Cochrane in Italia
Tra prove di efficacia e pratica clinica
Seminario n.3

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Temi trattati

I nuovi strumenti per la valutazione della qualità :

ROBINS-I

MECIR

La nuova organizzazione di Cochrane:

la centralizzazione della valutazione di qualità; la Cochrane Editorial Unit (CEU);

ROBINS-I

“Risk Of Bias In Non-randomized Studies - of Interventions “

Sterne J et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016;355:i4919

OBBIETTIVO DI UNA REVISIONE che include studi non randomizzati

- Valutare l'effetto/efficacia di un intervento
- Valutare la frequenza di eventi avversi/complicanze
- Analizzare i fattori di rischio di una malattia
- Valutare l'accuratezza diagnostica di un test
- Analizzare i fattori prognostici di una malattia

REVISIONI SISTEMATICHE DI STUDI NON RANDOMIZZATI

Tutto meno standardizzato, tutto meno certo, tutto più complesso

La maggioranza delle SR Cochrane non include studi non randomizzati

Negli ultimi anni Cochrane ha riconosciuto la necessità di considerare l'evidenza che deriva da studi osservazionali

Nel 2016 è stata pubblicata la checklist 'ufficiale' Cochrane per gli studi non randomizzati (ROBINS-I)

Criteri generali per includere NRS

- To provide evidence of the effects (benefit or harm) of **interventions that cannot be randomized**, or which are **extremely unlikely to be studied in randomized trials** (e.g. surgical intervention, rehabilitation intervention, psychotherapeutic intervention, mass media campaign, normative intervention, public health)
- To provide evidence of effects (benefit or harm) on **outcomes that cannot be adequately studied in randomized trials**, such as long-term , rare outcomes and adverse effects, or outcomes that were not known to be important when existing, major randomized trials were conducted.
- To provide evidence of effects of interventions for **participants unlikely to be included in RCTs** (e.g. children, rare disease, late stage of serious diseases) (Cochrane Handbook 2011)

Studi non randomizzati

- problema principale degli studi non rand: i **fattori prognostici e di confondimento** (noti e non noti) non sono bilanciati tra i gruppi perché l'assegnazione non è casuale. Quindi i gruppi possono essere e sono il più delle volte **non confrontabili al baseline**

- c'è molto meno controllo delle condizioni in cui si svolge lo studio :modalità di reclutamento, somministrazione del trattamento sperimentale, altri trattamenti (**cointervention)**, modalità di raccolta outcome. Sono studi osservazionali, cioè descrivono ciò che normalmente accade : raccolgono dati derivanti dalla pratica clinica, che non è standardizzata né precisa

- Il più delle volte il **quality of reporting** è scadente, quindi si fa fatica a capire cosa è stato effettivamente fatto (CONSORT per RCTs dal 2001, STROBE dal 2007)

- Sono **molto diversi fra loro**: si va da studi scritti molto chiaramente con metodologia rigorosa descritta nel dettaglio a studi in cui non si capisce quasi nulla e fatti molto male

Definizione di studio non randomizzato

I NRS sono molti e con disegni molto diversi

- Non tutti sono adatti per rispondere, in modo più o meno valido, alla domanda relativa alla esistenza di una relazione causa effetto fra la variabile indipendente e quella dipendente

Sperimentali

- Controlled before after studies (CBA)
- Interrupted time series analysis (ITS)

Osservazionali

- Studi di coorte prospettici e retrospettivi
- Studi caso controllo
- Serie di casi
- Indagini trasversali (cross sectional surveis)

Risk o bias

Quali checklist scegliere per la valutazione della qualità metodologica/rischio di bias?

The variety of study designs classified as NRS, and their varying susceptibility to different biases, makes it difficult to produce a generic robust tool that can be used to evaluate risk of bias. Within a review that includes NRS of different designs, several tools for assessment of risk of bias may need to be created.

Inclusion of a knowledgeable methodologist in the review team is essential to identify the key areas of weakness in the included study designs. (Cochrane Handbook Higgins 2011)

Check list per risk of bias of NRS

- Cohort studies: New Castle Ottawa scale
- Case control studies: New Castle Ottawa scale
- Cross sectional surveis: New Castle Ottawa scale
- Controlled before after studies: criteria of the Cochrane EPOC group (Cochrane Effective Practice and Organisation of Care) (revised 2015)
- Interrupted time series analysis: criteria of the Cochrane EPOC group
- Uncontrolled case series: varie; nessuna raccomandata da Cochrane

Nuovo Risk of bias tool for NRS (ROBINS-I)

- Non è (ancora) obbligatorio usarlo
- Può essere utilizzato per studi controllati prospettici «cohort type», studi caso controllo, studi cross sectional
- Disponibile una guidance dettagliata solo (per ora) per gli studi cohort type;
- Le parti della guidance relative agli studi caso controllo e cross sectional devono ancora essere fatte

- Sterne JAC, Higgins JPT, Elbers RG, Reeves BC and the development group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance, updated 12 October 2016. Available from http://www.riskofbias.info

1° step: define the 'ideal' RCT

The Cochrane 'risk of bias' (RoB) tool for NRS is concerned with evaluating the risk of bias in the results of non-randomized studies that compare the health effects of two or more interventions.

Facilitated by considering each NRS as an attempt to emulate (mimic) a hypothetical randomized trial that compares the health effects of two or more interventions.

- If confounding is successfully controlled, the effect estimates from the observational study will be identical, except for sampling variation, to those from a target trial that randomly assigns individuals in the same study population to either intervention A or B.
- **The risk of bias arising from the observational design is a function of how imperfectly the observational study emulates the target trial.**

1° step: define the 'ideal' RCT

We refer to such a hypothetical randomized trial as the "**target randomized trial"**.

At the protocol stage

define hypothetical "**target randomized trial"**, the RCT that would be "ideal " to answer the review question

Participants

Intervention

Comparator

Outcomes (benefits and/or harms)

2° step: Specify whether interested in the effect of initiating (ITT) or initiating and adhering to (per protocol) intervention

- When the effect of interest is that of **assignment to the intervention** at baseline (randomized trials) or starting intervention at baseline (NRSs), **risk of bias assessments for both types of study need not be concerned with post-baseline departures from intended interventions** that reflect the natural course of events
- When the effect of interest is the **per protocol effect**, risk of bias assessments of both randomized and nonrandomized studies may **have to consider intervention discontinuation, switches between interventions, or departures from intended interventions**.

3°step: Identify possible confounding domains

- A confounding domain is a pre-intervention prognostic factor that predicts whether an individual receives one or the other intervention of interest. Some common examples are severity of pre-existing disease, physician prescribing practices, health care utilization, adiposity, and socio-economic status.
- We recommend that **subject-matter experts be included in the team** writing the review protocol, and encourage the **listing of confounding domains (defined below) in the review protocol**, based on initial discussions among the review authors

- **At protocol stage list the confounding domains relevant to all or most studies eligible for the review**

4°step: Identify possible co-interventions

- Relevant co-interventions are the interventions or exposures that individuals might receive after or with initiation of the intervention of interest, which are related to the intervention received and which are prognostic for the outcome of interest.
- These are also likely to be identified through the expert knowledge of members of the review group, via initial (scoping) reviews of the literature, and after discussions with health professional
  - **At protocol stage list the possible co-interventions that could differ between intervention groups and have an impact on study outcomes**.

Risk of bias tool - 7 domains

Pre-intervention

1. Bias due to baseline confounding
2. Bias in selection of participants into the study

At intervention

3. Bias in measurement of the interventions

Post-intervention

4. Bias due to departures from intended interventions (performance bias)
5. Bias due to missing data (attrition bias)
6. Bias in measurement of outcomes or Interventions (detection bias)
7. Bias in selection of the reported result (outcome reporting bias)

ROBINS-I

Pre-intervention

1. Bias due to baseline confounding
2. Bias in selection of participants into the study

At intervention

3. Bias in classification of the interventions

Post-intervention

4. Bias due to departures from intended interventions (performance bias)
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Pre or at intervention features for which consideration of bias in NRS are mainly distinct from those in RCTs

Post intervention features for which many considerations are similar to those in RCTs

Signalling questions

To help reviewer… for each domain some signalling question have been proposed

- **Signalling questions**: possible answers:

Yes

Probably yes

Probably no

No

No information

Responses of ‘Yes’ and ‘Probably yes’ (also of ‘No’ and ‘Probably no’) have similar implications.

Judgment of risk of risk of bias

Assessment must be done **at the outcome level**: (e.g. 5 outcomes in the review and 10 included studies: for each study you should assess risk of bias separately for each outcome , i.e. 5 times; total 50 risk of bias table….)

- **5°step**: assess risk of bias for a given outcome for each of the 7 domain
- **6° step**: make an overall judgment of risk of bias for that outcome at the study level
- **7° step**: make an overal judgment of risk of bias for that outcome across all the studies
- **8° 9° 10° etc step**… repeat all of these for each outcome

6° step : Judgments at each domain level

Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain);

Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial);

Serious risk of bias (the study has some important problems in this domain);

Critical risk of bias (the study is too problematic in this domain to provide any useful evidence);

No information on which to base a judgment about risk of bias for this domain.

6° step : overall judgment at the study level for each outcome

RESPONSE OPTION	CRITERIA
Low risk of bias (the study is comparable to a well-performed randomized trial);	The study is judged to be at **low risk of bias for all domains.**
Moderate risk of bias (the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial);	The study is judged to be at **low or moderate risk of bias for all domains.**
Serious risk of bias (the study has some important problems);	The study is judged to be at **serious risk of bias** in at least one domain, but not at critical risk of bias in any domain.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention);	The study is judged to be at **critical risk of bias in at least one domain.**
No information on which to base a judgement about risk of bias.	There is no clear indication that the study is at serious or critical risk of bias *and* there is a lack of information in one or more key domains of bias (*a judgement is required for this*).

Table 2. Reaching an overall RoB judgement for a specific outcome.

Declaring a study to be at a particular level of risk of bias for an individual domain will mean that the study as a whole has a risk of bias at least this severe (for the outcome being

7° step: overall judgment across all studies for the given outcome (following the GRADE approach)

- Outcome specific
- Do not average risk of bias across the studies
- Evaluate the extent to which each trial contributes toward the estimate of magnitude of effect. This contribution will usually reflect study sample size and number of outcome events -larger studies with many events will contribute more, much larger studies with many more events will contribute much more (look at the weight of each study in the forest plot)

8°and further step: overall judgment at the study level if you have several outcomes

Domain	O_1	O_2	O_3
Bias due to confounding	Serious risk	Moderate risk	Serious risk
Bias in selection of participants into the study	Low risk	Low risk	Low risk
Bias in measurement of interventions	Low risk	Low risk	Low risk
Bias due to departures from intended interventions	Moderate risk	Moderate risk	Moderate risk
Bias due to missing data	Low risk	No info	No info
Bias in measurement of outcomes	Low risk	Low risk	Serious risk
Bias in selection of the reported result	Moderate risk	Moderate risk	Serious risk
Overall*	*Serious risk*	*Moderate risk*	*Serious risk*

1. Bias due to confounding

8 signaling questions

Baseline confounding occurs when one or more pre-intervention prognostic factors predict the intervention received at baseline and the probability of the outcome

Es: frequenza e intensità di abuso , comorbidità psichiatrica , homelessness, livello culturale per efficacia MMT in pazienti TD

Es: patologia causa del ricovero , età, TOS, pillola contraccettiva, fumo, anamnesi positiva per VTE per efficacia tromboprofilassi in ospedale

Time-varying confounding occurs when the intervention received can change over time, (switches between the interventions) and when post-baseline prognostic factors affect the probability of switches received after baseline

2. Bias in selection of participants into the study

5 signalling questions

1. when some eligible participants, or the initial follow up time of some participants, are excluded in a way that leads to the association between intervention and outcome differing from the association that would have been observed in the target trial.

Es: valuto l'effetto di un farmaco somministrato in gravidanza e, per misurare incidenza AE, non considero le morti in utero o i nati morti

2. **when prevalent, rather than new (incident), users of the intervention are included in analyses**.

In both the situation this is analogous to starting the follow -up of the target trial some time after the start of intervention, so that some individuals who experienced the outcome after starting the intervention will have been excluded.

3.Bias in measurement of interventions

3 signalling questions

Bias may be introduced if intervention status is misclassified.

- **Lack of Clear description of the intervention** received, including doses, frequencies, intensity and timing
- **Recall bias**: if information about intervention status is obtained retrospectively and the information (or availability of information) on intervention status is influenced by outcomes

Es: pazienti malati tendono a ricordare meglio e di più le esposizioni passate che non i sani ; soggetti TD ricaduti possono ricordare meno e peggio quanto sono stati assidui nel prendere il metadone o utilizzare siringhe sterili di quelli che non ricadono

4. Bias due to departures from intended interventions

6 signalling questions

when there are systematic differences between intervention and comparator groups in the care provided, which represent a departure from the intended intervention(s). (**performance bias**)

- **cointerventions** (receipt of interventions other than the studied interventions, whose frequency may differ between intervention groups)
- **contamination** (inadvertent application of one of the studied interventions in participants intended to receive the other)
- **switches from the intended interventions** to other interventions not of interested to the review question
- **fidelity of implementation** (including non-adherence, non-compliance and failure to implement some or all of the intervention as intended)

5. Bias due to missing data

Attrition bias

5 signalling questions

- Amount of missing data
- Proportion and reasons of missing data comparable or not between groups
- Missing data adressed in the analysis

6. Bias in measurement of outcomes or interventions

Detection bias

4 signalling questions

- Blinding of outcome assessor
- Objective vs subjective (self report) outcome
- Different vs same data collection methods between groups

7. Bias in selection of the reported results

Selective reporting

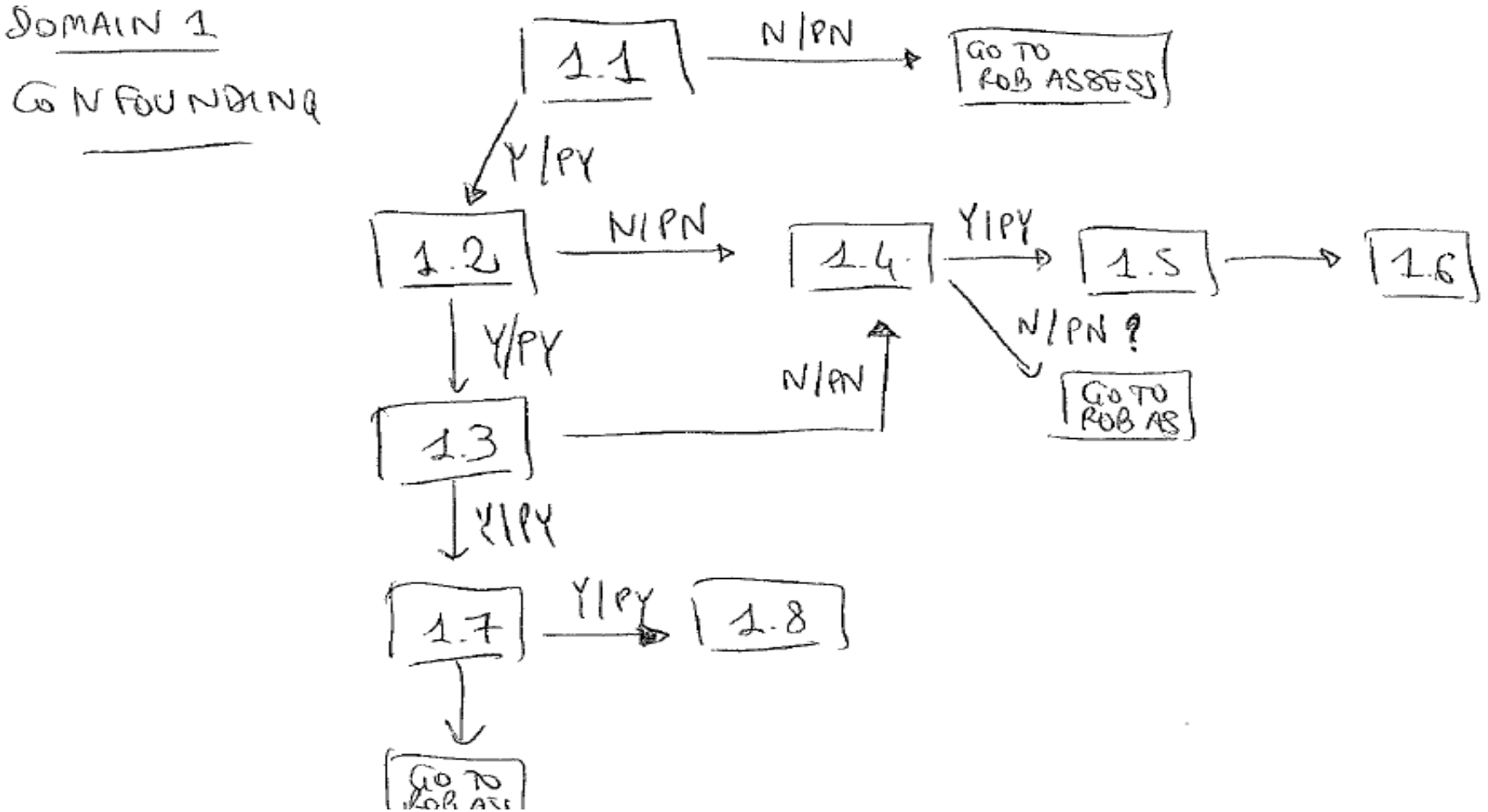
3 signalling questions

- (i) selective reporting of a **particular outcome measurement** from multiple measurements assessed within an outcome domain;
- (ii) selective reporting of a **particular analysis** from multiple analyses of a specific outcome measurement;
- (iii) selective reporting of a **subset of the participants**.

Signalling questions

Signalling questions	Elaboration	Response options
1.1 Is there potential for confounding of the effect of intervention in this study? **If N/PN to 1.1**: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding:	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomized trial. There is no NI (No information) option for this signalling question.	Y / PY / PN / N
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions.	NA / Y / PY / PN / N / NI
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required.	NA / Y / PY / PN / N / NI

Signalling questions



MECIR

http://methods.cochrane.org/mecir

MECIR :Methodological Expectations of Cochrane Intervention Reviews

Document containing standards for both conduct and reporting; detailed guidance on what and how do /report in each phase/section of the review;

- Ensuring that Cochrane Reviews represent the highest possible quality is critical if they are to inform decision making in clinical practice and health policy (*Strategy to 2020* goals 1 and 2).

drawn from the Cochrane Handbook for Systematic Reviews of Interventions

- Cochrane Review authors and the Cochrane Review Groups (editorial bases) are expected to meet these minimum quality standards in their reviews.
- These standards guarantee consistency of methodological practice across Cochrane Intervention Reviews and are an important element of the quality assurance of individual reviews.

MECIR

- Standards for the **conduct** of new Cochrane Intervention Reviews
- Standards for the **reporting of protocols** for new Cochrane Intervention Reviews
- Standards for the **reporting** of new Cochrane Intervention Reviews
- Standards for the **planning, conduct and reporting of updates** of Cochrane Intervention Reviews
- Standards for reporting in the **Plain Language summary**

Mandatory items: means that a new review will not be published if this is not done/reported

Highly desirable items: means that this should generally be done, but that there are justifiable exceptions

To be used by authors when undergo the review and write the draft and by the quality advisor to check quality of conduct and reporting

Standards for the conduct of new Cochrane Intervention Reviews

DEVELOPING THE PROTOCOL FOR THE REVIEW

- Setting the research question(s) to inform the scope of the review
- Setting eligibility criteria for including studies in the review
- Selecting outcomes to be addressed for studies included in the review
- Planning the review methods at protocol stage

PERFORMING THE REVIEW

- Searching for studies
- Selecting studies to include in the review
- Assessing risk of bias in included studies
- Synthesizing the results of included studies
- Assessing the quality of evidence and summarizing the findings

C10	Including randomized trials	Mandatory
Include randomized trials as eligible for inclusion in the review, *if it is feasible to conduct them to evaluate interventions and outcomes of interest.*	Randomized trials are the best study design for evaluating the efficacy of interventions. If it is feasible to conduct them to evaluate questions that are being addressed by the review, they must be considered eligible for the review. However, appropriate exclusion criteria may be put in place, for example regarding length of follow-up. See *Handbook* 5.5, 13.1.3	
C11	Justifying choice of study designs	Mandatory
Justify the choice of eligible study designs.	It might be difficult to address some interventions or some outcomes in randomized trials. Authors should be able to justify why they have chosen either to restrict the review to randomized trials or to include non-randomized studies. The particular study designs included should be justified with regard to appropriateness to the review question and with regard to potential for bias. See *Handbook* 13.1.2, 13.2.1.3	
C12	Excluding studies based on publication status	Mandatory
Include studies irrespective of their publication status, unless exclusion is explicitly justified.	Obtaining and including data from unpublished studies (including grey literature) can reduce the effects of publication bias. However, the unpublished studies that can be located may be an unrepresentative sample of all unpublished studies. See *Handbook 10.3.2*	

Standards for reporting

Section of the review	N items	mandatory
Title and authors	2	1
Abstracts	15	13
Background and objectives	11	2
Inclusion criteria	6	6
Searching for studies	5	4
Data collection and analysis	14	10
Results- description of studies	17	13
risk of bias	3	2
Effects of interventions	24	12
Discussion	2	1
Conclusions	2	2
Total:	**101**	**66**

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R13	Abstract, Main results: adverse effects	**Mandatory**
Ensure that any findings related to adverse effects are reported. If adverse effects data were sought, but availability of data was limited, this should be reported.	The Abstract of the review should aim to reflect a balanced summary of the benefits and harms of the intervention. See *Handbook* 11.8	
R14	Abstract, Main results: format of numerical results	**Mandatory**
Present summaries of statistical analyses in the same way as they are reported in the review and in a standard way, ensuring that readers will understand the direction of benefit and the measurement scale used, and that confidence intervals are included where appropriate.	The standard format for reporting the results of statistical analysis includes an indication of the summary measure, point estimate and confidence interval, e.g. odds ratio 0.75 (95% confidence interval 0.62 to 0.89).	

MECIR -UPDATE

- Since its inception, Cochrane has advocated for the routine updating of systematic reviews, in order to take account of new evidence.
- Before undertaking an update, several important decisions are required.

1. whether the original review question is still relevant.
2. whether the general methodological approach is still appropriate to answer the review question: this will need a review of the original protocol.
3. whether the scope of the review is appropriate, whether it should be split into two or more reviews, or whether it should be merged with other reviews. Important changes of this nature indicate a need for a new protocol.

MECIR

Conduct: riassunto dei concetti fondamentali dell'handbook; riporta i passaggi fondamentale su **come si fa** una SR secondo gli standard Cochrane per gli autori

Reporting: riporta in modo dettagliato i contenuti e il livello di dettaglio da usare nel testo; **come si scrive** il protocollo o la full review

- per gli autori;
- usato dal managing editor o quality advisor del gruppo per verificare l'aderenza del draft agli standard
- Usato dal CEU per valutare qualità delle revisioni sottoposte a screening

Update: riporta i criteri e i metodi per fare l'update; **se e come si fa e come si scrive**

- Per gli autori
- Per il managing editor o quality advisor

I cambiamenti di Cochrane - La valutazione di qualità

IN PASSATO:

- ogni gruppo aveva la sua base editoriale, faceva il proprio processo editoriale e autorizzava la pubblicazione autonomamente (responsabile sign-off : coordinating editor del gruppo).
- Totale autonomia, come se ogni gruppo fosse una piccola rivista
- Conseguenze: grande diversità nella qualità tra le revisioni pubblicate dai diversi gruppi, sia per conduct sia per reporting

I cambiamenti di Cochrane - La valutazione di qualità

Nasce il CEU (Cochrane Central Editorial Unit):

- Screening di un campione delle revisioni di tutti i gruppi per valutarne la qualità
- Individua i gruppi con deficit maggiori e fornisce supporto
- Elabora il MECIR
- Produce documenti e organizza workshops sui «common error»

ADESSO

Ogni gruppo è autonomo ma

CEU fa valutazione di:

- SRs giudicate di alta priorità
- Singole SRs su richiesta dei gruppi
- Singole SRs se vengono segnalazioni/commenti dall'esterno

I cambiamenti di Cochrane - La valutazione di qualità

IN FUTURO (PROSSIMO)

- Creazione dei network (raggruppamenti dei gruppi di revisione per argomento)
- Ogni network avrà un senior editor e un associate editor
- Ogni revisione (o un campione, o a richiesta) verrà valutata dall'associate editor, nominato dal CEU («mini-CEU»)
- Responsabile sign-off: senior editor