which we are interested

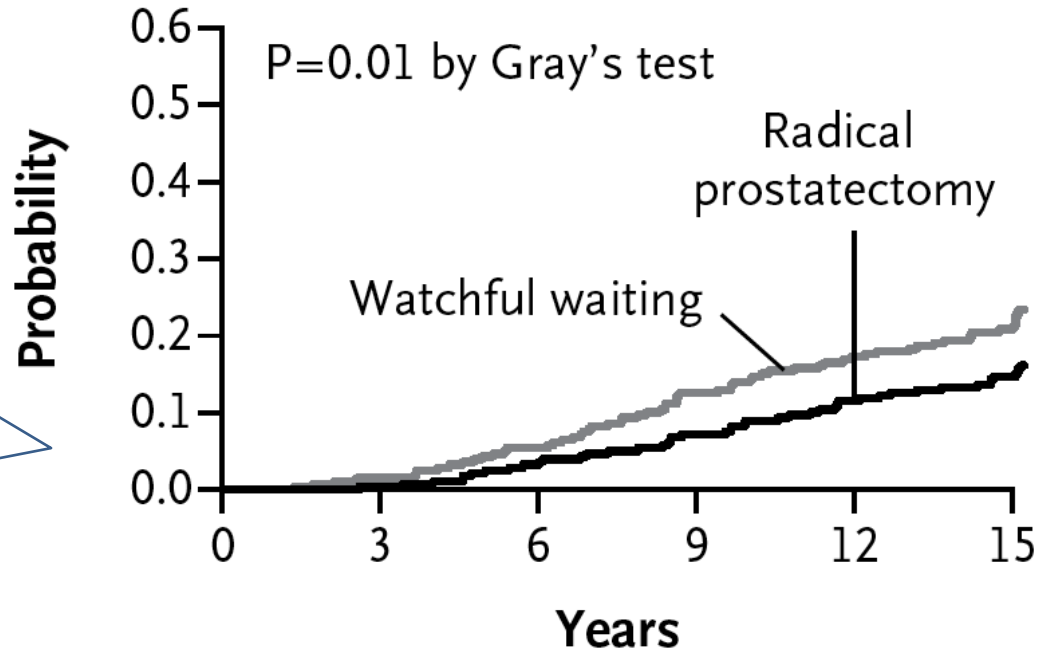

GRADE
P
• Population
I
• Intervention
C
• Comparison
O
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

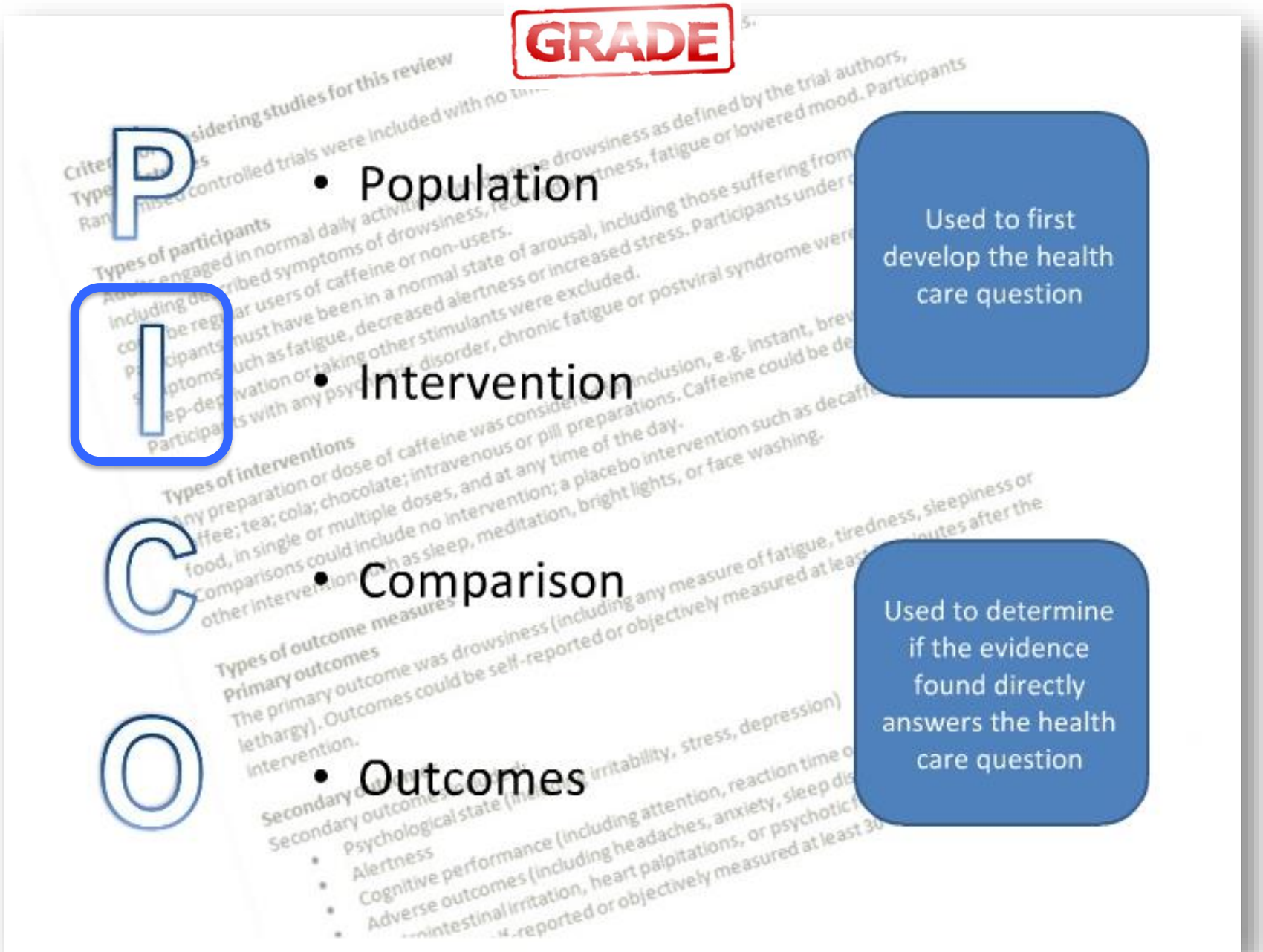
Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Mirja Ruutu, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Stark, Sc.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D., for the SPCG-4 Investigators*

N Engl J Med 2011;364:1708-17.

Pazienti in era pre-PSA

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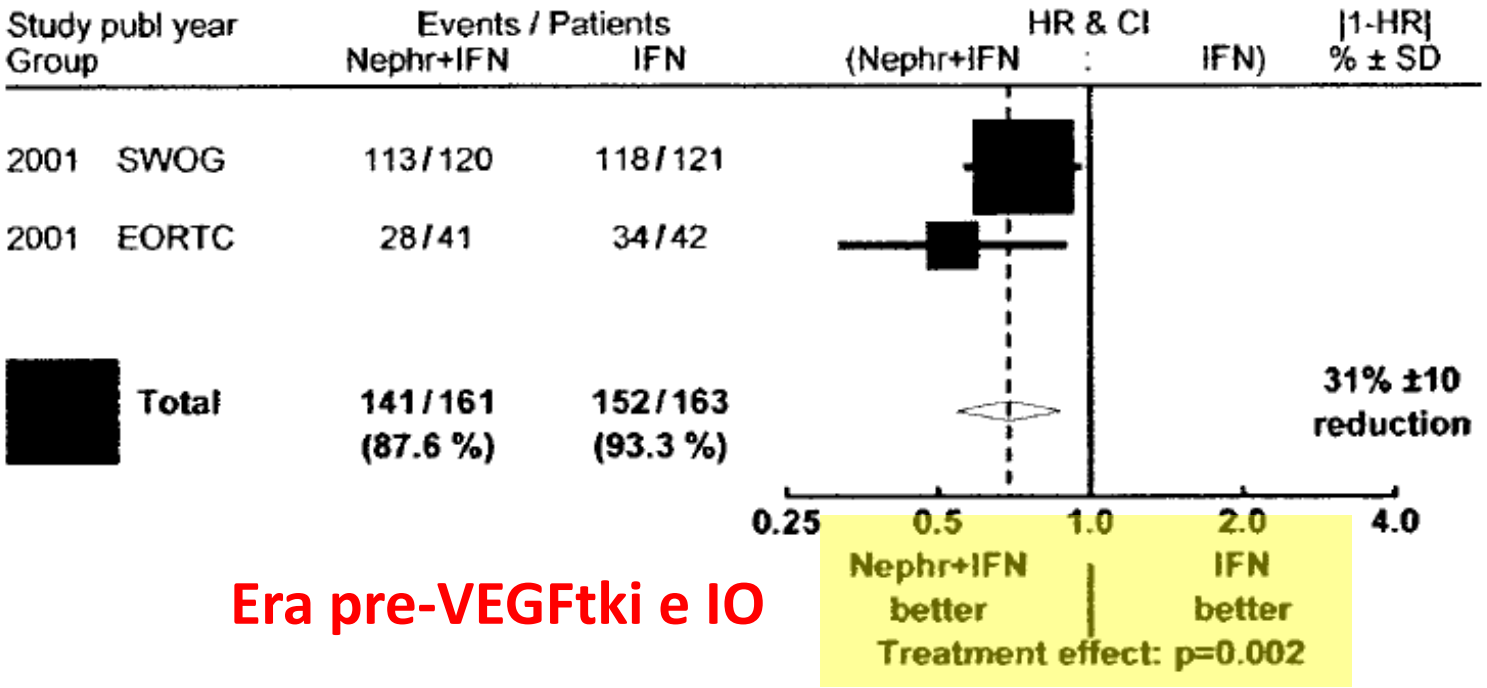
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

CYTOREDUCTIVE NEPHRECTOMY IN PATIENTS WITH METASTATIC RENAL CANCER: A COMBINED ANALYSIS

ROBERT C. FLANIGAN,* G. MICKISCH, RICHARD SYLVESTER, CATHY TANGEN,†
H. VAN POPPEL AND E. DAVID CRAWFORD

From the Southwest Oncology Group and European Organization for the Research and Treatment of Cancer Genitourinary Group, Loyola University Medical Center (RCF), Maywood, Illinois, Centrum Fuer Operative Urologie (GM), Bremen, Germany, European Organization for the Research and Treatment of Cancer Data Center (RS), Brussels and UZ Gasthuisberg (HVP), Leuven, Belgium, Southwest Oncology Group Statistical Center (CT), Seattle, Washington, and University of Colorado Medical Center (EDC), Denver, Colorado

THE JOURNAL OF UROLOGY® Vol. 171, 1071–1076, March 2004



Era pre-VEGFtki e IO

Long-term oncologic outcomes of postoperative adjuvant versus salvage radiotherapy in prostate cancer: Systemic review and meta-analysis of 5-year and 10-year follow-up data

Ja Yoon Ku[1], Chan Ho Lee[1], Hong Koo Ha[1,2]

Korean J Urol 2015;56:735-741.

The present systemic review has the following limitations that must be taken into account.

The first limitation is that we heterogeneously recruit randomized controlled studies and retrospective studies: in retrospective studies, the initiation timing of radiotherapy is somewhat different in each study.

The second limitation is that there is a difference in dose and modality (2-dimensional, 3-dimensional, or intensity modulated radiation therapy) of radiation compared to recent practice, which may alter oncologic outcomes.

The third limitation

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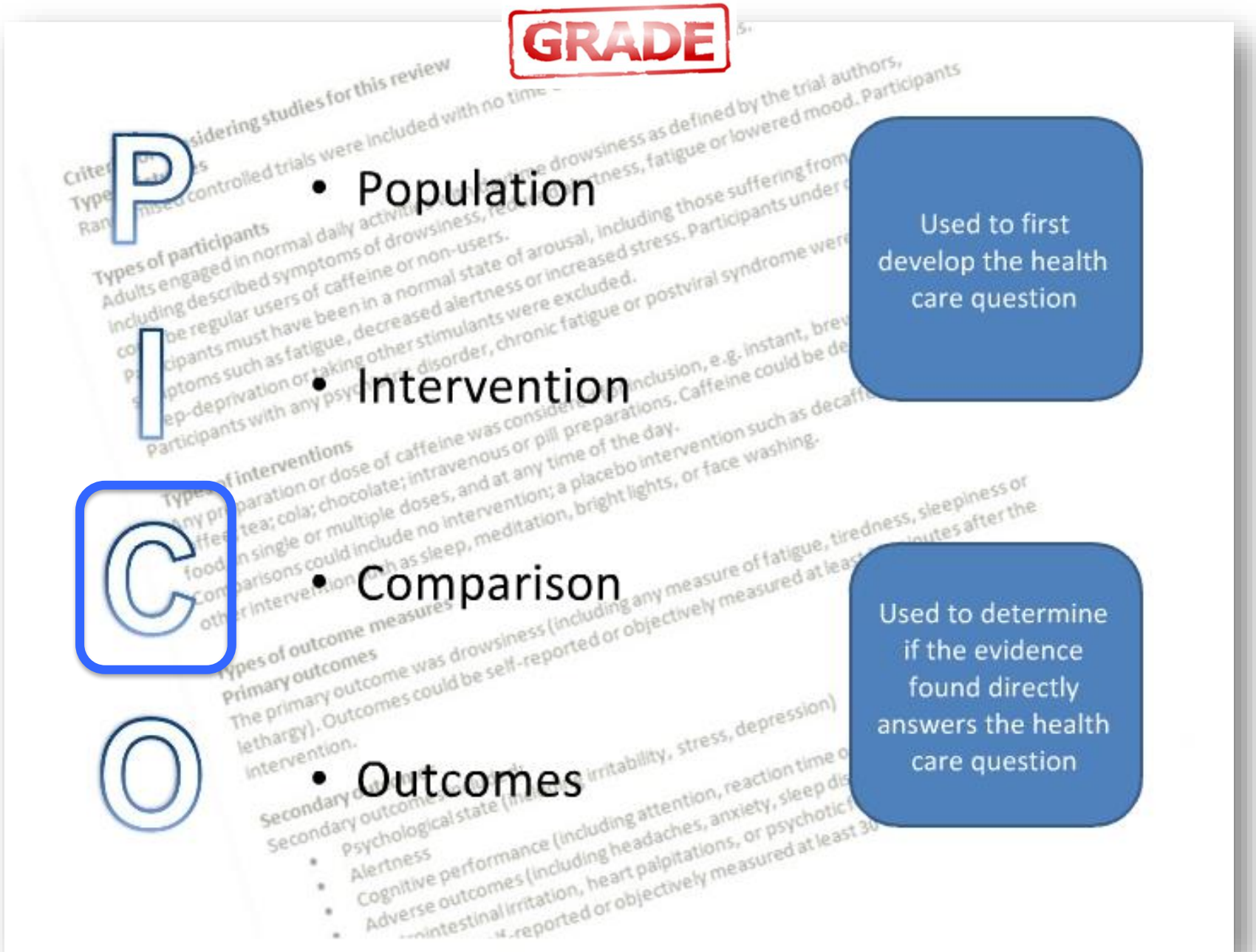
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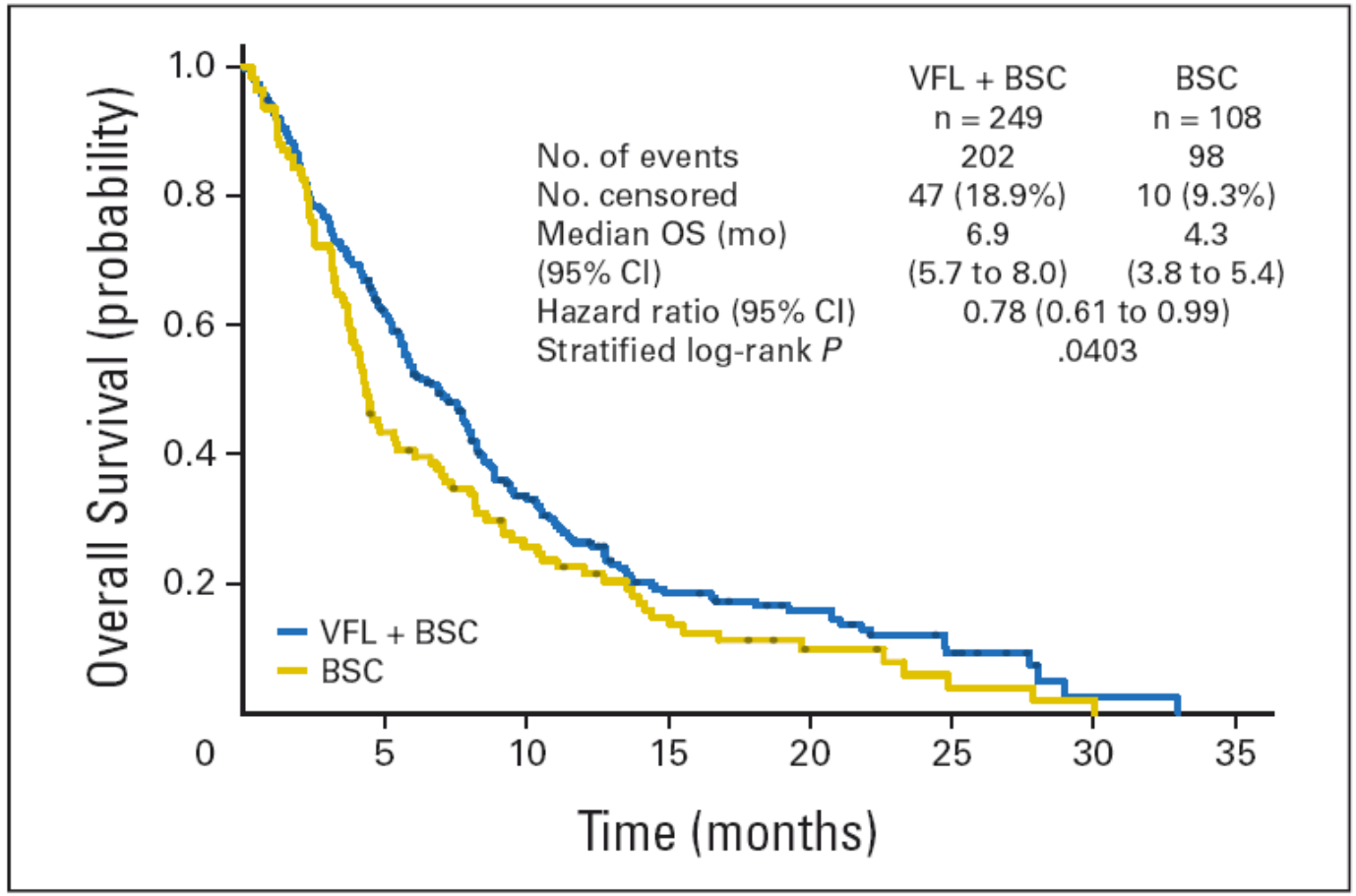
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

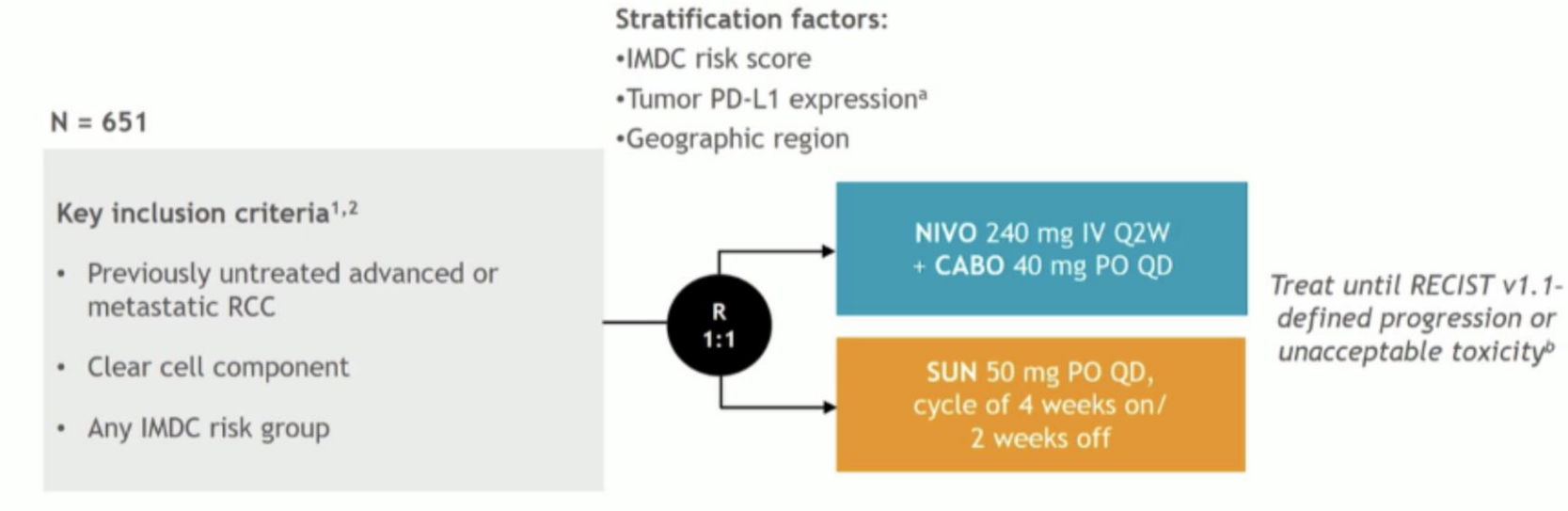
Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

Joaquim Bellmunt, Christine Théodore, Tomasz Demkov, Boris Komyakov, Lisa Sengelov, Gedske Daugaard, Armelle Caty, Joan Carles, Agnieszka Jagiello-Gruszfeld, Oleg Karyakin, François-Michel Delgado, Patrick Hurteloup, Eric Winquist, Nassim Morsli, Yacine Salhi, Stéphane Culine, and Hans von der Maase

J Clin Oncol 27:4454-4461. © 2009 by American Society of Clinical Oncology

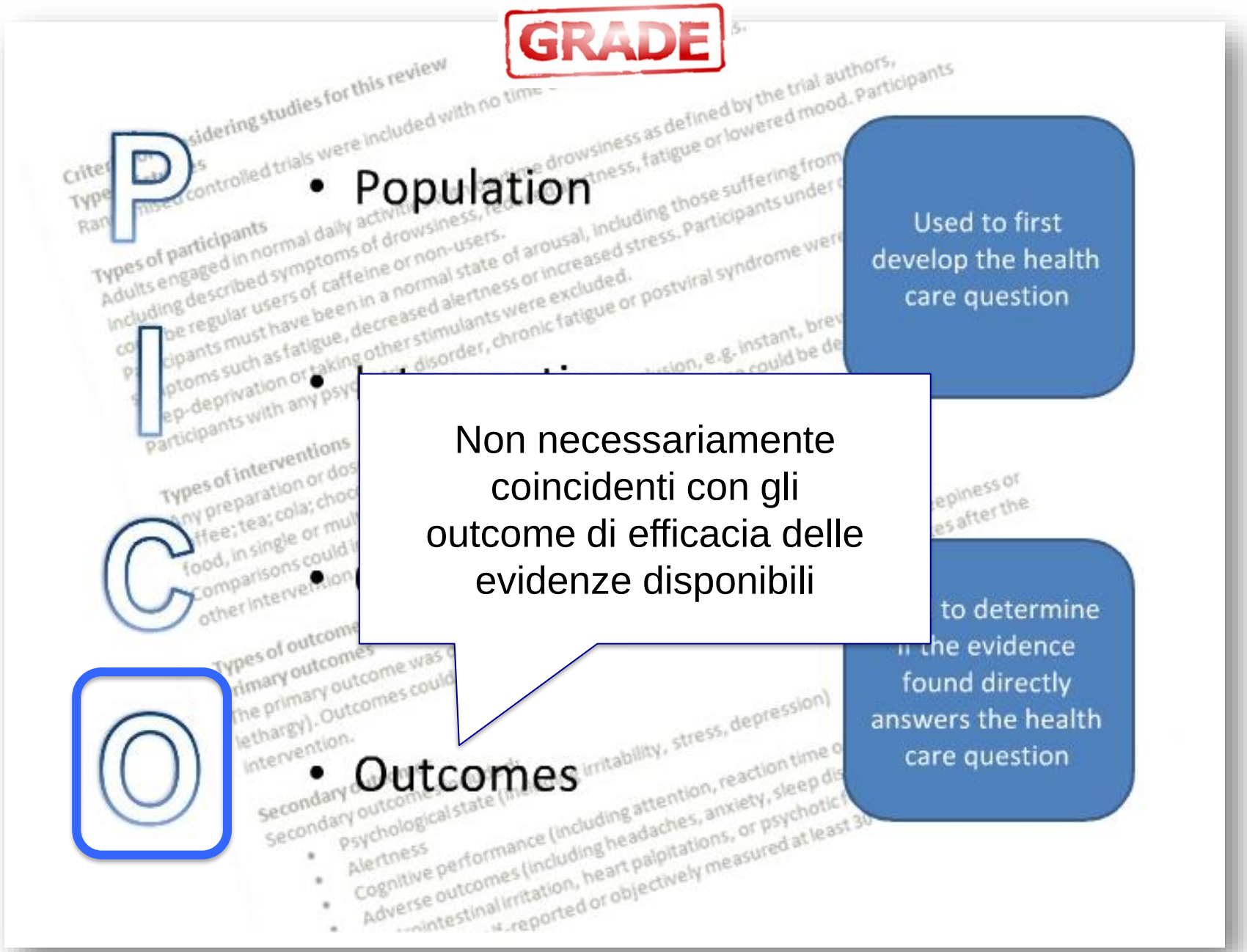


CheckMate 9ER: Study design

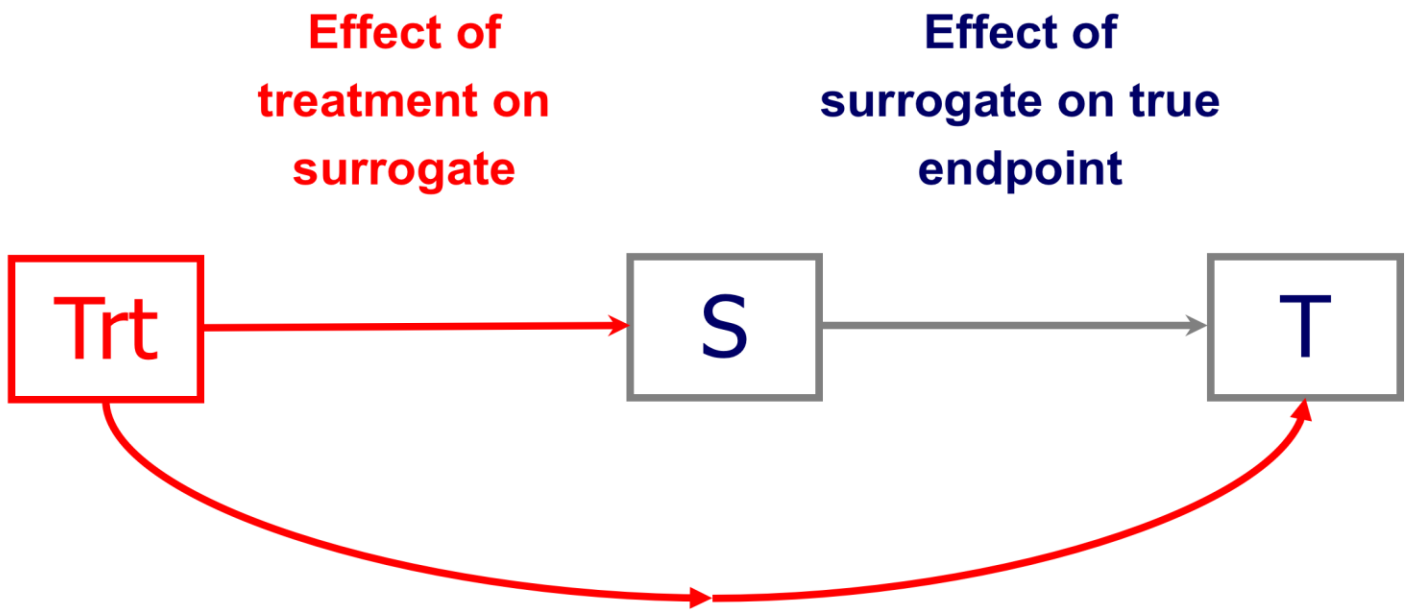


Pembrolizumab
Axitinib

Certezza globale delle prove	Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	Nei pazienti affetti da carcinoma renale metastatico variante istologica a cellule chiare, rischio intermedio-alto sec. Heng, il trattamento di prima linea con pembrolizumab-axitinib dovrebbe essere preso in considerazione come approccio terapeutico di prima scelta	**Forte a Favore**


GRADE
P
• Population
I
C
O
• Outcomes
Used to first develop the health care question
Non necessariamente coincidenti con gli outcome di efficacia delle evidenze disponibili
to determine
the evidence
found directly
answers the health
care question

VALIDATION OF SURROGATE ENDPOINTS: "FULL CAPTURE OF EFFECT"



*Prentice, Statist Med 1989;**8**:431.*

THE IDOLATRY OF THE SURROGATE

Easier to measure surrogate outcomes are often used instead of patient important outcomes such as death, quality of life, or functional capacity when assessing treatments. **John Yudkin, Kasia Lipska, and Victor Montori** argue that our obsession with surrogates is damaging patient care

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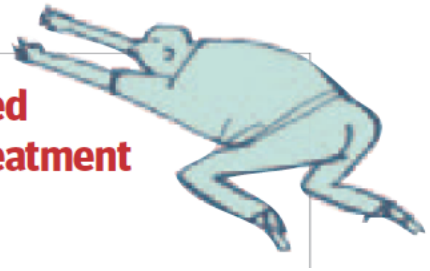
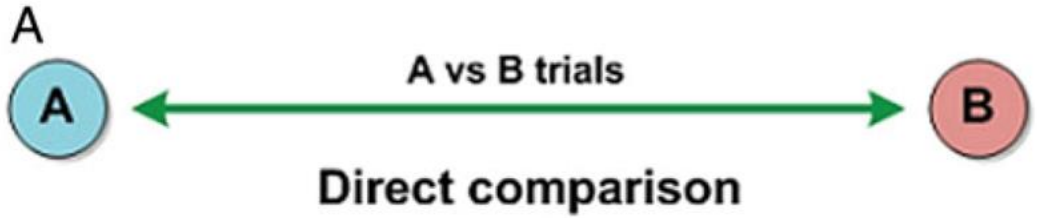
Since they respond sooner than outcomes that are important to patients, surrogates are better suited as end points in clinical trials that need to be completed quickly and at low cost

Surrogate markers are not intrinsically flawed. When interpreted appropriately, they can be helpful in risk stratification and in treatment



In order to fully engage our patients in treatment decisions, we must understand how therapies affect outcomes that are important to them. Surrogate end-points will not provide us with these answers.

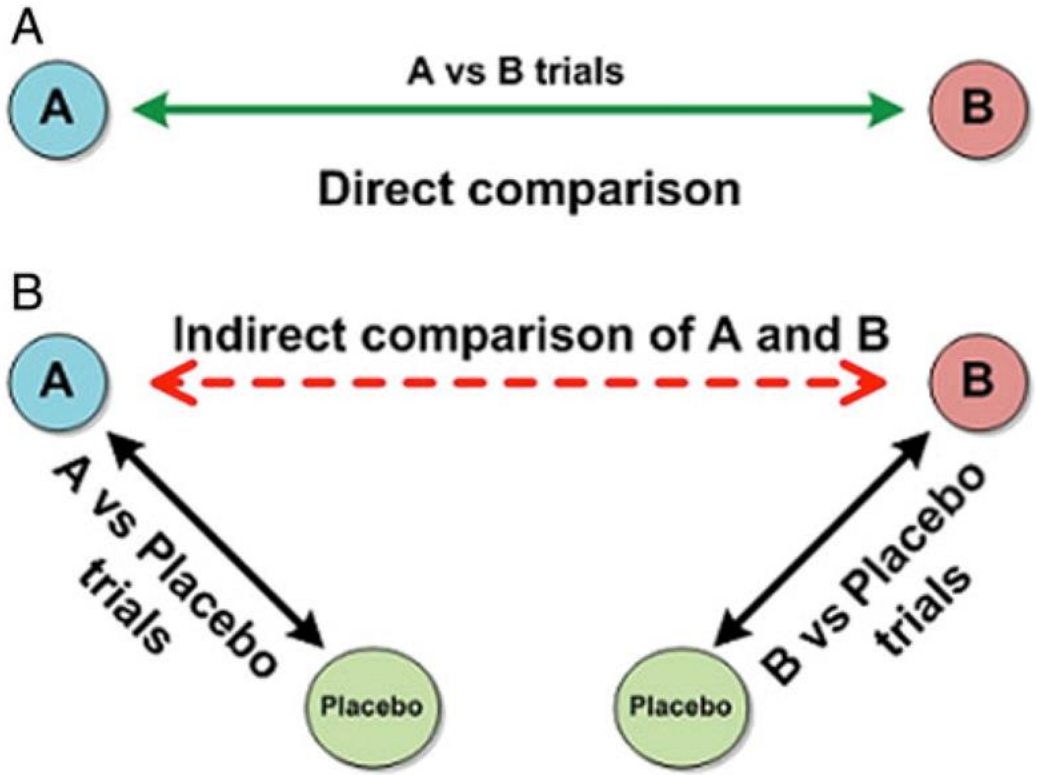


Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

Health Technology Assessment 2005; Vol. 9: No. 26

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.



through a

Common Comparator

Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

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HTA

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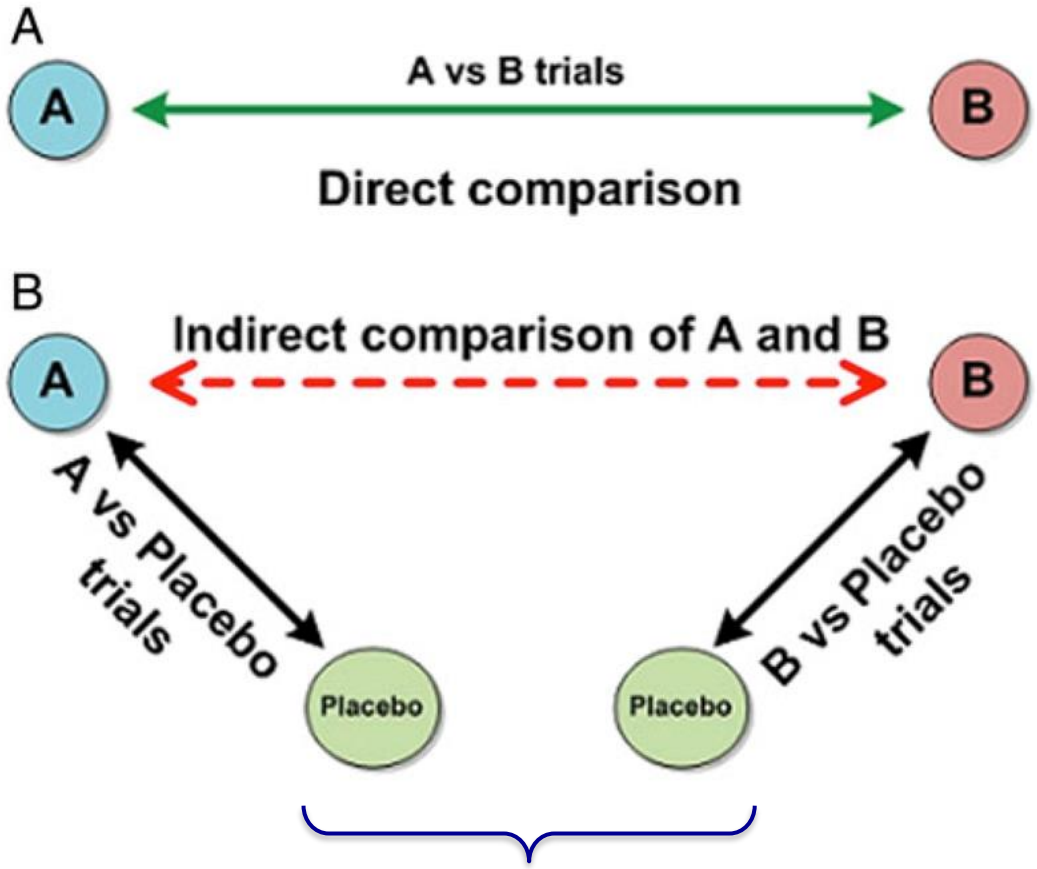

Similarity Assumption

trials must be comparable on effect modifiers to obtain an unbiased pooled estimate.

Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

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NEGRAR DI VALPOLICELLA (VR)

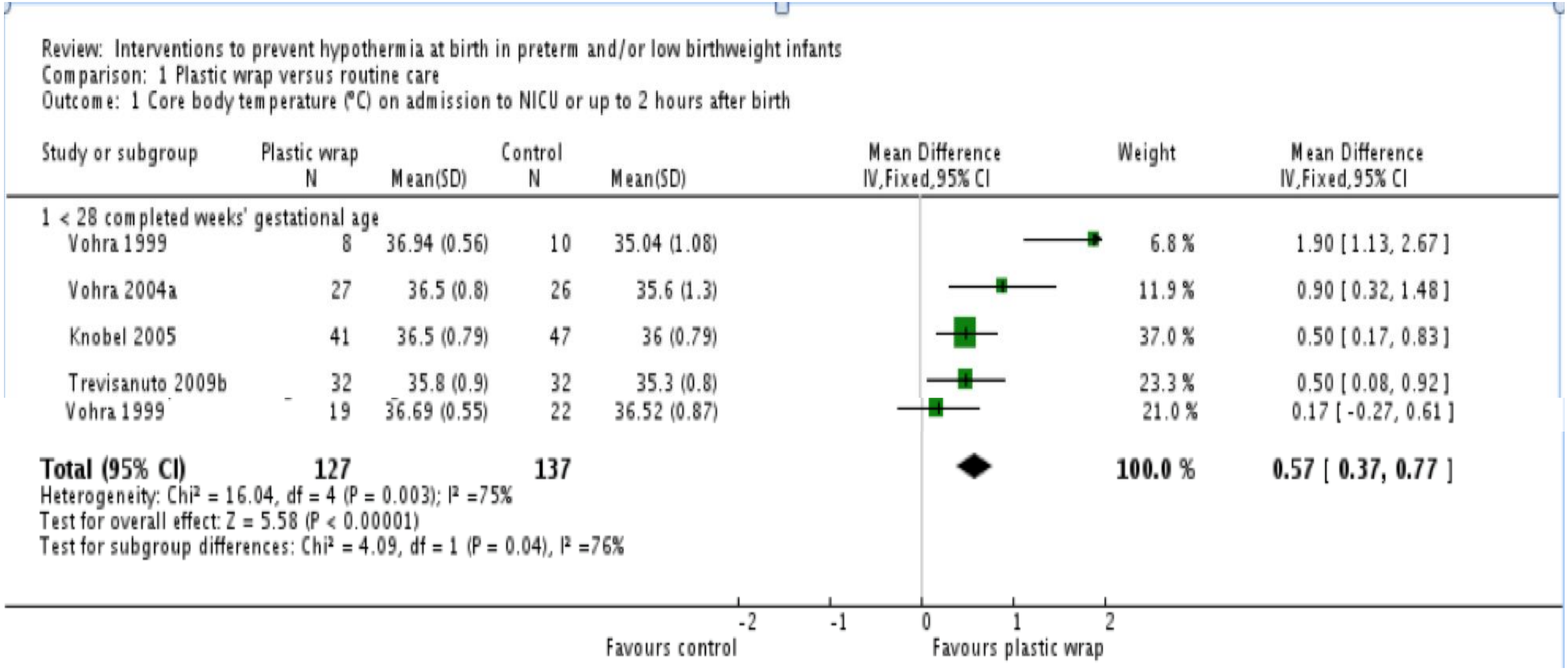
Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

GRADE

La valutazione della qualità delle prove (4): *inconsistency, publication bias*

(Michela Cinquini)

Esempio di Metaview



What is heterogeneity?

Differences between studies with respect to:

Clinical heterogeneity (clinical diversity)

- *Participants*

  e.g. conditions under investigation, eligibility criteria for trials, geographical variation

- *Interventions*

  e.g. intensity / dose / duration, sub-type of drug, mode of administration, experience of practitioners, nature of the control (placebo/none/standard care)

- *Outcomes*

  e.g. definition of an event, follow-up duration, ways of measuring outcomes, cut-off points on scales

What is heterogeneity?

Differences between studies with respect to:

Methodological heterogeneity (methodological diversity)

- *Design*

  e.g. randomised vs non-randomised,
  crossover vs parallel group vs cluster randomised,
  pre-test and long follow up

- *Conduct*

  e.g. allocation concealment, blinding etc,
  approach to analysis, imputation methods for
  missing data

What is heterogeneity?

What do we do if there ***is*** statistical heterogeneity?

Variation in the *true effects* underlying the studies

...which may manifest itself in more observed variation than expected by chance alone

May be due to clinical diversity (different treatment effects) or methodological diversity (different biases)

Inconsistency is important only when it reduces confidence in results in relation to a particular decision.

Come si misura questa eterogeneità?

Confidence interval overlapping Eyeball test

Cochran's Q: to assess whether observed differences in results are compatible with change alone

χ^2 distribution; low power (small number of studies, small sample size)

p=<0.10 (heterogeneity)

I^2 quantifing heterogeneity (describes the percentage of variation across studies that is due to heterogeneity rather than chance)

0-40% might not be important

30-60% may represent moderate heterogeneity

50-90% may represent substantial heterogeneity

75-100% considerable heterogeneity

Tau….

Unexplained heterogeneity

Differenza fra effetto grande e piccolo.

Non importante se anche l''effetto piccolo è clinicamente significativo.

Rilevante se ci sono differenze clinicamente rilevanti (impatto sul paziente) fra effetto piccolo e effetto grande

Downgrade: dipende

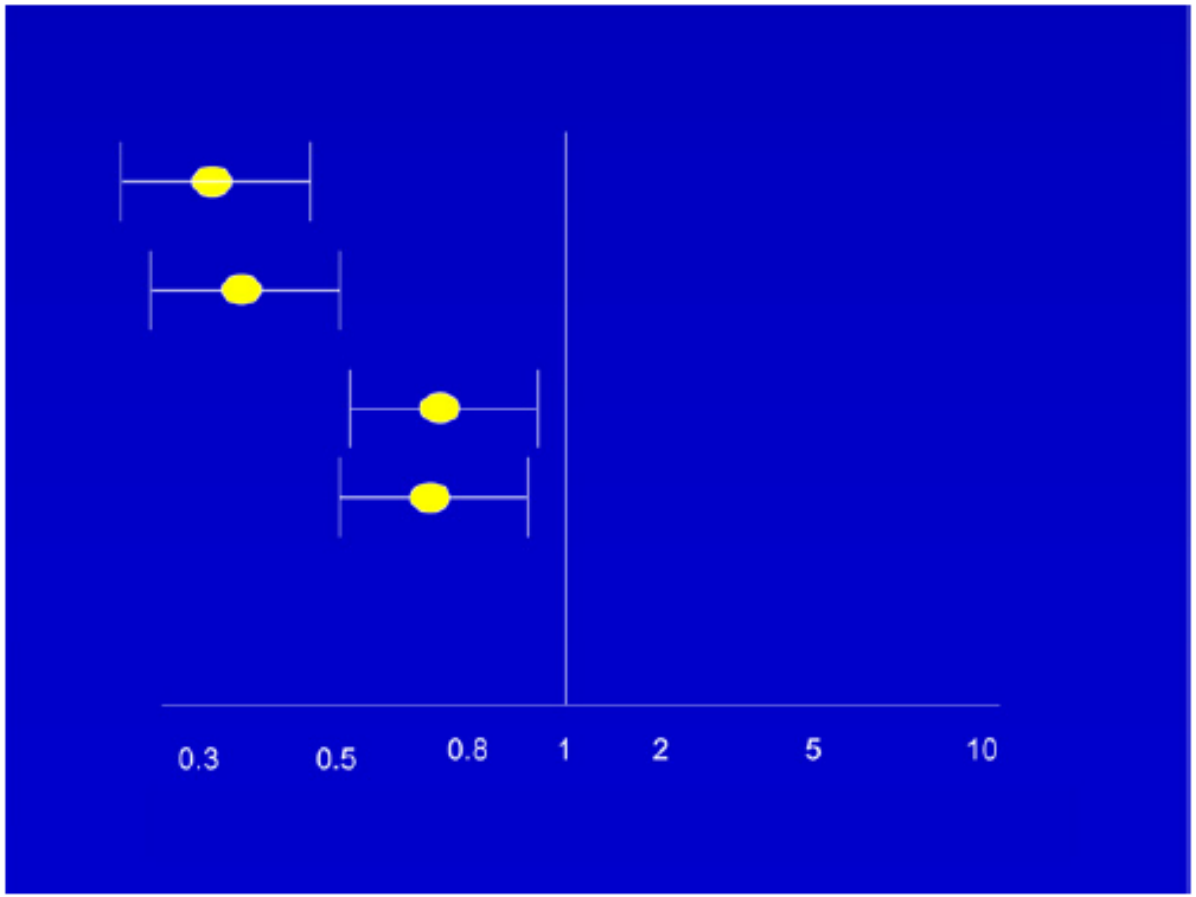


Fig. 2. Substantial heterogeneity, but of questionable importance.

Unexplained heterogeneity

La grandezza della variabilità è la stessa ma in questo caso due studi vanno in una direzione e due in un'altra.

Inconsistency importante

Pooled estimate di non effetto ma con grande eterogeneità

Downgrade: sì

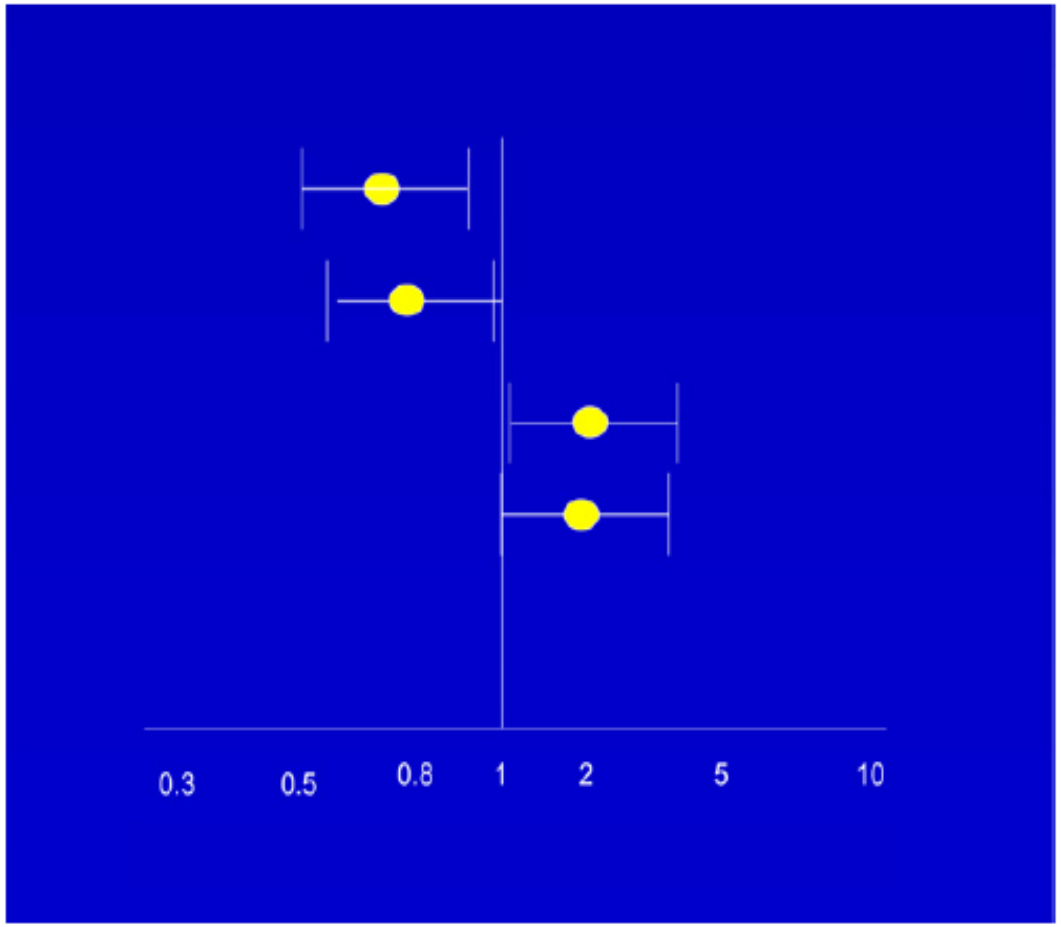


Fig. 3. Substantial heterogeneity, of unequivocal importance.

Unexplained heterogeneity

Pooled estimate di non effetto, come prima, ma in questo caso le differenze fra gli studi sono piccole , tutti concludono per differenze piccole e non significative

Downgrade: no

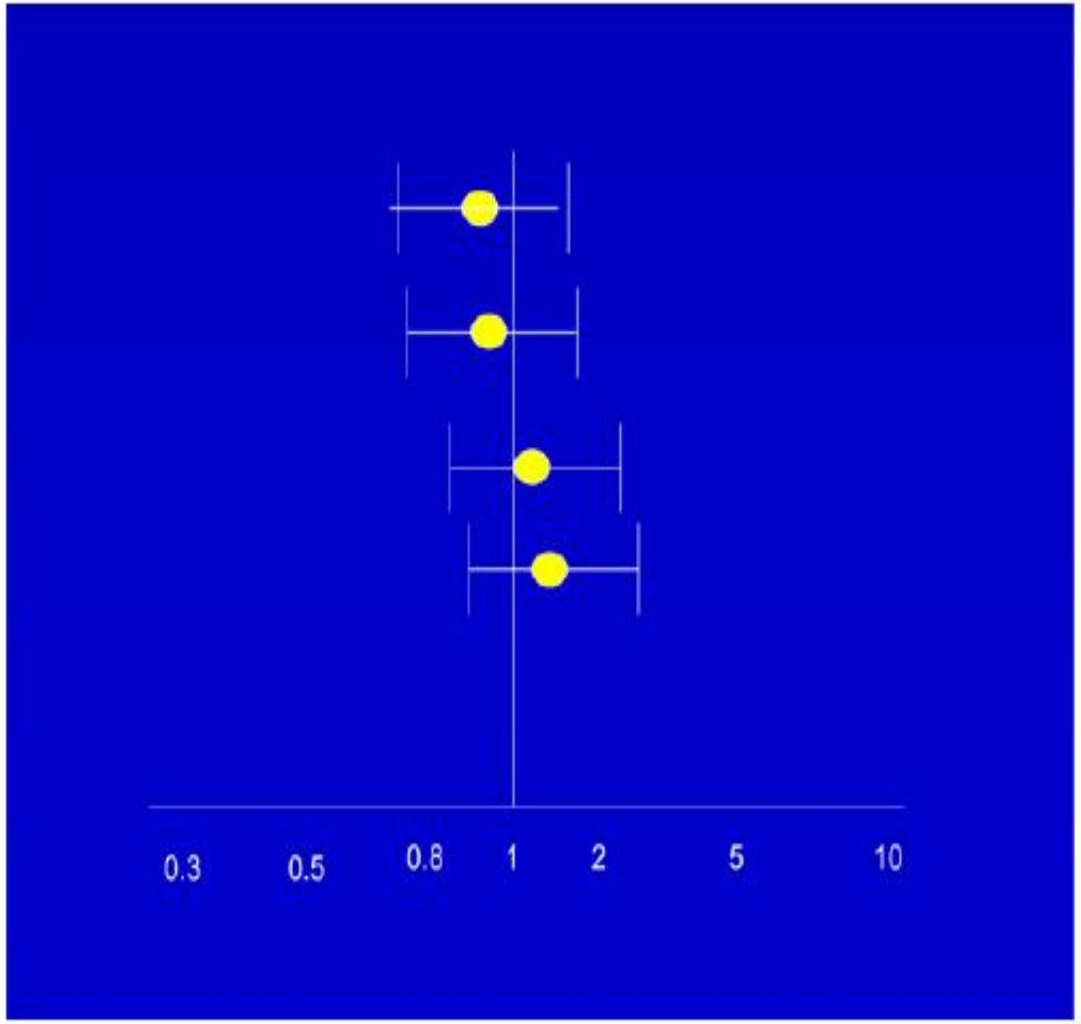


Fig. 1. Differences in direction, but minimal heterogeneity.

Publication bias

- Selective reporting bias: outcome dichiarato nel protocollo ma risultati non riportati: uno dei domini del risk of bias
- Publication bias: mancata pubblicazione di un intero studio

✓English language bias

✓Time lag bias

✓Citation bias

- Sovrastima dell'effetto del trattamento

Publication bias in context

Publication bias and other related biases can be summarised as statistically significant, 'positive' results being:

- more likely to be published (publication bias)
- more likely to be published rapidly (time lag bias)
- more likely to be published in English (language bias)
- more likely to be published more than once (multiple publication bias)
- more likely to be cited by others (citation bias)

[The Cochrane Collaboration]

Publication bias: come valutarne il rischio?

Sezione metodi della revisione:

Cercati studi non pubblicati?

Solo studi in lingua inglese?

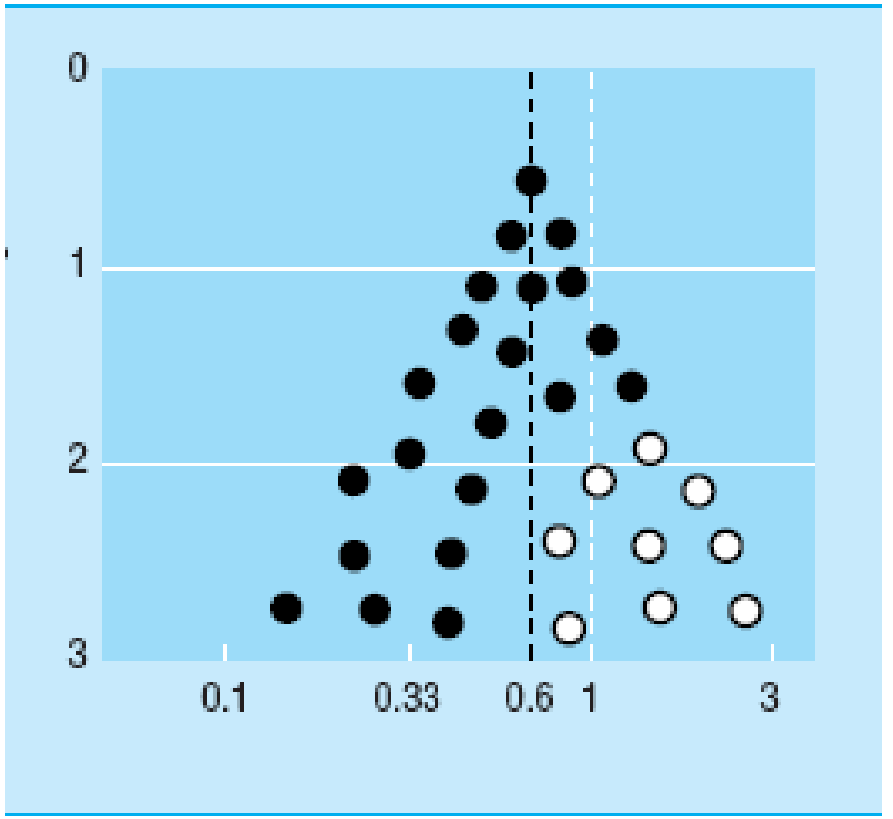
Revisione su nuova terapia introdotta da poco?

Trials piccoli e sponsorizzati da industria farmaceutica?

Funnel plot?

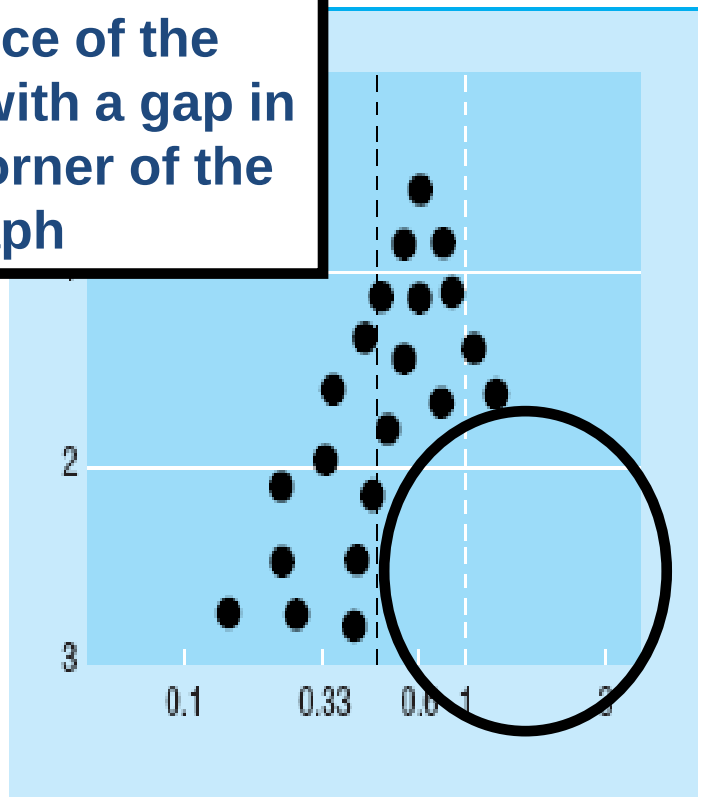
Studi osservazionali? Rischio maggiore perché non obbligatoria registrazione

Publication of All Trials

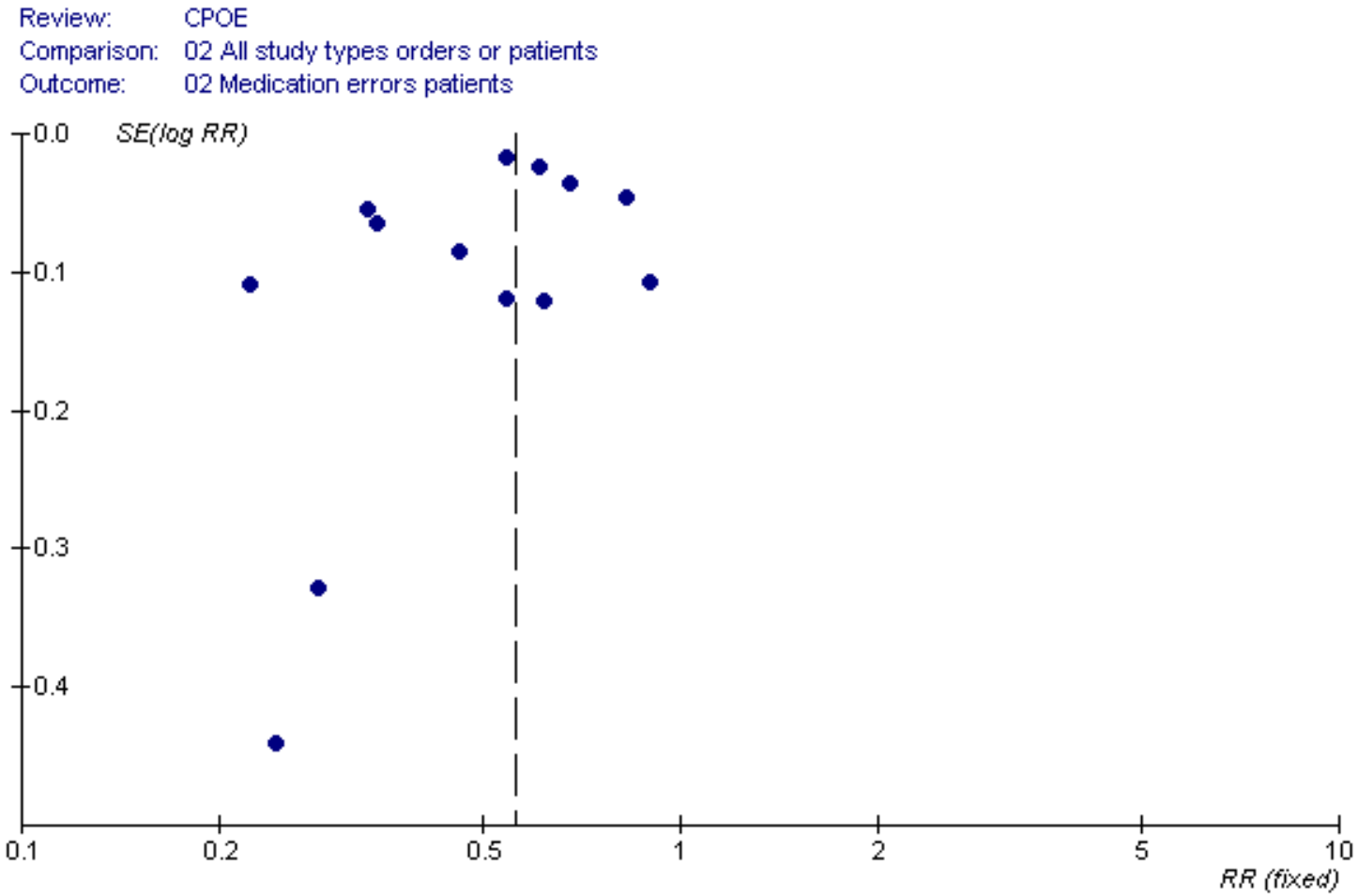


Publication Bias

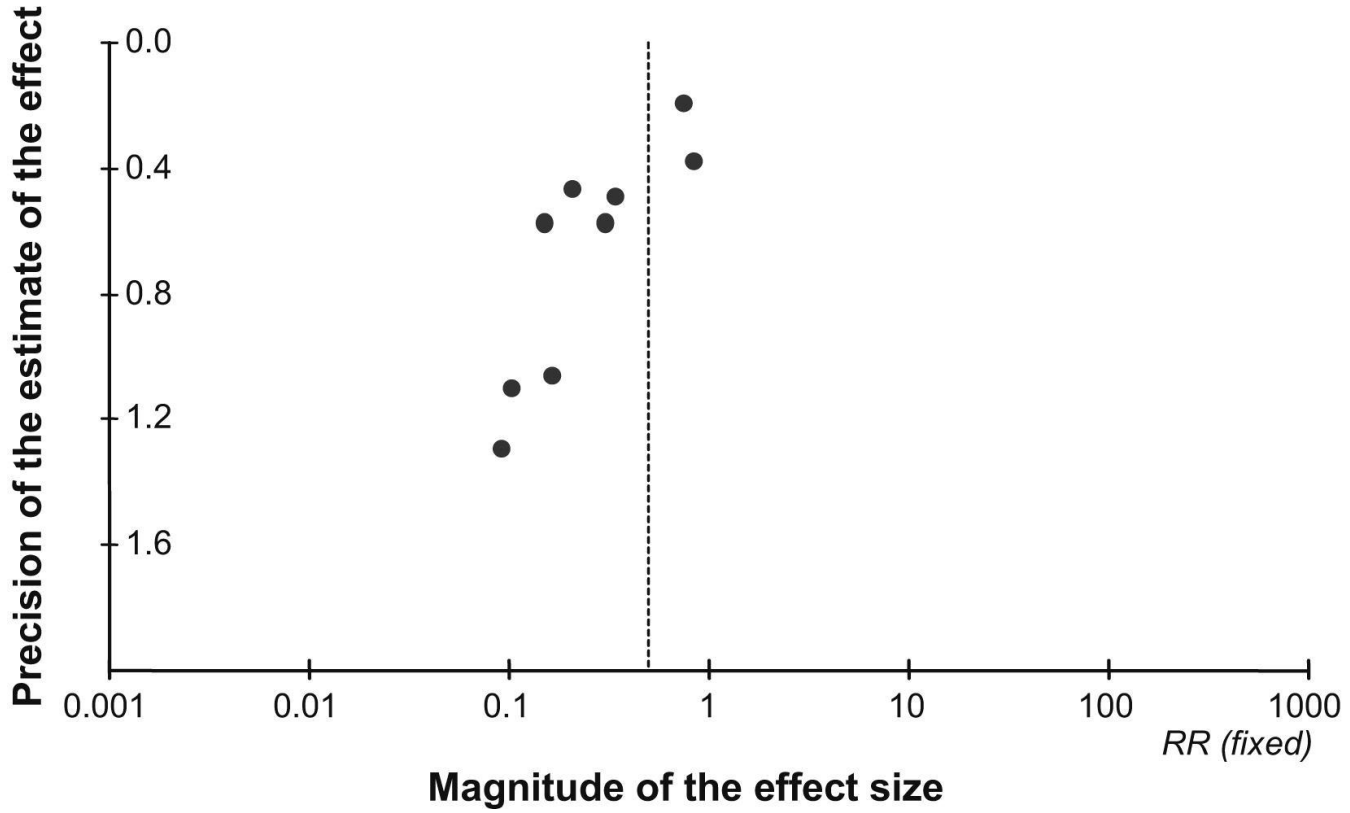
Asymmetrical appearance of the funnel plot with a gap in a bottom corner of the graph



Study 2: Effects of CPOE on medication errors / ADEs



Funnel plot of studies of flavonoids for ameliorating symptoms in patients with hemorrhoids



Terms and Conditions

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GRADE

La valutazione della qualità delle prove (5): gli studi non randomizzati

(Michela Cinquini)

Observational studies

Quality starts as low

Then it can be further downgraded for one of the reasons cited above (risk of bias, inconsistency, imprecision, indirectness, publication bias)

Then it can be upgraded ;

The circumstances under which we may wish to rate up the quality of evidence for intervention studies will likely occur infrequently and are primarily relevant to observational studies.

Indeed, although it is theoretically possible to rate up results from randomized control trials (RCTs), we have yet to find a compelling example of such an instance.

What can raise quality?

1. **large magnitude of effect** can upgrade (**RRR 50%/RR 2**)
   - very large two levels **(**RRR 80%/RR 5) ; modeling studies suggests that confounding (from nonrandom allocation) alone is unlikely to explain associations with a relative risk (RR) greater than 2 (or less than 0.5), and very unlikely to explain associations with an RR greater than 5 (or less than 0.2)
   - Es: relationship between infant sleeping position and sudden infant death syndrome (SIDS) found an odds ratio (OR) of 4.1 (95% confidence interval [CI]: 3.1, 5.5) of SIDS occurring with front vs. back sleeping positions

Large magnitude of effect

Further consideration for rating up:

- rapidity of treatment response, and the previous underlying trajectory of the condition

E.g.: we feel confident that hip replacement has a large effect on reducing pain and functional limitations in severe osteoarthritis not only because of the size of the treatment response, but because the natural history of hip osteoarthritis is a progressive deterioration that surgery rapidly and uniformly reverses

- indirect evidence that provides further support for large treatment effects.

E.g. : the effectiveness of antibiotic prophylaxis in a variety of other situations supports observational studies that suggest that antibiotic prophylaxis results in an 89% RR reduction in meningococcal disease in contacts of patients who have suffered the illness

What can raise quality?

2. dose response relation

e.g.: childhood lymphoblastic leukemia: risk for CNS malignancies 15 years after cranial irradiation

- no radiation: 1% (95% CI 0% to 2.1%)
- 12 Gy: 1.6% (95% CI 0% to 3.4%)
- 18 Gy: 3.3% (95% CI 0.9% to 5.6%)

E.g.: systematic review of observational studies on cyclooxygenase-2 inhibitors on cardiovascular events:

- RR 1.33 (95% CI: 1.00, 1.79) with doses less than 25 mg/d
- RR 2.19 (95% CI: 1.64, 2.91) with doses more than 25 mg/d

Residual confounding

- **3.** all **plausible residual confounding** may be working to reduce the demonstrated effect or increase the effect if no effect was observed (underestimate of the treatment effect)

- Es: effect of condom use on HIV infection among men who have sex with men RR: 0.34 [0.21, 0.54] (RRR: 66%) in favor of condom use compared with no condom use. Condom users were more likely to have more partners (but studies did not adjust for this confounding factor in their analyses). Considering the number of partners would, if anything, strengthen the effect estimate in favor of condom use.

Residual confounding

- Es: SR di studi osservazionali: mortalità per tutte le cause in ospedali privati for profit vs ospedali privati not – for profit: RR 1.020, 95% CI 1.003-1.038 : mortalità leggermente superiore in for profit
- Fattori confondenti per cui non hanno aggiustato: livello di reddito dei pazienti e disponibilità risorse ospedali (> in for profit) che dovrebbe essere associato a < mortalità. Quindi in caso di aggiustamento l'effetto (RR) sarebbe stato maggiore

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GRADE

L'organizzazione delle evidenze: *Evidence Table*

(Ivan Moschetti)

La Table of evidence (ToEs)

Evidence profile: use of antibiotics (penicillin) versus no use of antibiotics in children with sickle cell disease. Source: Hirst et al. 4

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin prophylaxis	Standard care	Relative (95% CI)	Absolute (95% CI)		
Incidence of pneumococcal infection, for initiation of treatment - Initiation of penicillin												
2	Randomized trials	Not serious [1]	serious [2]	not serious [3]	serious [4]	none [5]	9/248 (3.6%)	19/209 (9.1%)	**OR 0.37** (0.16 to 0.86)	55 fewer per 1000 (from 12 fewer to 75 fewer)	⊕⊕◯◯ LOW	CRITICAL
Deaths, for initiation of treatment - Initiation of penicillin												
1	randomized trials	not serious [6]	not serious	not serious	serious [4]	none [5]	0/105 (0.0%)	4/110 (3.6%)	**OR 0.11** (0.01 to 2.11)	32 fewer per 1000 (from 36 fewer to 37 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse drug effects - Nausea and vomiting												
1	randomized trials	not serious [6]	not serious	not serious	serious [4]	none [5]	2/201 (1.0%)	1/199 (0.5%)	**OR 1.99** (0.18 to 22.12)	5 more per 1000 (from 4 fewer to 95 more)	⊕⊕⊕◯ MODERATE	CRITICAL

1.blinding and concealment were not clear for one of the two studies
2.heterogeneity exists; p-value for testing heterogeneity is 0.07 and I2=69%
3.the question addressed is the same for the evidence regarding the population, intervention, comparator and outcome
4.total sample size is small, and the total number of events is <300 (a threshold rule-of-thumb value)
5.insufficient number of studies to assess publication bias
6.unclear allocation concealment

Domanda: Agopuntura rispetto a trattamento non farmacologico per lombalgia cronica aspecifica

Certainty assessment							Nº di pazienti		Effetto		Certo	Importanza
Nº degli studi	Disegno dello studio	Rischio di distorsione	Mancanza di riproducibilità dei risultati	Mancanza di generalizzabilità	Imprecisione	Ulteriori considerazioni	agopuntura	trattamento non farmacologico	Relativo (95% CI)	Assoluto (95% CI)		
dolore al termine del trattamento (follow up: intervallo 4 settimane a 5 settimane; valutato con: VAS)												
3[1,2,3]	studi randomizzati	serio[a]	non importante	non importante	serio[b]	nessuno	76	65	-	**MD 0.1 maggiore** (15.05 inferiore a 15.25 maggiore)	⨁⨁◯◯ Bassa	CRITICAL
Qualità della vita al termine del trattamento Agopuntura media intensità (follow up: medio 4 settimane; valutato con: SF 36 totale)												
1[1]	studi randomizzati	serio[a]	non importante	non importante	molto serio[c]	nessuno	39	29	-	**MD 4.2 inferiore** (10.11 inferiore a 1.71 maggiore)	⨁◯◯◯ Molto bassa	CRITICAL
partecipanti con uso analgesici al termine del trattamento. agopuntura media intensità (follow up: medio 10 settimane)												
1[4]	studi randomizzati	serio[a]	non importante	non importante	molto serio[d]	nessuno	48/94 (51.1%)	37/78 (47.4%)	**RR 1.08** (0.79 a 1.46)	**4 più per 100** (da 10 meno a 22 più)	⨁◯◯◯ Molto bassa	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference

Spiegazioni

a. abbassato di un livello per alto rischio di performance e detection bias

b. abbassato di un livello per imprecisione: meno di 400 partecipanti

c. abbassato di due livelli per imprecisione: meno di 100 partecipanti

d. abbassato di due livelli per imprecisione: meno di 100 eventi e intervalli di confidenza molto ampi

Sintesi dei risultati:

Agopuntura rispetto a trattamento non farmacologico per lombalgia cronica aspecifica

Paziente o popolazione: lombalgia cronica aspecifica

Intervento: agopuntura

Confronto: trattamento non farmacologico

Esiti	Effetto assoluto anticipato* (95% CI)		Effetto relativo (95% CI)	№ dei partecipanti (studi)	Certezza delle prove (GRADE)	Commenti
	Rischio con trattamento non farmacologico	Rischio con agopuntura				
dolore al termine del trattamento valutato con: VAS follow up: intervallo 4 settimane a 5 settimane	La media dolore al termine del trattamento era **37.64**	MD **0.1 maggiore** (15.05 inferiore a 15.25 maggiore)	-	141 (3 RCT)[1,2,3]	⨁⨁◯◯ Bassa[a,b]	
Qualità della vita al termine del trattamento Agopuntura media intensità valutato con: SF 36 totale follow up: medio 4 settimane	La media qualità della vita al termine del trattamento Agopuntura media intensità era **32.6**	MD **4.2 inferiore** (10.11 inferiore a 1.71 maggiore)	-	68 (1 RCT)[1]	⨁◯◯◯ Molto bassa[a,c]	
partecipanti con uso analgesici al termine del trattamento. agopuntura media intensità follow up: medio 10 settimane	47 per 100	**51 per 100** (37 a 69)	**RR 1.08** (0.79 a 1.46)	172 (1 RCT)[4]	⨁◯◯◯ Molto bassa[a,d]	

* **Il rischio nel gruppo di intervento** (e il suo intervallo di confidenza (IC) al 95%) si basa sul rischio assunto nel gruppo di controllo e **sull'effetto relativo** dell'intervento (e il suo IC al 95 %).

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GRADE

Evidence to Decision Framework e formulazione della Raccomandazione

(Michela Cinquini)

The Evidence-to-Decision framework

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction

Pablo Alonso-Coello,[1,2] Holger J Schünemann,[2,3] Jenny Moberg,[4] Romina Brignardello-Petersen,[2,5] Elie A Akl,[2,6] Marina Davoli,[7] Shaun Treweek,[8] Reem A Mustafa,[2,9] Gabriel Rada,[10,11,12] Sarah Rosenbaum,[4] Angela Morelli,[4] Gordon H Guyatt,[2,3] Andrew D Oxman[4] the GRADE Working Group

BMJ 2016;353:i2016

GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines

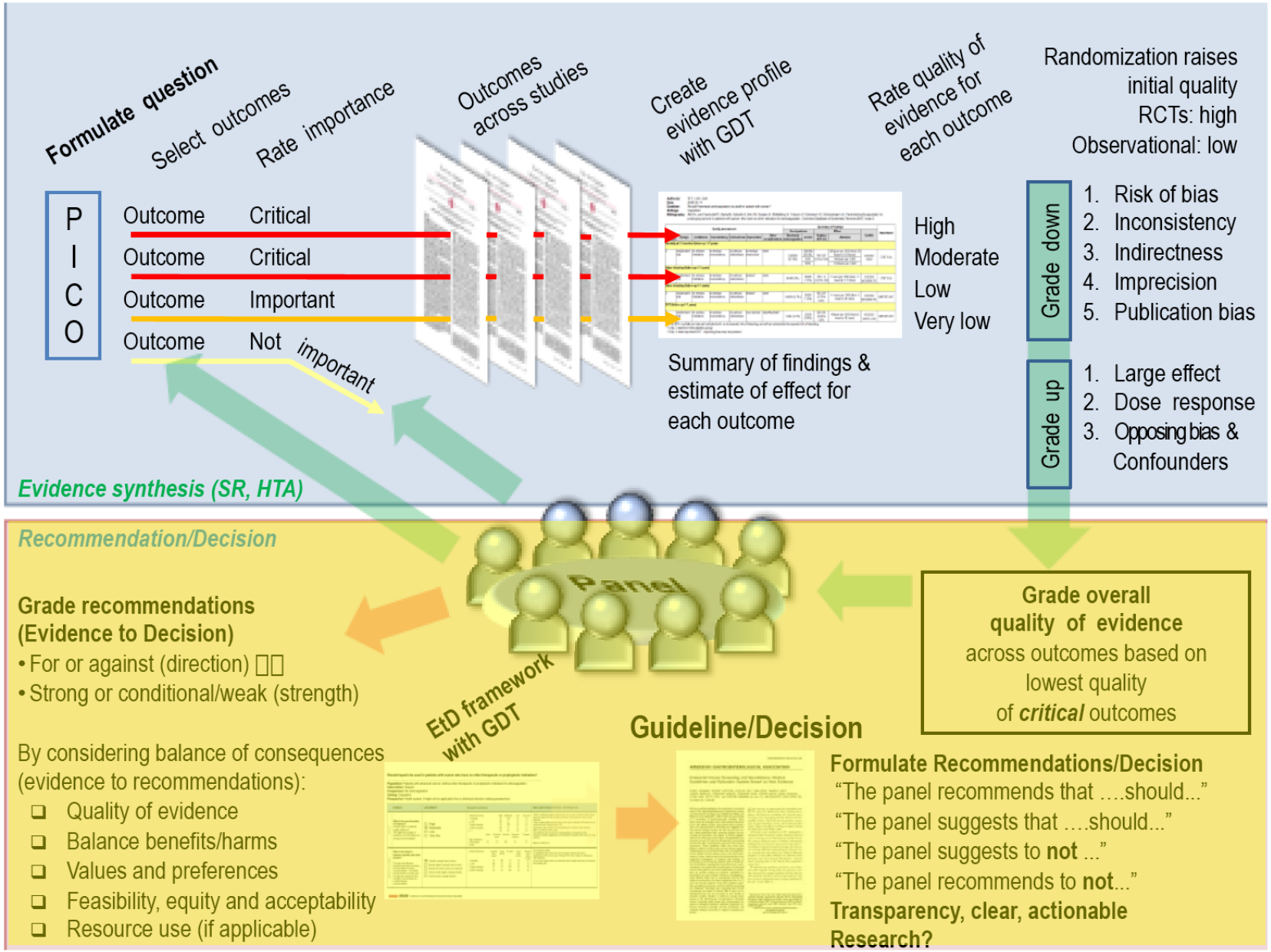
Pablo Alonso-Coello,[1,2] Andrew D Oxman,[3] Jenny Moberg,[3] Romina Brignardello-Petersen,[2,4] Elie A Akl,[2,5] Marina Davoli,[6] Shaun Treweek,[7] Reem A Mustafa,[2,8] Per O Vandvik,[3] Joerg Meerpohl,[9] Gordon H Guyatt,[2,10] Holger J Schünemann,[2,10] the GRADE Working Group

BMJ 2016;353:i2089

SUMMARY POINTS

- Explicit and transparent systems for decision making can help to ensure that all important criteria are considered and that decisions are informed by the best available research evidence
- The purpose of Evidence to Decision (EtD) frameworks is to help people use evidence in a structured and transparent way to inform decisions in the context of clinical recommendations, coverage decisions, and health system or public health recommendations and decisions
- EtD frameworks inform users about the judgments that were made and the evidence supporting those judgments by making the basis for decisions transparent to target audiences

The GRADE process in developing guidelines



GRADEpro GDT

Should Patisiran vs. [placebo] be used in Hereditary Transthyretin Amyloidosis (mNIS+7 analysis)?

Bottom panel | Explanations

1 **Problem**
Is the problem a priority?

2 **Desirable Effects**
How substantial are the desirable anticipated effects?

3 **Undesirable Effects**
How substantial are the undesirable anticipated effects?

4 **Certainty of evidence**
What is the overall certainty of the evidence of effects?

5 **Values**
Is there important uncertainty about or variability in how much people value the main outcomes?

6 **Balance of effects**
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

7 **Resources required**
How large are the resource requirements (costs)?

8 **Certainty of evidence of required resources**
What is the certainty of the evidence of resource requirements (costs)?

9 **Cost effectiveness**
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

10 **Equity**
What would be the impact on health equity?

11 **Acceptability**
Is the intervention acceptable to key stakeholders?

12 **Feasibility**
Is the intervention feasible to implement?

GRADEpro GDT

Should Patisiran vs. [placebo] be used in Hereditary Transthyretin Amyloidosis (mNIS+7 analysis)?

Bottom panel | Explanations

CRITERIA	SUMMARY OF JUDGEMENTS							IMPORTANCE FOR DECISION
PROBLEM	No	Probably no	Probably yes	**Yes**	Varies	Don't know		**HIGH**
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**	Varies	Don't know		**HIGH**
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial	Varies	Don't know		**HIGH**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**	No included studies			**MODERATE**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**				**HIGH**
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	**HIGH**
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	**LOW**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High	No included studies			**LOW**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	**LOW**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know	**MODERATE**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know		**LOW**
FEASIBILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know		**MODERATE**

Valutazione della qualità globale delle prove

Dopo la valutazione della qualità per i singoli outcome importanti effettuata dall'ERT (Sezione 4.5) si deve formulare il giudizio complessivo di qualità. Il metodo GRADE suggerisce di procedere considerando soltanto gli outcome critici per la formulazione della raccomandazione relativa al quesito clinico.

Valutazione della qualità globale delle prove

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- se i risultati vanno in direzioni opposte (es. il trattamento oggetto della raccomandazione è migliore in termini di efficacia ma peggiore per quanto riguarda gli effetti indesiderati), la qualità globale viene attribuita basandosi sulla valutazione peggiore ossia assumendo come più rappresentativo l'outcome che ha ottenuto la più bassa valutazione di qualità;
- se i risultati vanno nella stessa direzione per tutti gli outcome (beneficio o danno), viene assunta come qualità globale delle prove la qualità di un singolo outcome critico che da solo basterebbe per formulare compiutamente la raccomandazione;

Valutazione della qualità globale delle prove

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Defining Strength of recommendation

- The extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended.

Strength of recommendation

- A recommendation can have one of 2 strength:
  - **Strong** : panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects (or vice versa).
  - **Conditional** : panel concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects (or vice versa), but is not confident.

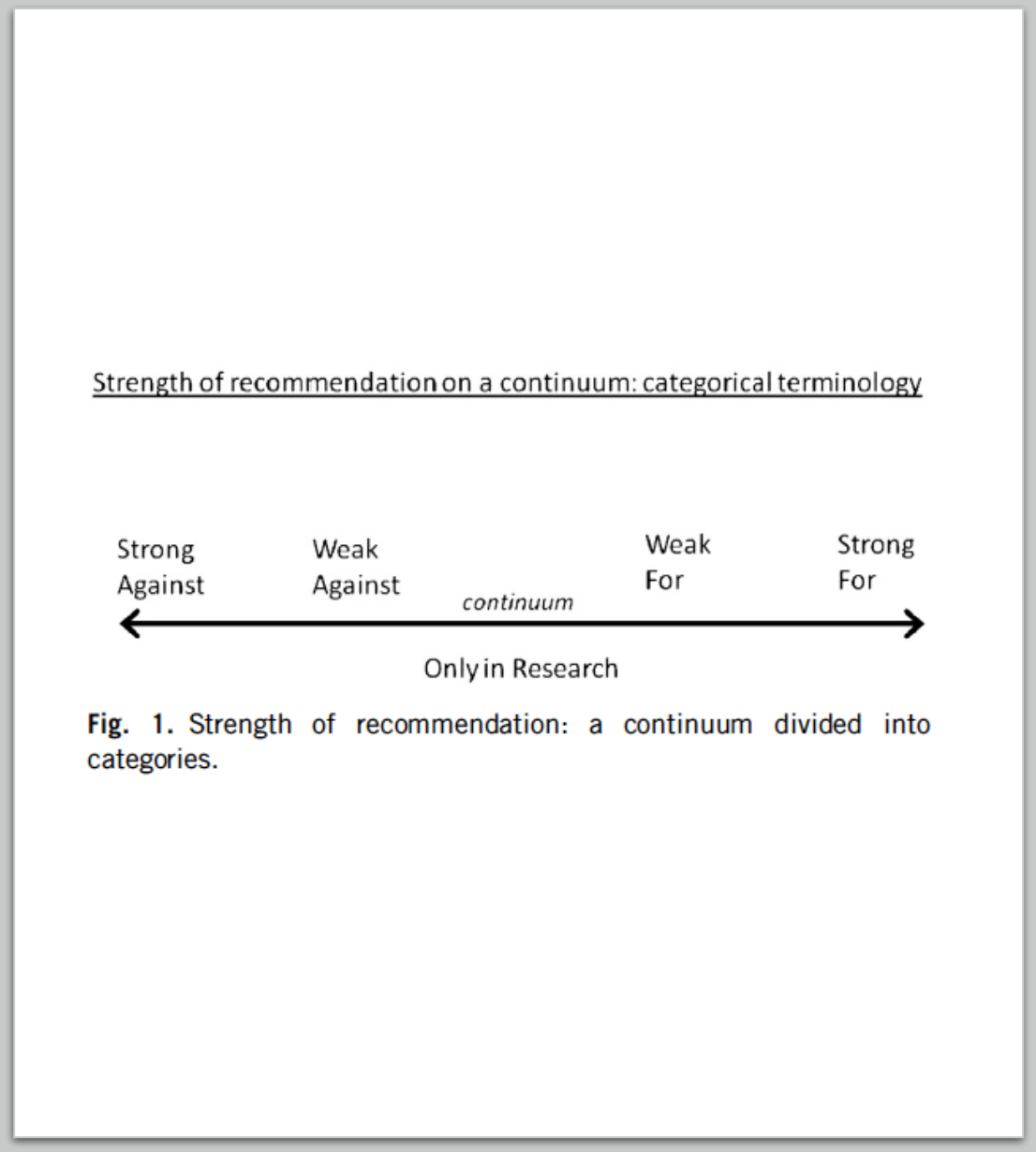


Fig. 1. Strength of recommendation: a continuum divided into categories.

Implications of strong and conditional recommendations

	Strong recommendation	Conditional recommendation
Patients	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action, but many would not
Clinicians		
Policy makers		

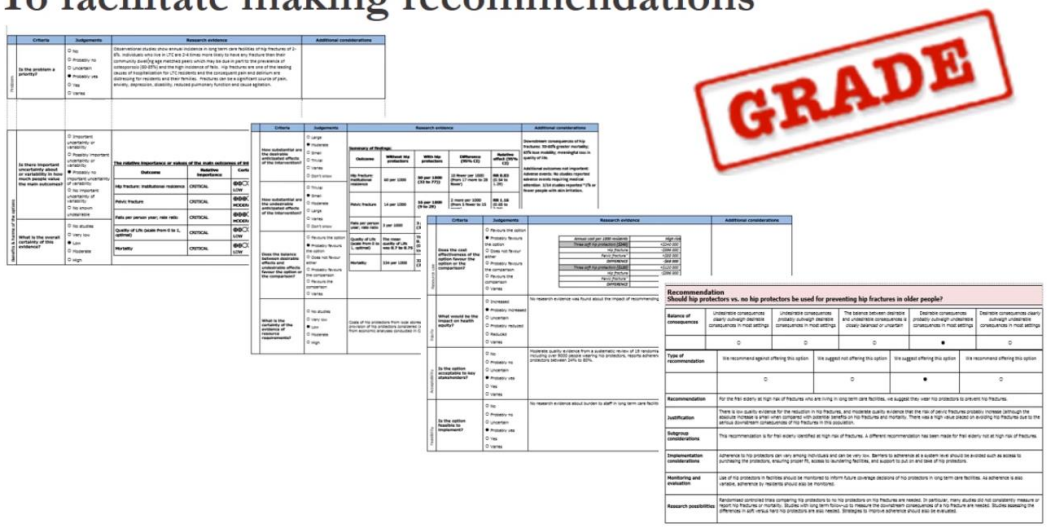
Implications of strong and conditional recommendations

	Strong recommendation	Conditional recommendation
Patients	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action, but many would not
Clinicians	Most patients should receive the recommended course of action	Be prepared to help patients to make a decision that is consistent with their own values
Policy makers		

Implications of strong and conditional recommendations

	Strong recommendation	Conditional recommendation
Patients	Most people in your situation would want the recommended course of action and only a small proportion would not	The majority of people in your situation would want the recommended course of action, but many would not
Clinicians	Most patients should receive the recommended course of action	Be prepared to help patients to make a decision that is consistent with their own values
Policy makers	The recommendation can be adapted as a policy in most situations	There is a need for substantial debate and involvement of stakeholders

Evidence to Decision Table:
To facilitate making recommendations

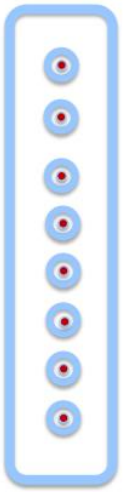


GRADE

Criteria

- Problem/priority?
- Benefits & harms of the options
- Certainty of evidence
- Values
- Resource use
- Equity
- Acceptability
- Feasibility

Evidence from Systematic Reviews



Formulazione delle Raccomandazioni LG AIOM (14 febbraio 2021)

Forza della raccomandazione clinica	Terminologia	Significato
Forte a Favore	"Nei pazienti con (criteri di selezione) l'intervento xxx dovrebbe essere preso in considerazione come opzione terapeutica di prima intenzione"	l'intervento in esame dovrebbe essere considerato come prima opzione terapeutica (**evidenza che i benefici sono prevalenti sui danni**)
Condizionata a Favore	"Nei pazienti con (criteri di selezione) l'intervento xxx può essere preso in considerazione come opzione terapeutica di prima intenzione, in alternativa a yyy"	l'intervento in esame può essere considerato come opzione di prima intenzione, consapevoli dell'esistenza di alternative ugualmente proponibili (**incertezza riguardo alla prevalenza dei benefici sui danni**)
Condizionata a Sfavore	"Nei pazienti con (criteri di selezione) l'intervento xxx non dovrebbe essere preso in considerazione come opzione terapeutica di prima intenzione, in alternativa a yyy"	l'intervento in esame non dovrebbe essere considerato come opzione di prima intenzione; esso potrebbe comunque essere suscettibile di impiego in casi altamente selezionati e previa completa condivisione con il paziente (**incertezza riguardo alla prevalenza dei danni sui benefici**)
Forte a Sfavore	"Nei pazienti con (criteri di selezione) l'intervento xxx non deve essere preso in considerazione come opzione terapeutica di prima intenzione"	l'intervento in esame non deve essere in alcun caso preso in considerazione (**evidenza che i danni sono prevalenti sui benefici**)

SACRO CUORE DON CALABRIA I R C C S

ECI CANCER CENTRE

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2024 - 10ª EDIZIONE

MODULI SPECIALISTICI - S2

VENERDÌ 12 - SABATO 13 APRILE 2024

NEGRAR DI VALPOLICELLA (VR)

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

GRADE

Metodiche di valutazione di una Linea Guida e normativa vigente

(Ivan Moschetti)

Accreditamento delle linee guida

l'Italia si munisce quindi di un sistema di accreditamento, monitoraggio ed aggiornamento delle linee guida (2017)

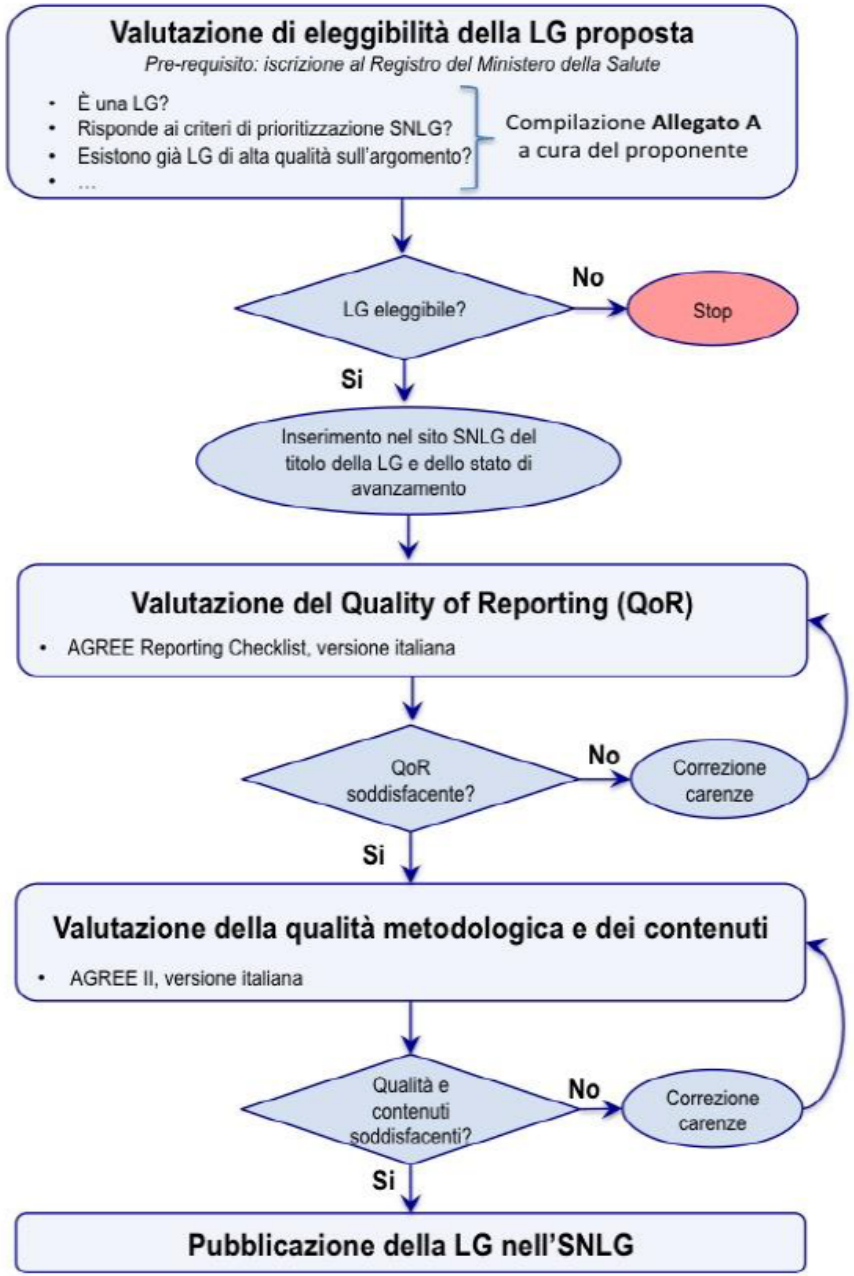
- Attività di **verifica su linee guida** che, ai sensi del comma l, sono «**elaborate da**:
  - **enti** ed **istituzioni** pubblici e privati nonché dalle **società scientifiche** e dalle **associazioni tecnico-scientifiche** delle professioni sanitarie iscritte in **apposito elenco** istituito e regolamentato con decreto del Ministro della salute,
    - da aggiornare con cadenza biennale

Courtesy of Primiano Iannone

Sistema nazionale linee guida - ISS

Processo di valutazione delle LG proposte da soggetti ex art.5 L. n.24/17 per la pubblicazione nell'SNLG

Courtesy of Primiano Iannone



Le richieste di valutazione vanno inviate online attraverso la **piattaforma SNLG**

Workflow sviluppato dal CNEC con il supporto del centro collaboratore **GIMBE**

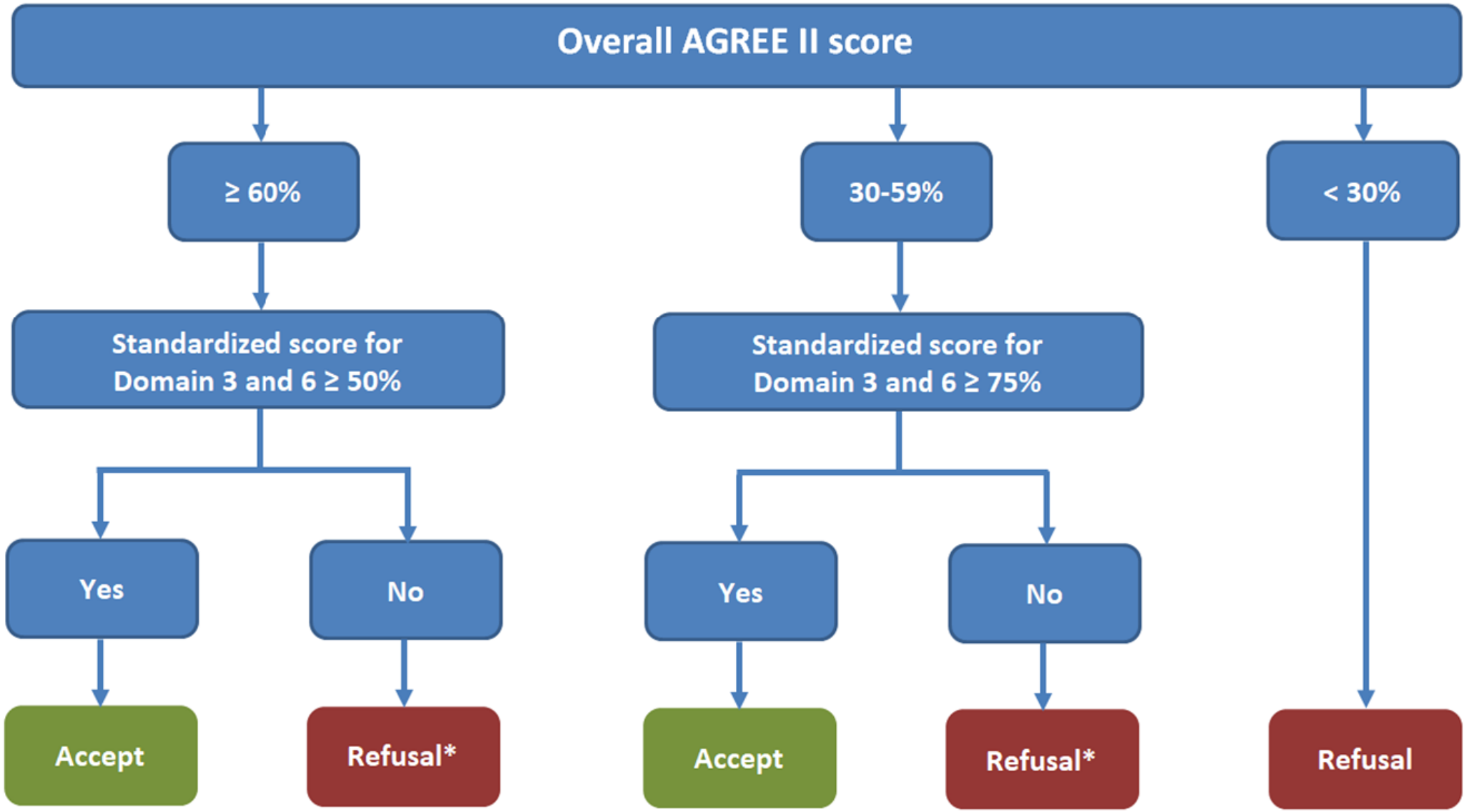
AGREE II e AGREE Reporting Checklist

APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION

Dimensione 1	OBIETTIVI E AMBITI DI APPLICAZIONE (1-3)
Dimensione 2	COINVOLGIMENTO DEGLI STAKEHOLDER (4-6)
Dimensione 3	RIGORE METODOLOGICO (7-14)
Dimensione 4	CHIAREZZA ESPOSITIVA (15-17)
Dimensione 5	APPLICABILITÀ (18-21)
Dimensione 6	INDIPENDENZA EDITORIALE (22-23)

benefici potenziali LG proporzionali alla loro qualità → **strumento di valutazione standardizzato**

Courtesy of Primiano Iannone



* Accept with reserve if no other CPG on specific topic is available

Courtesy of Primiano Iannone

Archivi categoria: *Produzione*

Strumenti per gli sviluppatori di LG

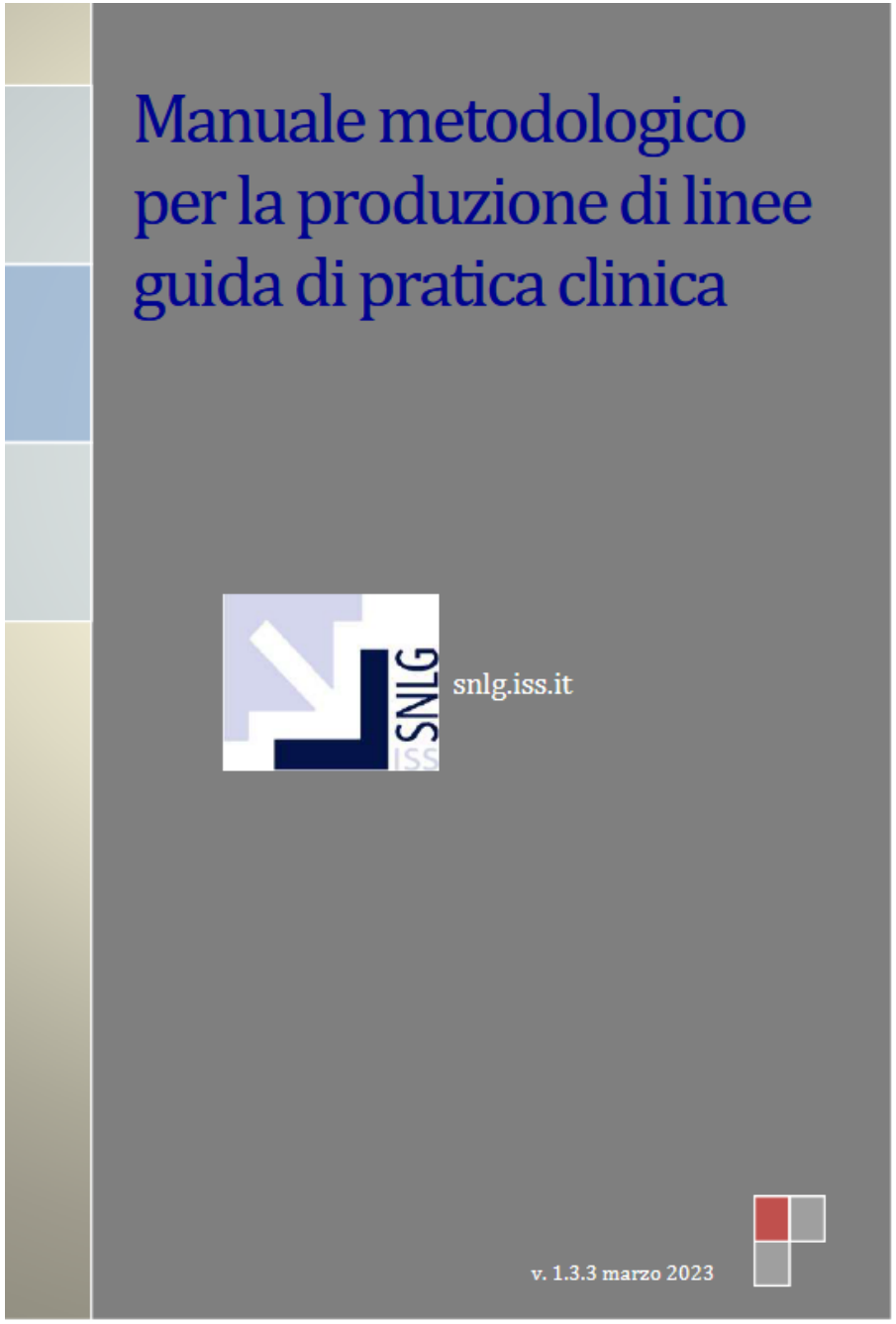
In questa sezione sono riportati gli **standard metodologici di riferimento** che il CNEC raccomanda per la produzione e la valutazione critica di LG destinate a essere pubblicate nel sito SNLG.

Manuale metodologico ISS per la produzione di LG: rappresenta il nuovo manuale di riferimento per la produzione di LG dell'Istituto Superiore di Sanità. Incorpora la metodologia GRADE e tiene conto dell'esperienza maturata nella produzione di LG da parte delle maggiori organizzazioni internazionali dedicate allo scopo, adattata al contesto italiano.

E' disponibile una nuova versione del manuale [v. 1.3.2, scarica qui]. Rispetto alla v .1.3, sono state apportate delle modifiche, tra cui:

- aggiornamento Sezione 6.1

Il metodo GRADE [scarica file]: è il metodo adottato da un numero sempre maggiore di organizzazioni internazionali e agenzie di sanità pubblica quale standard di riferimento per la valutazione della qualità delle prove e la produzione di raccomandazioni cliniche che tengano conto in modo esplicito dei diversi fattori che, oltre alla qualità delle evidenze, condizionano la forza e la direzione delle raccomandazioni, incluso un chiaro bilancio dei rischi e dei benefici delle opzioni



Versione 2023

Sviluppato dal CNEC in collaborazione con il GRADE Working Group

Perché il metodo GRADE?

Vantaggi del GRADE rispetto precedenti sistemi di grading:

- netta separazione tra valutazione della qualità delle evidenze e forza delle raccomandazioni
- valutazione esplicita dell'importanza degli outcome di strategie alternative
- criteri espliciti per aumentare e ridurre il rating della qualità delle evidenze
- processo sistematico e trasparente che porta dalle evidenze alle raccomandazioni
- considerazione dei valori e delle preferenze dei pazienti e dei professionisti
- interpretazione chiara delle raccomandazioni forti e deboli per medici, pazienti e *policy maker*

Courtesy of Primiano Iannone

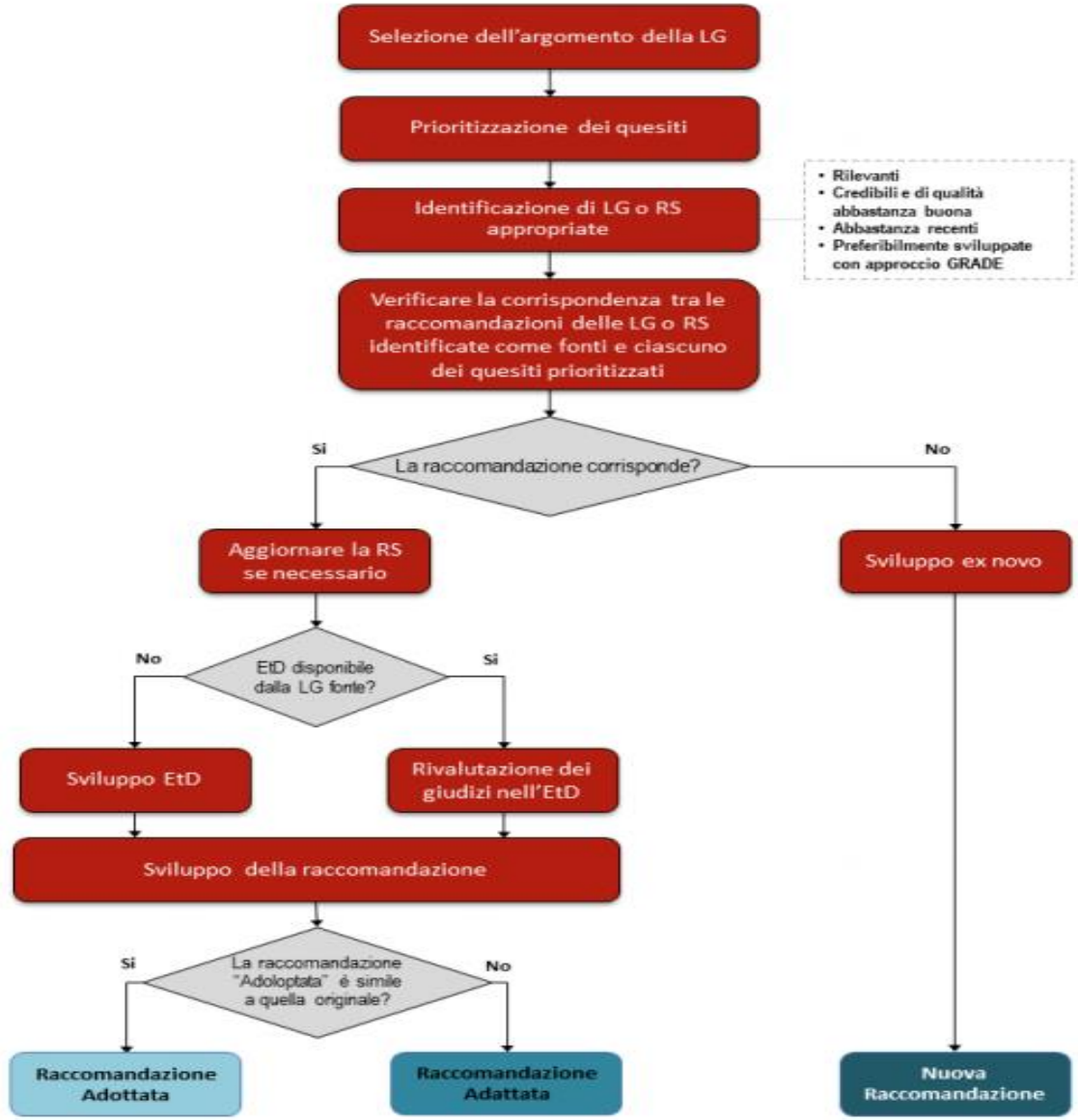


Figura 3 – Tradotta da: *Journal of Clinical Epidemiology* 2017 81, 101-110DOI: (10.1016/j.jclinepi.2016.09.009)

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Istituto Superiore di Sanità

Piattaforma SNLG 2.0

Finalità

Inserimento e valutazione di linee guida per la pubblicazione nel Sistema Nazionale Linee Guida

Gli utenti abilitati* possono richiedere la valutazione di linee guida (LG) per la loro pubblicazione nel SNLG in linea con la legge n° 24/2017 e relativi decreti attuativi.

Il CNEC:

1. verifica l'eleggibilità della LG in base a requisiti di priorità e non ridondanza
2. verifica la presenza nella LG di una previsione di impatto delle raccomandazioni sui Livelli Essenziali di Assistenza (LEA)
3. valuta la LG con criteri espliciti in termini di qualità del reporting, metodologia adottata e rilevanza delle raccomandazioni rispetto alle evidenze citate
4. invia eventuali feedback al proponente per correzioni e revisioni
5. pubblica la LG nel SNLG in caso di esito positivo della valutazione

Per i dettagli riferirsi al manuale operativo.

**Enti e istituzioni pubbliche e private, società scientifiche e associazioni tecnico-scientifiche delle professioni sanitarie iscritte in apposito elenco istituito e regolamentato con DM 2 agosto 2017 (GU n. 186 del 10-8-2017).*

Un indirizzo e-mail può essere associato ad un solo account. Finché l'account non viene approvato dal CNEC è possibile registrarsi nuovamente indicando il medesimo indirizzo e-mail nel qual caso fa fede l'ultima registrazione effettuata

Login

Registrazione Produttore di linee guida

Registrazione Valutatori di linee guida

Area stakeholder per le LG prodotte dall'ISS

Gli stakeholder possono partecipare allo sviluppo delle LG ISS attraverso la procedura di consultazione pubblica

Procedure di invio e valutazione di Linee Guida per la pubblicazione nel SNLG

Manuale operativo

CENTRO NAZIONALE
ECCELLENZA CLINICA,
QUALITÀ E SICUREZZA DELLE CURE

Versione 3.1 – marzo 2023