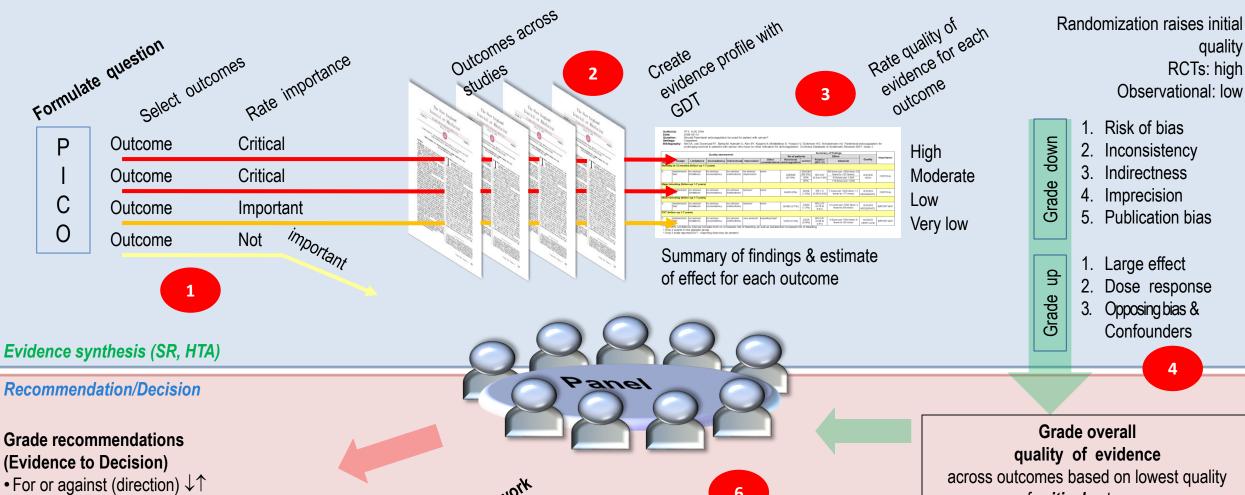
# SOF: Summary of Findings tables



quality RCTs: high Observational: low 1. Risk of bias 2. Inconsistency

3. Indirectness

4. Imprecision

5. Publication bias

1. Large effect

2. Dose response

3. Opposing bias & Confounders

#### quality of evidence

across outcomes based on lowest quality of *critical* outcomes

## EtD framework with GRADEpro

Strong or conditional/weak (strength)

recommendations):

Quality of evidence

Balance benefits/harms

Values and preferences

Resource use (if applicable)

Feasibility, equity and acceptability

By considering balance of consequences (evidence to

Ind Co Se	regulataken. Plasetes with advorwed conners, welforut either dherespectic or prophylatric indication for articosopolation integration. Fix anticosopolation with a properties of the property of the applicable form a individual discription making perspective).								
	DOMAIN	AMMENT	Research unidence	EXPLANATION ADDITIONAL INFORMATION					
11/2003	What is the contail quality of exhibition? In their high or endersite quality existence? The higher the quality of exclusion, the during the during transmissendation.	☐ High ☑ Micdenate ☐ Low ☐ Very low	Office Chicago. Algo Medicals Law Pleas 1. Harysten II III III II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II 1. Harysten II II II II II II II II 1. Harysten II II II II II II II II II 1. Harysten II 1. Harysten II	deal NY wildow Vis-del of food and down and increase the risk of heading. There is high-quality evolutions that at one past, treatment with to solve the third of approximate VIE. Expendition was an assessment for down girding for nonfactorings class (MMC) 4, 500 for 3 and 2 and					
10/01/21 1 1/1/83	What is the balance below to the bolished below to the balance below to the below the balance below to the below the balance below to the balance below to be bal	Earselin colonigi herrori harises	1. Marketing C	Access the evolution profits in continue profits in continue profits the continue profits of the profit for the					

**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?

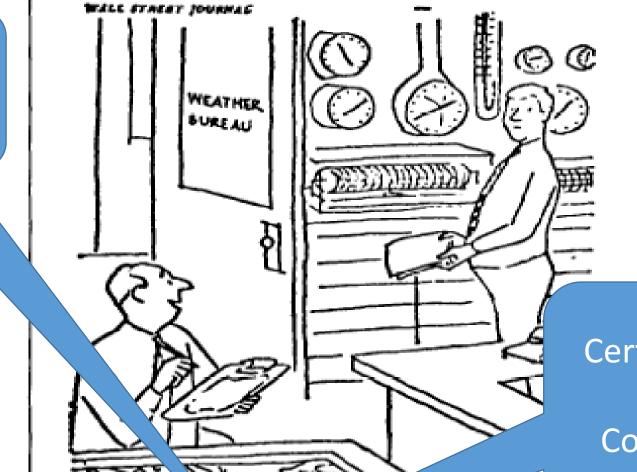
#### What are we grading?

- two components
- quality of body of evidence
  - extent to which confidence in estimate of effect adequate to support decision
    - high, moderate, low, very low
- strength of recommendation
  - strong and weak

#### grades of evidence and Interpretation

Quality of evidence = certainty of the results

### Magnitude of Effect



Likelihood of and certainty in the evidence or effect

Certainty or Quality of evidence
Confidence in effect

I figure there's a 40% chance of showers and a 10% chance we know what we are talking about.

#### RISK OF BIAS/QUALITY OF EVIDENCE

• RISK OF BIAS: concerns with the internal validity of study results, i.e. the systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted

### Risk of bias table for RCTs Cochrane Collaboration

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk of bias	
(selection bias)	High risk of bias	
	Unclear risk of bias	
Allocation concealment (selection	Low risk of bias	
bias)	High risk of bias	
	Unclear risk of bias	
Blinding of participants and personnel	Low risk of bias	
(performance bias)	High risk of bias	
	Unclear risk of bias	
Blinding of outcome assessment	Low risk of bias	
(detection bias)	High risk of bias	
	Unclear risk of bias	
Incomplete outcome data (attrition	Low risk of bias	
bias)	High risk of bias	
	Unclear risk of bias	
Selective reporting (reporting bias)	Low risk of bias	
	High risk of bias	
	Unclear risk of bias	

#### RISK OF BIAS/QUALITY OF EVIDENCE

- QUALITY OF EVIDENCE (according to GRADE): more extensive evaluation considering also other domains:
- risk of bias
- inconsistency of the results across the studies
- imprecision
- indirectness
- risk of publication bias
- magnitude of the effect
- dose response gradient
- Residual confounding

#### **Quality of evidence**

- GRADE is "outcome centric":
  - rating is made for each outcome, and quality may differ -indeed, is likely to differ - from one outcome to another within a single study and across a body of evidence
- E.g.: <u>subjective</u> outcomes are prone to performance and detection bias, while <u>objective</u> outcomes are not
- E.g. **one outcome** within a review **could have imprecision** in the pooled estimate of the effect, while **another could have not**

#### grades of evidence and Interpretation

Symbol	Quality?	Interpretation 2
$\bigcirc \bigcirc $	High≀	Wellare Ivery Iton fident It hat It he It rue Ite ffect It ies It lose Ito It hat Ito fill
	nigne	the the the theoretical the theoretical th
		Wetaremoderatelyconfidentingheteffectestimate: The true?
$\oplus \oplus \ominus \bigcirc \boxed{?}$	<b>Moderate</b> ?	effect 13 solikely 13 to 3 be 13 to set to 13 the 12 stimate 13 for the 12 for the 12 for the 13 fo
		there is the possibility in the table is the real state of the rea
$\bigcirc$	Low?	Our at onfidence and the affect as timate as a limited: The arue affect a
		may@be@substantially@different@from@the@estimate@of@the@effect@
		Welhavelverydittleltonfidencednatheleffectlestimate: The drue?
	Very low?	effect 13 dikely 12 o be 3 ubstantially 12 different 12 rom 12 he 12 stimate 15 f 2
		effect?

#### **Evidence profile and Summary of findings**

**Evidence profile**: summary of evidence for a given question with a detailed quality assessment and a explicit judgment of each factor that determines the quality. Used by guideline producers

**Summary of findings**: summary of evidence for a given question with quality assessment but not the detailed judgments. Prepared within SRs

#### For each outcome:

- a) Relative risk with 95%CI
- b) Absolute risk: **SoF** presents the absolute risks in intervention and control groups with a CI around the intervention group rate, **EP** presents the risk difference with 95%CI.
- c) Number of participants (n of studies) included

### **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											
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin prophylaxis	Standard care	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Incidence of pne	incidence of pneumococcal infection, for initiation of treatment - Initiation of penicillin											
2	Randomized trials	Not serious <sup>1</sup>	serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	none <sup>5</sup>	9/248 (3.6%)	19/209 (9.1%)	<b>OR 0.37</b> (0.16 to 0.86)	55 fewer per 1000 (from 12 fewer to 75 fewer)	⊕⊕⊖⊖ LOW	CRITICAL
Deaths, for initia	ation of treatment -	Initiation of penicill	lin									
1	randomized trials	not serious <sup>6</sup>	not serious	not serious	serious <sup>4</sup>	none <sup>5</sup>	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 ef	Adverse drug effects - Nausea and vomiting											
1	randomized trials	not serious <sup>6</sup>	not serious	not serious	serious <sup>4</sup>	none <sup>5</sup>	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

#### Quando e perché fare le SoF

- Da aggiungere ad una SR che volete pubblicare per sintetizzare i risultati e la loro qualità (Summary of Findings)
- Nelle revisioni Cochrane è obbligatorio (Summary of Findings)
- Come strumento di lavoro /materiale di sintesi delle evidenze per la elaborazione di Linee Guida cliniche (Evidence Profile)

#### 1. Scegliere quali comparisons

• Molto spesso le revisioni hanno numerose comparisons

Es: ogni tipo di antipsicotico vs placebo, singoli tipi di antipsicotico vs placebo, antipsicotico A vs antipsicotico B

Es: tutti gli studi (tutti i pazienti con dipendenza da cocaina), sottogruppi di studi che includono solo certe tipologie di pazienti (solo pazienti con doppia dipendenza: eroinomani in terapia di mantenimento con metadone e dipendenti da cocaina)

• Bisogna scegliere solo le comparison più importanti (al max 4)

Es: ogni tipo di antipsicotico, tutti i pazienti

Una SoF per comparison

#### 2. Scegliere quali outcomes per la SoF

Di interesse per i pazienti e decisori

Utili per prendere decisioni cliniche

E' possibile riportarne al massimo 7 (desiderabili e indesiderabili)

In genere solo gli outcomes primari della revisione

Dovrebbero essere definiti nel protocollo

#### Outcomes

Should be importance driven NOT evidence driven

#### **Summary of findings**

Summary of finding: antibiotics for acute otitis media in children

Antibiotics compared with placebo for acute otitis media in children

Patient or population: Children with acute otitis media

Setting: High- and middle-income countries

Intervention: Antibiotics Comparison: Placebo

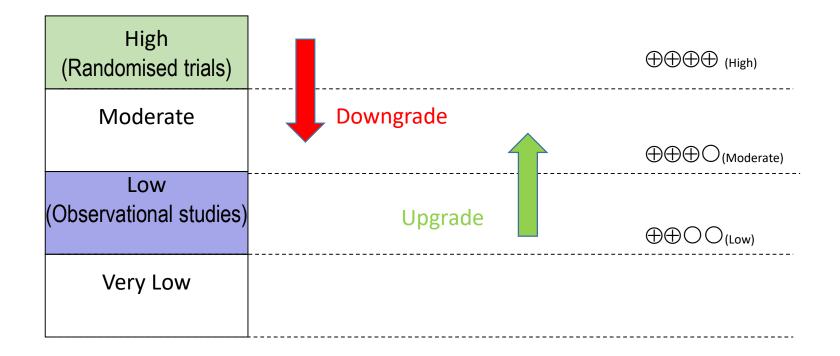
	Estimated risks	(95% CI)			Quality of the evidence (GRADE) $\oplus \oplus \oplus \oplus$ High	
	Control risk <sup>a</sup>	Intervention risk		No. of Participants		
Outcomes	Placebo	Antibiotics	Relative effect (95% CI)	(studies)		
Pain at 24h	367 per 1,000	330 per 1,000 (286-382)	RR 0.9 (0.78-1.04)	1229 (5)		
Pain at 2-7 d	257 per 1,000	185 per 1,000 (159-213)	RR 0.72 (0.62-0.83)	2791 (10)	⊕ ⊕ ⊕ ⊕ High	
Hearing, inferred from the surrogate outcome abnormal tympanometry—1 mo	350 per 1,000	311 per 1,000 (262-375)	RR 0.89 (0.75-1.07)	927 (4)	⊕ ⊕ ⊕ ○ Moderate <sup>b</sup>	
Hearing, inferred from the surrogate outcome abnormal tympanometry—3 mo	234 per 1,000	227 per 1,000 (178-290)	RR 0.97 (0.76-1.24)	808 (3)	⊕ ⊕ ⊕ ○ Moderate <sup>b</sup>	
Vomiting, diarrhea, or rash	113 per 1,000	156 per 1,000 (123-199)	RR 1.38 (1.09-1.76)	1,401 (5)	⊕ ⊕ ⊕ ○ Moderate <sup>c</sup>	

#### **QUALITY OF EVIDENCE**

Patient or population Settings: primary car Intervention: self ma Comparision: usual of	e, community, outpati nagement <sup>1</sup>	ic obstructive pulmonary ent	disease				
Outcomes	Illustrative compara		Relative effect (95% CI)	No of Participants (studies)	Quality of the	Comments	
	Assumed risk	. 3			evidence (GRADE)		
	usual care	self management					
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was <b>2.58 lower</b> (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.	
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was 0.53 lower (0.96 to 0.1 lower)		144 (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement	
Number and See comment See comment severity of exacerbations <sup>5</sup>			Not estimable <sup>5</sup>	591 (3)	See comment	Effect is uncertain	
Respiratory-related	Low risk population	6	<b>OR 0.64</b> -(0.47 to 0.89)	966	$\oplus\oplus\oplus\ominus\bigcirc$		
hospital admissions (follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)		(8)	moderate <sup>7</sup>		
,	High risk population	n <sup>6</sup>	-				
	50 per 100	35 per 100 (27 to 46)	-				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕⊖ moderate <sup>4</sup>		
Doctor and nurse visitsThe mean doctor and nurse visitsThe mean nurse visits(follow-up: 6 to 12 months)ranged across control groups frominterventi 0.02 high		The mean Doctor and nurse visits in the intervention groups was <b>0.02 higher</b> (1 lower to 1 higher)		629 (8)	⊕⊕⊕⊖ moderate <sup>8</sup>		

#### Rating quality of evidence

GRADE's approach begins with the study design.
Randomized controlled trials (RCTs) start as high-quality evidence and observational studies as low-quality evidence supporting estimates of intervention effects



## Determinants of quality/certainty of a body of evidence

- RCTs ⊕⊕⊕⊕
- observational studies ⊕⊕○○
- 5 factors that can lower quality
  - 1. limitations in detailed study design and execution (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



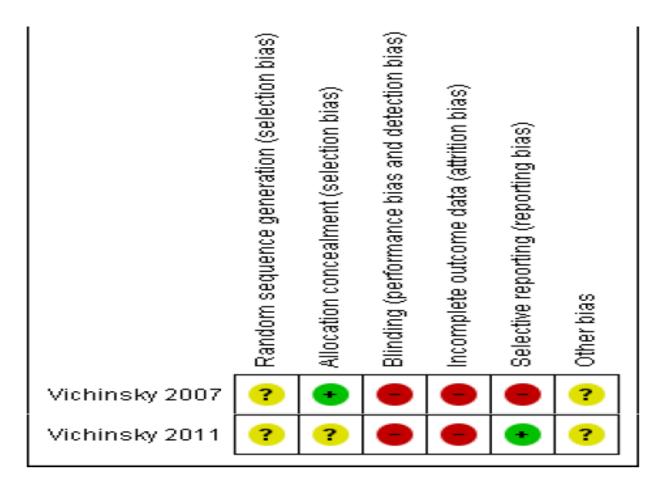






#### 1. risk of bias

Deferasirox for managing transfusional iron overload in people with sickle cell disease (Review)



#### Risk of bias

- Outcome specific
  - each trial contributes toward the estimate of magnitude of effect.
  - larger trials with many events will contribute more (look at the weight of each study in the forest plot)

## 2.Inconsistency (heterogeneity) between studies results

- Variation in size of effect (Point estimates vary widely across studies)
- Confidence intervals (CIs) show minimal or no overlap
- The statistical test for heterogeneity which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect shows a low P-value (< 0.05)</li>
- The I<sup>2</sup> which quantifies the proportion of the variation in point estimates due to among-study differences (< 40% : low, 30 e 60% :moderate, 50% e 90% :substantial, 75 e 100% : considerable)
- All statistical approaches have limitations, and their results should be seen in the context of a subjective examination of the variability in point estimates and the overlap in Cls.

	Any ant	tispsych	notic	P	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
Kampman 2003	1.3	0.8	15	1	0.9	15	28.3%	0.30 [-0.31, 0.91]	-
Reid 2005	6.1	2.1	16	3.5	2.3	15	20.3%	2.60 [1.05, 4.15]	_ <del>-</del>
Tapp 2015	0.4	1.26	29	1.63	2.39	31	25.6%	-1.23 [-2.19, -0.27]	-
Winhusen 2007	2.8	2.45	60	3.44	2.76	59	25.8%	-0.64 [-1.58, 0.30]	
Total (95% CI)			120			120	100.0%	0.13 [-1.08, 1.35]	•
Heterogeneity: Tau <sup>2</sup> = 1.26; Chi <sup>2</sup> = 19.78, df = 3 (P = 0.0002); I <sup>2</sup> = 85° Test for overall effect: $Z = 0.22$ (P = 0.83)					)002);	² = 85°	<b>%</b>		-10 -5 0 5 10 Favours any antipsychotic Favours placebo

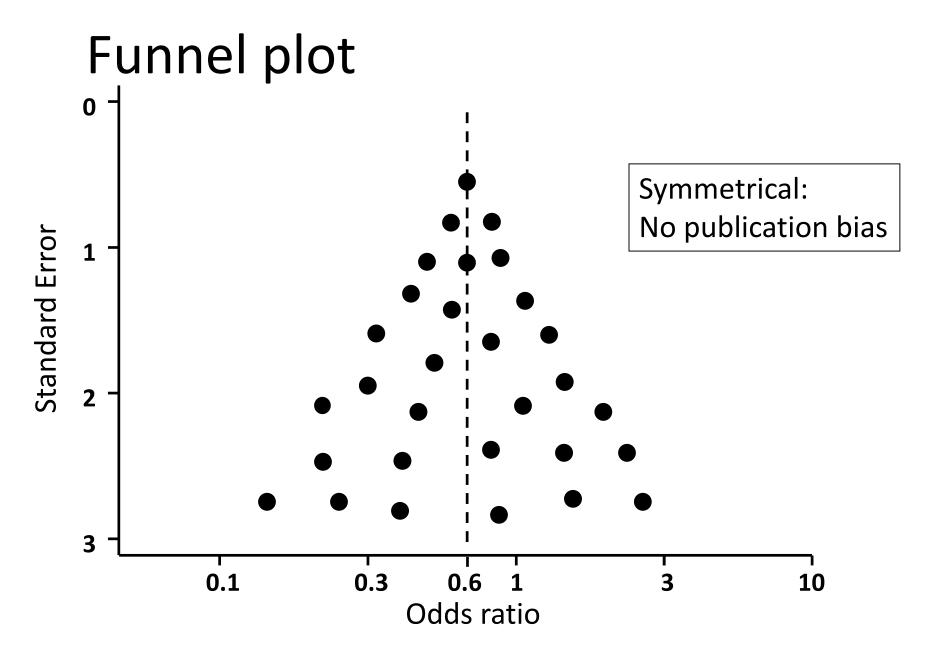
### 3. Directness of Evidence generalizability, transferability, applicability

- differences between PICO and available evidence in
  - populations/patients (interested in children found adults population)
  - interventions (interested in high dosage, found low dosage, interested in long treatment, found short, etc)
  - outcomes (interested in important but we found surrogate; e.g hip fracture vs bone density; interested in long term but found short term results)
- indirect comparisons
  - interested in A versus B
  - found A versus C and B versus C

#### 4. Publication Bias

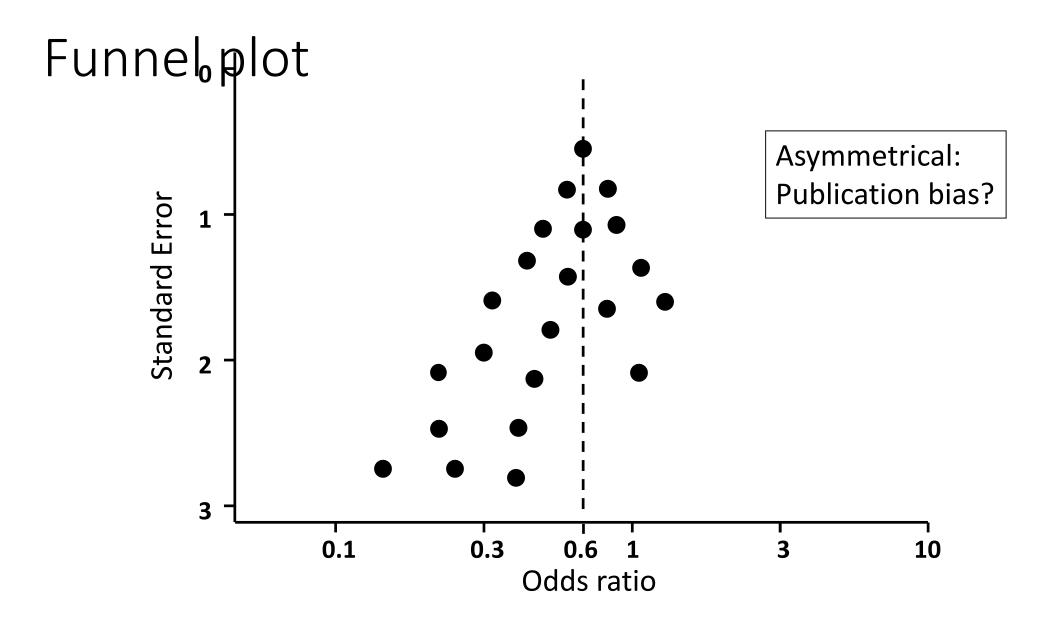
#### Consider rating down if:

- You find systematic reviews performed early, when only few initial studies are available, that will overestimate effects when "negative" studies face delayed publication. Early positive studies, particularly if small in size, are suspect.
- You find only small "positive" studies, mainly if sponsored by industry
- Funnel plot showing asimmetry but
- Funnel plot should be seen as a generic means of displaying small-study effects a tendency for the intervention effects estimated in smaller studies to differ from those estimated in larger studies (Sterne 2000). Small-study effects may be due to reasons other than publication bias (low methodological quality, chance, patients characteristics).
- Funnel plot should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry



#### **Funnel plot**

- On the horizontal axis: measure of treatment effect
- On the **vertical axis**: standard error (SE) of the intervention effect estimate: measure of **precision of the estimate**; SE is determined by sample size, and by the number of participants experiencing the event for dichotomous outcomes, and the standard deviation of responses for continuous outcomes.
- Precision of the estimated intervention effect increases as the size of the study increases. Effect estimates from small studies will therefore scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias the plot should approximately resemble a symmetrical funnel plot.



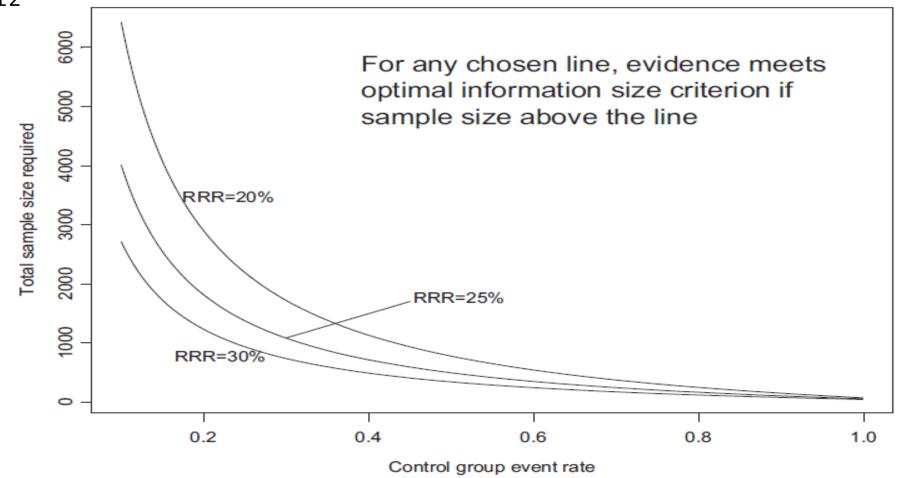
#### 5. Imprecision of the overall estimate

- Wide confidence intervals (CIs inform the impact of random error on evidence quality; CI expresses the range in which the truth plausibly lies)
- Small number of events
- Small sample size

#### **Optimal information size**

- We suggest the following:
- if the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial, consider rating down for imprecision. Authors have referred to this threshold as the "optimal information size" (OIS)

Required sample size (assuming  $\alpha$  of 0.05, and  $\beta$  of 0.2) for RRR of 20%, 25%, and 30% across varying control event rates. For example, if the best estimate of control event rate was 0.2 and one specifies an RRR of 25%, the OIS is approximately 2,000 patients (GRADE guideline n.6 Journal of Clinical Epidemiology 64 (2011) 128361203)



stimal information size given  $\alpha$  of 0.05 and  $\beta$  of 0.2 for varying control event rates and relative risks.

#### Power is more closely related to number of events than to sample size

(GRADE guideline n.6 Journal of Clinical Epidemiology 64 (2011) 1283e1293)

Calculating the OIS for dichotomous outcome requires specifying:

- probability of detecting a false effect type I error (a; usually 0.05)
- probability of detecting a true effect power (usually 80% [power = 1 type II error; β; usually 0.20])
- realistic relative risk reduction (RRR; we suggest a default of 25%)
- control event rate (we suggest the median of the available trials, or the rate from a dominating trial, if it exists).

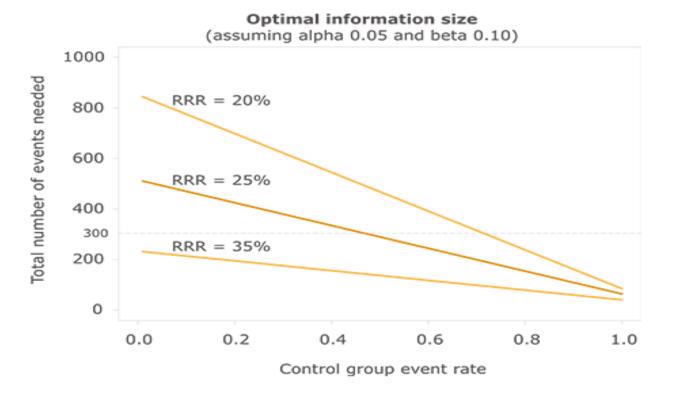


Table 1: Optimal information size implications from Figure above

400 or more

Total Number of Events	Relative Risk Reduction	Implications for meeting OIS threshold
100 or less	<u>&lt;</u> 30%	Will almost never meet threshold whatever control event rate
200	30%	Will meet threshold for control event rates for ~ 25% or greater
200	25%	Will meet threshold for control event rates for ~ 50% or greater
200	20%	Will meet threshold only for control event rates for ~ 80% or greater
300	≥ 30%	Will meet threshold
300	25%	Will meet threshold for control event rates ~ 25% or greater
300	20%	Will meet threshold for control event rates ~ 60% or greater
400 or more	≥ <b>25</b> %	Will meet threshold for any control event rate

20%

Will meet threshold for control event rates of ~ 40% or greater

#### OIS for continuous outcomes

- Authors can calculate the OIS for continuous variables in exactly the same way they can for binary variables by specifying the  $\alpha$  and  $\beta$  errors (we have suggested 0.05 and 0.2) and the  $\Delta$  ( i.e. the difference one wishes to detect as clinically relevant ), and choosing an appropriate standard deviation from one of the relevant studies.
- A particular challenge in calculating the OIS for continuous variables arises when studies have used different instruments to measure a construct, and the pooled estimate is calculated using a standardized mean difference.
- we suggest authors choose one of the available instruments (ideally, one in which an estimate of the minimally important difference is available) and calculate an OIS using that instrument

#### OIS for <u>continuous</u> outcomes

whenever there are sample sizes that are less than 400, review authors and guideline developers should certainly consider rating down for imprecision.

## **Downgrading and OIS**

- if OIS **not met** downgrade for imprecision
- If OIS met and the 95% CI excludes a relative risk (RR) of 1.0 (statistically significant results), precision is adequate.
- if OIS met but the 95% CI includes a RR of 1 (null effect), authors should consider whether CIs include appreciable benefit or harm (we suggest a RR of under 0.75 or over 1.25 as a rough guide); if yes downgrading for imprecision may be appropriate.

## 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

## What can raise quality?

### 2. dose response relation

- higher INR increased bleeding
- 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%)

## 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.

### Cos'è la Summary Of Findings

• Summary of findings: tabular presentation of key information about relevant outcomes of alternative health care interventions. It presents information about the body of evidence, key numerical results, and summary judgment about the certainty of underlying evidence for each outcome. SoF table has been chosen by the Cochrane Collaboration to present main findings of a systematic review.

**Evidence profile**: summary of evidence for a given question; it presentes relevant information about the body of evidence, key numerical results, and a **detailed quality assessment** and a explicit judgment of each factor that determines the quality. Used by guideline producers

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

		-	Quality assessment				Nº of pa	atients		Effect		Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin prophylaxis	Standard care	Relative (95% CI)	Absolute (95% CI)	Quality	
Incidence of pne	ncidence of pneumococcal infection, for initiation of treatment - Initiation of penicillin											
2	Randomized trials	Not serious <sup>1</sup>	serious <sup>2</sup>	not serious <sup>3</sup>	serious <sup>4</sup>	none <sup>5</sup>	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 initia	ation of treatment -	Initiation of penicil	lin									
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Adverse drug ef	Adverse drug effects - Nausea and vomiting										•	
1	randomized trials	not serious <sup>6</sup>	not serious	not serious	serious <sup>4</sup>	none <sup>5</sup>	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

### **PICO**

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes	Illustrative compara	Relative effect	No of Participants	Quality of the	Comments	
	Assumed risk	Corresponding risk	(95% CI)	(studies)	evidence (GRADE)	
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	life ranged across control groups from	The mean Quality of Life in the intervention groups was 2.58 lower (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was <b>0.53 lower</b> (0.96 to 0.1 lower)		1 <b>44</b> (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement
Number and	See comment	See comment	Not	591	See .	Effect is uncertain
severity of exacerbations <sup>5</sup>			estimable <sup>5</sup>	(3)	comment	
Respiratory-related hospital admissions	LOW risk bobulation		OR 0.64 -(0.47 to	966 (8)	⊕⊕⊕()	
(follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)	0.89)	(0)	moderate <sup>7</sup>	
,	High risk population					
	50 per 100	35 per 100 (27 to 46)	-			
Emergency	The mean	The mean Emergency		328	$\oplus\oplus\oplus\ominus$	
department visits for lung diseases (follow-up: 6 to 12 months)	emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per	department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		(4)	moderate <sup>4</sup>	
Doctor and nurse	person per year The mean doctor	The mean Doctor and		629	###O	
visits (follow-up: 6 to 12 months)	and nurse visits ranged across control groups from 1 to 5 vists per	nurse visits in the intervention groups was <b>0.02 higher</b> (1 lower to 1 higher)		(8)	moderate <sup>8</sup>	

## Primary outcomes – up to 7

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes	Illustrative compara Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was <b>2.58 lower</b> (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to b important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was <b>0.53 lower</b> (0.96 to 0.1 lower)		1 <b>44</b> (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement
Number and severity of exacerbations <sup>5</sup>	See comment	See comment	Not estimable <sup>5</sup>	591 (3)	See comment	Effect is uncertain
Respiratory-related	Low risk population	OR 0.64	966	$\oplus \oplus \oplus \bigcirc$		
hospital admissions (follow-up: 3 to 12 months)	10 per 100	- 400	-(0.47 to 0.89)	(8)	moderate <sup>7</sup>	
,	High risk population	n <sup>6</sup>	-			
	50 per 100	35 per 100 (27 to 46)	-			
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕⊖ moderate <sup>4</sup>	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 vists per	The mean Doctor and nurse visits in the intervention groups was <b>0.02 higher</b> (1 lower to 1 higher)		629 (8)	⊕⊕⊕⊖ moderate <sup>8</sup>	

- Choose primary outcomes early – avoid reporting bias
- Choose patient important outcomes
- Include primary outcomes
   even if no information
- Describe the outcome scale, follow-up

### Results – Baseline risks (Assumed Risk)

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

**Settings:** primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes	Illustrative compara Assumed risk	effect	No of Participants (studies)	Quality of the evidence	Comments	
	usual care	self management			(GRADE)	
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was 2.58 lower (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was <b>0.53 lower</b> (0.96 to 0.1 lower)		144 (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement
Number and severity of exacerbations <sup>5</sup>	See comment	See comment	Not estimable <sup>5</sup>	591 (3)	See comment	Effect is uncertain
Respiratory-related	Low risk population	OR 0.64	966	$\oplus\oplus\oplus\bigcirc$		
hospital admissions (follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)	-(0.47 to 0.89)	(8)	moderate <sup>7</sup>	
,	High risk population <sup>6</sup>		_			
	50 per 100	35 per 100 (27 to 46)	-			
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕⊜ moderate <sup>4</sup>	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 vists per	The mean Doctor and nurse visits in the intervention groups was 0.02 higher (1 lower to 1 higher)		629 (8)	⊕⊕⊕⊖ moderate <sup>8</sup>	

- From meta-analysis
- Needs to be representative of population
- Can present mean, range, low risk, moderate risk, high risk

# Results – Risk with intervention (Corresponding Risk)

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes	Illustrative compara	Relative	No of	Quality of	Comments	
	Assumed risk	Corresponding risk	effect (95% CI)	Participants (studies)	the evidence (GRADE)	
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was <b>2.58 lower</b> (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was <b>0.53 lower</b> (0.96 to 0.1 lower)		144 (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement
Number and severity of exacerbations <sup>5</sup>	See comment	See comment	Not estimable <sup>5</sup>	591 (3)	See comment	Effect is uncertain
Respiratory-related	Low risk population	OR 0.64	966	$\oplus \oplus \oplus \bigcirc$		
hospital admissions (follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)	(0.47 to 0.89)	(8)	moderate <sup>7</sup>	
•	High risk populatio					
	50 per 100	<b>35 per 100</b> (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕⊖ moderate <sup>4</sup>	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 vists per	The mean Doctor and nurse visits in the intervention groups was <b>0.02 higher</b> (1 lower to 1 higher)		629 (8)	⊕⊕⊕⊜ moderate <sup>8</sup>	

- Calculated using the Relative Effect or Mean Differences
- Confidence intervals provided

### Results – Relative effects

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes	Illustrative compara	Relative effect	No of Participants	Quality of the	Comments	
	Assumed risk	Corresponding risk	(95% CI)	(studies)	evidence (GRADE)	
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was 2.58 lower (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea i the intervention groups was <b>0.53 lower</b> (0.96 to 0.1 lower)	•	144 (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement
Number and severity of exacerbations <sup>5</sup>	See comment	See comment	Not estimable <sup>5</sup>	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions	Low risk population	OR 0.64 (0.47 to	966 (8)	⊕⊕⊕⊖		
(follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)	0.89)	(0)	moderate <sup>7</sup>	
,	High risk population					
	50 per 100	<b>35 per 100</b> (27 to 46)	_			
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups ware 0.1 higher (0.2 lower to 0.3 higher		328 (4)	⊕⊕⊕⊖ moderate <sup>4</sup>	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 vists per	The mean Doctor and nurse visits in the intervention groups we <b>0.02 higher</b> (1 lower to 1 higher)	s	629 (8)	⊕⊕⊕⊖ moderate <sup>8</sup>	

- From meta-analysis
- Relative Risks, Odds ratios, Hazard ratios, etc.

### Results – Number of Participants/studies

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes	Illustrative compara	Relative effect	No of Participants	Quality of the	Comments	
	Assumed risk	Corresponding risk	(95% CI)	(studies)	evidence (GRADE)	
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	·	The mean Quality of Life in the intervention groups was <b>2.58 lower</b> (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊜ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was <b>0.53 lower</b> (0.96 to 0.1 lower)		144 (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement
Number and severity of exacerbations <sup>5</sup>	See comment	See comment	Not estimable	591 5 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions	Low risk population	OR 0.64 -(0.47 to	966 (8)	⊕⊕⊕()		
(follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)	0.89)	(0)	moderate <sup>7</sup>	
,	High risk population					
	50 per 100	35 per 100 (27 to 46)	_			
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		328 ( <b>4</b> )	⊕⊕⊕⊖ moderate <sup>4</sup>	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 vists per	The mean Doctor and nurse visits in the intervention groups was <b>0.02 higher</b> (1 lower to 1 higher)	i	629 (8)	⊕⊕⊕⊖ moderate <sup>8</sup>	

- From meta-analysis
- Or when no meta-analysis from individual studies

### Results

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes			Relative effect	No of Participants	Quality of the	Comments
	Assumed risk	Corresponding risk	(95% CI)	(studies)	evidence (GRADE)	
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)		The mean Quality of Life in the intervention groups was 2.58 lower (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	ranged across control groups from 1.2 to 4.1 points	the mean Dysphoea in the intervention groups was 0.53 lower (0.96 to 0.1 lower)		(2)	low <sup>3,4</sup>	improvement
Number and severity of exacerbations <sup>5</sup>	See comment	See comment	Not estimable <sup>5</sup>	591 (3)	See comment	Effect is uncertain
Respiratory-related	Low risk population <sup>6</sup>		OR 0.64	966	⊕⊕⊕⊖	
hospital admissions (follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)	-(0.47 to 0.89) -	(8)	moderate <sup>7</sup>	
·	High risk population	n <sup>6</sup>				
	50 per 100	35 per 100 (27 to 46)	_			
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕⊖ moderate <sup>4</sup>	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 vists per	The mean Doctor and nurse visits in the intervention groups was <b>0.02 higher</b> (1 lower to 1 higher)		629 (8)	⊕⊕⊕⊖ moderate <sup>8</sup>	

- Describes the score on a scale (38 to 60 points)
- Describes change on the scale with intervention (2.58 points lower)

### Results – Outcomes not reported / not measured / not pooled

#### Self management for patients with chronic obstructive pulmonary disease Patient or population: patients with chronic obstructive pulmonary disease **Settings:** primary care, community, outpatient Intervention: self management<sup>1</sup> Comparision: usual care **Outcomes** Illustrative comparative risks\* (95% CI) Relative No of Quality of Comments Participants the effect Assumed risk Corresponding risk (95% CI) (studies) evidence (GRADE) usual care self management **Quality of Life** The mean quality of The mean Quality of 698 $\bigcirc \oplus \oplus \bigcirc$ Lower score indicates St George's life ranged across Life in the intervention (7) better quality of life. A moderate<sup>2</sup> control groups from change of less than 4 Respiratory groups was Questionnaire. Scale 38 to 60 points points is not shown to be 2.58 lower from: 0 to 100. (5.14 to 0.02 lower) important to patients. (follow-up: 3 to 12 months) Dyspnoea The mean dyspnoea The mean Dyspnoea in 144 Lower score indicates $\Theta\Theta\ThetaOO$ Borg Scale, Scale ranged across the intervention groups (2) $low^{3,4}$ improvement from: 0 to 10. control groups from (follow-up: 3 to 6 0.53 lower 1.2 to 4.1 points months) (0.96 to 0.1 lower) See comment 591 Number and See comment Not See Effect is uncertain severity of estimable<sup>5</sup> (3) comment exacerbations<sup>5</sup> Respiratory-related OR 0.64 966 Low risk population<sup>6</sup> $\Theta \oplus \Theta \cap$ hospital admissions (0.47 to (8) moderate<sup>7</sup> 10 per 100 7 per 100 (follow-up: 3 to 12 0.89) (5 to 9) months) High risk population<sup>6</sup> 50 per 100 35 per 100 (27 to 46) The mean Emergency 328 Emergency The mean $\Theta \oplus \Theta \cap$ department visits department visits for emergency **(4)** moderate<sup>4</sup> for lung diseases department visits for lung diseases in the (follow-up: 6 to 12 lung diseases intervention groups was months) ranged across 0.1 higher control groups from (0.2 lower to 0.3 higher) 0.2 to 0.7 visits per person per year Doctor and nurse The mean doctor The mean Doctor and 629 $\Theta \oplus \Theta \oplus$ and nurse visits nurse visits in the (8) visits moderate<sup>8</sup> (follow-up: 6 to 12 ranged across intervention groups was months) control groups from 0.02 higher

(1 lower to 1 higher)

1 to 5 vists per

- Outcomes without data are still presented
- Outcomes not pooled are still presented and graded

### Comments

#### Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management<sup>1</sup>

Outcomes	Illustrative compara	Relative effect	No of Participants	Quality of the	Comments	
	Assumed risk	Corresponding risk	(95% CI)	(studies)	evidence (GRADE)	
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was <b>2.58 lower</b> (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate <sup>2</sup>	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was <b>0.53 lower</b> (0.96 to 0.1 lower)		144 (2)	⊕⊕⊖⊖ low <sup>3,4</sup>	Lower score indicates improvement
Number and severity of exacerbations <sup>5</sup>	See comment	See comment	Not estimable <sup>5</sup>	591 (3)	See comment	Effect is uncertain
Respiratory-related	Low risk population	OR 0.64	966	$\oplus \oplus \oplus \bigcirc$		
hospital admissions (follow-up: 3 to 12 months)	10 per 100	<b>7 per 100</b> (5 to 9)	-(0.47 to 0.89)	(8)	moderate <sup>7</sup>	
,	High risk populatio					
	50 per 100	35 per 100 (27 to 46)	_			
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was <b>0.1 higher</b> (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕⊖ moderate <sup>4</sup>	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 vists per	The mean Doctor and nurse visits in the intervention groups was <b>0.02 higher</b> (1 lower to 1 higher)		629 (8)	⊕⊕⊕⊖ moderate <sup>8</sup>	

- More description
- E.g. relevance of findings, notes when no data, no meta-analysis, or metaanalysis plus studies not in meta-analysis

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