Il contributo delle revisioni sistematiche alla prioritarizzazione della ricerca

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Di cosa parlerò?

- I primi passi delle RS in Medicina
- Gli “hot issues” del dibattito pro e contro
- Alcuni (pochi) dati empirici anche italiani
- I rischi nell’uso delle RS
- Qualche considerazione conclusiva

I primi passi…..

SPECIAL ARTICLE

EFFECT OF INTRAVENOUS STREPTOKINASE ON ACUTE MYOCARDIAL INFARCTION

Pooled Results from Randomized Trials

MEIR J. STAMPFER, M.D., SAMUEL Z. GOLDHABER, M.D., SALIM YUSUF, M.R.C.P., D.PHIL., RICHARD PETO, M.SC., AND CHARLES H. HENNEKENS, M.D.

INTRACORONARY infusion of streptokinase in patients with acute myocardial infarction is an exciting and innovative technique for reperfusion of the ischemic myocardium,[1-4] but its net benefits have not yet been reliably estimated.

Intravenous infusion of streptokinase is less invasive, less expensive, and easier than intracoronary infusion, and its effects have already been studied in randomized trials. Inevitably, when several trials address the same or a similar question, they are unlikely to yield identical results, and in these circumstances an overview of the results of all the strictly randomized trials can be useful.[5-7] Although the play of chance may well produce distortions in one direction or another in particular trials, such effects are likely to cancel each other out when several trials are viewed together. In this analysis, we therefore examine the mortality results from all eight identified randomized trials that have tested intravenous streptokinase in acute myocardial infarction. As we will show, the results suggest that this therapy, given early, significantly reduces mortality over subsequent weeks.

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Dr. Stampfer was supported by a National Institute of Environmental Health Sciences National Research Service Award (5T32 ES 07069), Dr. Goldhaber by a National Research Service Award Training Grant (HL 07049), and Dr. Hennekens by a Research Career Development Award (HL 00286).

METHODS

Selection of Trials for Pooling

Initially, we included all published trials in which subjects were randomized to intravenous-streptokinase treatment or to a control group receiving either placebo or anticoagulation. Mortality was used as an end point, with a follow-up period of approximately 40 days for increased comparability. We then examined more closely comparable trials that also met the following more stringent criteria: a reasonably similar treatment protocol using a uniform loading dose of 250,000 IU followed by continuous infusion therapy, and initiation of therapy within 24 hours of onset of symptoms.

Statistical Techniques

Patients admitted to one trial are likely to differ systematically from those admitted to another, and so one should compare patients in one trial only with other patients in that trial and not with patients in other trials. Therefore, to provide an overview of several trials, we have employed the statistical methods that are commonly used in a single study to obtain an overall estimate across different levels (or strata) of a confounding variable — for example, across different age groups. In our analysis we treat each separate trial as one stratum. Information from each stratum is then combined to provide an estimate of the mean overall effect without the need to compare patients in one trial directly with those in another. For any one trial, we define the risk ratio as the proportion of deaths in streptokinase-treated patients divided by that among the controls. We calculated a weighted average of these risk ratios by assigning a weight to the risk ratio derived from each individual study. Each trial's assigned weight is proportional to the precision of that trial's results (the inverse of the variance of the risk ratio).[8] Thus, each trial's contribution to the overall result is directly related to the amount of information it provides. For example, a large trial would carry more weight than a smaller trial. The formula is

N Engl J Med 1982

Table 1. Characteristics of Randomized Trials of Intravenous Streptokinase in Acute Myocardial Infarction.

Trial	Duration of Symptoms	Loading Dose	Infusion Dose	Period	Placebo Controls?	Follow-up Period	Mortality		Risk Ratio (95% Confidence Limits)		Two-Tailed P Value
							Drug Group	Controls			
	hours	*thousands of IU*		*hours*		*days*	*no. dead/total*				
1st European trial, 1969[12]	72	1250	104	72	No	HS	20/83 (24.1%)	15/84 (17.9%)	1.35	(0.74–2.45)	0.32
2d European trial, 1971[13] *	24	250	100	24	No	HS †	69/373 (18.5%)	94/357 (26.3%)	0.70	(0.53–0.92)	0.01
Finnish study, 1971[14]	72	600	Varied	Varied	No	42	22/219 (10.0%)	17/207 (8.2%)	1.22	(0.67–2.24)	0.51
Italian study (CCU), 1971[15] *	12	250	150	12	No	40	19/164 (11.6%)	18/157 (11.5%)	1.01	(0.55–1.85)	0.97
2d Frankfurt study, 1972[16] *	12	250	200	2.5	Yes	HS	13/102 (12.7%)	29/104 (27.9%)	0.46	(0.26–0.81)	0.007
Australian trial (CCU), 1973[17] *	24	250	100	17	No	40 ‡	21/264 (8.0%)	23/253 (9.1%)	0.88	(0.50–1.54)	0.64
						90 §	26/264 (9.8%)	32/253 (12.6%)	0.78 §	(0.48–1.27)	0.31
British study (CCU), 1976[18] *	24	250	100	24	Yes	42 ‡	43/302 (14.2%)	44/293 (15.0%)	0.95	(0.64–1.40)	0.79
						6 mo §	48/302 (15.9%)	52/293 (17.7%)	0.90 §	(0.63–1.28)	0.55
European Study Group (CCU), 1979[19] *	12	250	100	24	Yes	21 ‡	18/156 (11.5%)	30/159 (18.9%)	0.61	(0.36–1.04)	0.07
						6 mo §	25/156 (16.0%)	50/159 (31.4%)	0.51 §	(0.34–0.77)	0.001

*Trial meets criteria for comparable protocol. CCU denotes coronary-care unit.

†The mean hospital stay (HS) was 43 days.

‡The primary follow-up period was longer; these data are derived from published reports.

§More prolonged follow-up of the same trial participants, pooled separately (see text).

Revisioni sistematiche……

A Quality Assessment of Randomized Control Trials of Primary Treatment of Breast Cancer

By Alessandro Liberati, Harvey N. Himel, and Thomas C. Chalmers

The methodology of randomized control trials (RCTs) of the primary treatment of early breast cancer has been reviewed using a quantitative method. Sixty-three RCTs comparing various treatment modalities tested on over 34,000 patients and reported in 119 papers were evaluated according to a standardized scoring system. A percentage score was developed to assess the internal validity of a study (referring to the quality of its design and execution) and its external validity (referring to presentation of information required to determine its generalizability). An overall score was also calculated as the combination of the two. The mean overall score for the 63 RCTs was 50% (95% confidence interval [CI] = 46% to 54%) with small and nonstatistically significant differences between types of trial. The most common methodologic deficiencies encountered in these studies were related to the randomization process (only 27 of the 63 RCTs adopted a truly blinded procedure), the handling of withdrawals (only 26 RCTs included all patients in the analyses), the description of the follow-up schedule (only 12 RCTs reported adequately), the report of side effects (adequate information given in 33 RCTs), and the description of the patient population (satisfactory in 29 RCTs). Telephone calls to the principal investigators improved the quality scores by seven points on a scale of 100, indicating that some of the deficiencies lay in reporting rather than performance. There was evidence that quality has improved over time and that the increasing tendency of involving a biostatistician in the research team was positively associated with the improvement of the internal validity but not with the external.

J Clin Oncol 4:942–951.

e metanalisi…….

Adjuvant Chemotherapy for Breast Cancer

A Pooled Estimate Based on Published Randomized Control Trials

Harvey N. Himel, MD, MPH; Alessandro Liberati, MD; Richard D. Gelber, PhD; Thomas C. Chalmers, MD

The use of adjuvant chemotherapy for treating patients with operable breast cancer remains a worldwide controversy. Using the data from published randomized control trials with a minimum two-year follow-up, pooled estimates of relapse-free survival rates and overall survival rates were calculated. Relapse-free survival rates were improved by 12.5% (95% confidence interval [CI] ±4.5%) at three years and by 8% (CI ±6%) at five years, with studies using multiple agents showing a greater effect. A significant advantage was also present in overall survival rates at three years, but only for studies involving multiple agents (4%±3.5%). Results from combining data for other types of trials were inconclusive. The use of this method is presented to illustrate its value as an explicit and systematic one for combining data from several randomized control trials in assessing a therapeutic controversy.

(*JAMA* 1986;256:1148-1159)

has been challenged[12] because of three major causes of heterogeneity in the data to be combined: differences in patients to be studied, differences in therapeutic regimens applied, and differences in the quality of the RCTs. While the first two can be corrected for to some extent by analytic methods such as stratified analysis, the relative effect of bias on the validity of pooling has not been assessed previously. In another publication, we analyzed the quality of the RCTs for adjuvant chemotherapy of stage II breast can-

A favore

- RS e MA sono necessarie per
  - Fare il punto sullo stato delle conoscenze e permettere lo sviluppo di raccomandazioni e linee guida
  - Permettere una stima quantitativa dell'impatto plausibile degli interventi
  - Identificare le aree per lo sviluppo della ricerca

Contro…..

- Soprattutto le MA sono pericolose per
  - Combinano i risultati di studi tra loro molto diversi ed eterogenei per qualità metodologica, tipologia di pazienti e interventi
  - Bloccano lo sviluppo della ricerca in aree promettenti ma ancora in fase precoce di sviluppo
  - Offrono solo “risultati medi” di scarsa utilità per il clinico e per le decisioni sanitarie

I primi tentativi di sistematizzare i possibili contributi di RS e MA ……

META-ANALYSIS IN MEDICINE

WHERE WE ARE AND WHERE WE WANT TO GO*

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(*Received in revised form* 27 *June* 1988)

Abstract—An epidemiologically impeccable study does not bring answers to all the important questions. A structured and systematic integration of information from different studies of a given problem with a view to answering the original question or bringing additional information is the essence and objective of the meta-analytic approach to health problem solving. Original studies in medicine, being very heterogeneous in nature and structure require not only a quantitative approach (as in classical meta-analysis) but also an additional "qualitative meta-analysis" as well. The latter represents not only a systematic accumulation of both information and the characteristics of different studies, but also an assessment of quality, uncertainty, missing data, random error and bias across studies of interest. The greatest challenge of meta-analysis in medicine lies in the integration of the qualitative and quantitative assessment of given information (scoring of quality, weighing of the effect size by quality score, etc.). Meta-analysis in medicine must go beyond a simple pooling of data. It should become the "epidemiology of results of independent studies of a common topic of interest". Further development of meta-analysis in such an expanded way may have an important impact on decision-making in clinical medicine, and in health policies.

J Clin Epidemiol 1989

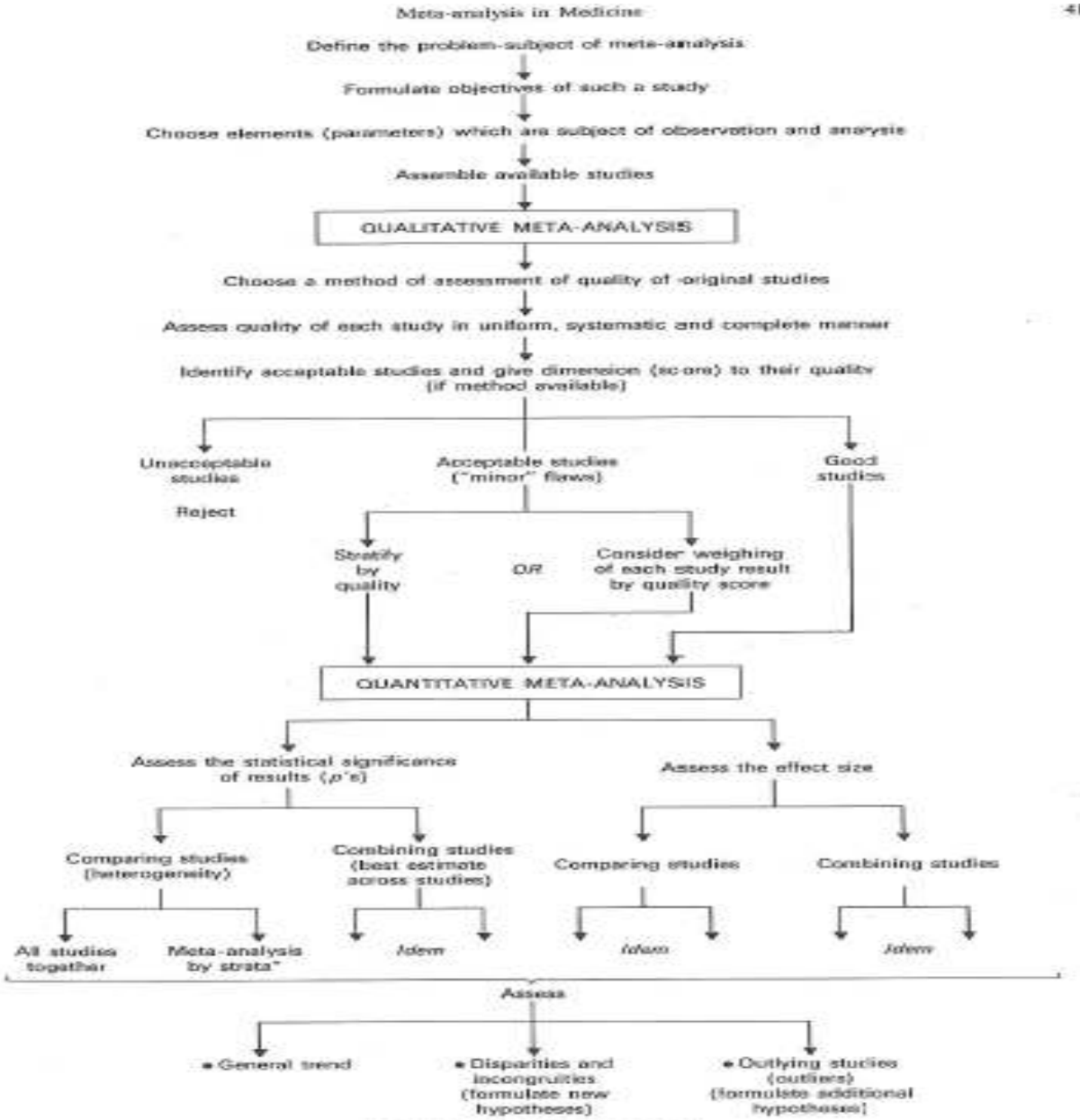

Fig. 1. Flowchart of meta-analysis.

Alcuni (pochi) dati empirici

International Journal of Technology Assessment in Health Care, 16:3 (2000), 743–750.

WHAT ARE THE RELATIVE MERITS OF THE SOURCES USED TO IDENTIFY POTENTIAL RESEARCH PRIORITIES FOR THE NHS HTA PROGRAMME?

Deborah Chase
Ruairidh Milne
University of Southampton

Ken Stein
North and East Devon Health Authority

Andrew Stevens
University of Birmingham

The findings

Abstract

The NHS Health Technology Assessment (HTA) Programme runs an annual process of identifying suggestions for health technology assessment. The objective of this paper is to describe and evaluate the relative importance of the different sources used by the program in 1998 to identify potential priorities. There were four different sources: a) a widespread consultation of healthcare commissioners, providers and consumers; b) research recommendations from systematic reviews; c) reconsidering previous research priorities which had not been taken forward for funding; and d) horizon scanning. Collectively, the four sources generated just over 1,100 HTA suggestions. By far the largest source of suggestions and priorities was the widespread consultation. However, the success rate of this source, in terms of being commissioned, was low. Research recommendations from systematic reviews provided the second largest source of priorities and the best success rate of all sources. Value was found from different sources for different healthcare areas.

The findings

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Research recommendations from SRs provided the second largest source and had the best success rate of all sources

Relative Citation Impact of Various Study Designs in the Health Sciences

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Apostolos A. Analatos
John P. A. Ioannidis, MD

Context The relative merits of various study designs and their placement in hierarchies of evidence are often discussed. However, there is limited knowledge about the relative citation impact of articles using various study designs.

Objective To determine whether the type of study design affects the rate of citation in subsequent articles.

Design and Setting We measured the citation impact of articles using various study designs—including meta-analyses, randomized controlled trials, cohort studies, case-control studies, case reports, nonsystematic reviews, and decision analysis or cost-effectiveness analysis—published in 1991 and in 2001 for a sample of 2646 articles.

Main Outcome Measure The citation count through the end of the second year after the year of publication and the total received citations.

Results Meta-analyses received more citations than any other study design both in 1991 ($P<.05$ for all comparisons) and in 2001 ($P<.001$ for all comparisons) and both in the first 2 years and in the longer term. More than 10 citations in the first 2 years were received by 32.4% of meta-analyses published in 1991 and 43.6% of meta-analyses published in 2001. Randomized controlled trials did not differ significantly from epidemiological studies and nonsystematic review articles in 1991 but clearly became the second-cited study design in 2001. Epidemiological studies, nonsystematic review articles, and decision and cost-effectiveness analyses had relatively similar impact; case reports received negligible citations. Meta-analyses were cited significantly more often than all other designs after adjusting for year of publication, high journal impact factor, and country of origin. When limited to studies addressing treatment effects, meta-analyses received more citations than randomized trials.

Conclusion Overall, the citation impact of various study designs is commensurate with most proposed hierarchies of evidence.

JAMA. 2005;293:2362-2366 www.jama.com

SEVERAL AUTHORS AND ORGANIzations have proposed hierarchies of evidence, based on the relative reliability of various types of study designs.[1-4] Although many people recognize that expert opinions and nonsystematic reviews provide the least reliable level of information,[5,6] such articles continue to have a massive influential presence.[7] Controlled studies assume higher places in hierarchies of evidence than uncontrolled studies, and randomized trials are considered the gold standard for clinical research.[1-4] However, randomized trials cannot be conducted for all questions of interest[8] and there is debate on whether they give different results than nonrandomized studies.[9-14] Finally, meta-analyses are becoming increasingly frequent in the literature. Meta-analyses are often placed at the highest level of evidence [1-4] despite their

Meta-analyses received more citations than any other study design both in 1991 and in 2001… both in the short and in the longer term.

The usefulness of Cochrane Review for planning of research

Lorcan Clarke, Tom Clarke and Mike Clarke
UK Cochrane Centre
(*Journal of Health Services Research and Policy, 2006*)

Cochrane Reviews

- All Cochrane reviews include
  - Authors' Conclusions
    - Implications for Practice
    - Implications for Research
- Analysis of 2530 Cochrane reviews

Categorised as

- Suggestions about specific types of intervention
- Suggestions about specific types of participant
- Suggestions about specific types of outcome measures
- Recommendation that no more research is needed or feasible
- Discussed the need for a new, expanded or updated systematic review

Suggestions for future research that were ignored

- That there should be “more trials” or “better research”.
- That would not be eligible for the review.
- That “new”, but unspecified, drugs or interventions should be assessed.
- If the suggestion for the types of participant to be included in future research simply restated the population that was the basis of the review title
- that outcome measures in future research should be “more appropriate”, “standardised”, etc.

Findings

- 2075 (82.0%) suggest specific types of intervention
- 765 (30.2%) suggest specific types of participant
- 1315 (51.9%) suggest specific types of outcome measures
- *429 (16.9%) covered all three*
- 82 (3.2%) recommend no more research
- 295 (11.6%) do not include a specific recommendation about any of the 3 categories
- 100 (3.9%) mention ongoing or planned trials
- 151 (6.0%) mention explicitly the need to update the current review or to conduct reviews of related topics.

Ongoing studies

- Implications for research
  - 100 reviews mention an ongoing study
  - of these, 78 included at least one in the Ongoing Studies section

- Ongoing Studies
  - 438 reviews include at least one Ongoing Study, without mentioning it in Implications for Research

- 538 Cochrane reviews mention an ongoing study

Message

- **There is ample room for improvement in the way Cochrane reviews can be prepared to inform future research**

- **Cochrane reviews include a large amount of residual uncertainty**

E’ in epoca piu recente…..

NIHR Health Technology Assessment programme

NHS National Institute for Health Research

Identifying and prioritising HTA research

Key messages

The programme identifies areas of genuine uncertainty by:

- consulting directly with key stakeholders within the NHS and NIHR and with external organisations
- extracting research recommendations from high quality evidence syntheses
- inviting direct suggestions through the HTA website
- inviting researchers to submit proposals

and later they say:

The HTA programme also systematically scans important research resources to identify recommendations for research to fill the evidence gaps in the NHS.

These include the National Institute for Health and Clinical Excellence (NICE), and completed reviews from the Cochrane Library and Clinical Evidence.

… e in Italia….

Agenzia Italiana del Farmaco

AIFA

BANDO AIFA 2009
PER LA RICERCA INDIPENDENTE SUI FARMACI

DOCUMENTO INTEGRALE

Le RS nel Bando AIFA

Revisioni sistematiche (RS) su quesiti terapeutici in campo farmacologico

caratterizzati da elevata incertezza e per i quali non esistano già RS disponibili nella letteratura scientifica

Le RS proposte non devono già essere disponibili (ed aggiornate negli ultimi due anni) sulla Cochrane Library o sugli altri principali database di revisioni sistematiche. Se prevista una valutazione farmacoeconomica è necessario che ci siano adeguate competenze nel team di ricerca e siano riportare le metodologie da utilizzare per l'analisi.

Motivazione alla tematica proposta:

Il metodo delle revisioni sistematiche (RS) di letteratura si è dimostrato utile per sintetizzare i risultati di studi primari sull'efficacia e il profilo beneficio-rischio di interventi farmacologici e per individuare le aree nelle quali si deve indirizzare la ricerca futura.

LE RS nel Bando AIFA (cont)

In questa tematica verranno considerate solamente proposte che documentino nella lettera di intenti la presenza di tutte le seguenti caratteristiche:

a) elevata incertezza sul profilo beneficio-rischio dello specifico intervento da valutare;

b) mancanza di RS già disponibili nella letteratura scientifica e/o nella produzione di agenzie di technology assessment internazionale;

c) esplicita finalizzazione della RS ad individuare con precisione le caratteristiche che dovrebbero avere gli studi primari mirati a verificare in modo affidabile l'effettiva efficacia ed il profilo beneficio-rischio dell'intervento;

d) raccordo con argomenti di particolare rilevanza per decisioni regolatorie dell'AIFA e con progetti già individuati come prioritari per la produzione di linee guida nell'ambito del Sistema Nazionale di Linee Guida (SNLG) da parte di istituzioni nazionali e regionali.

Examples of SRs funded within the AIFA - 2007

PI	Istituzione	Titolo	Stato
NN	**Università degli Studi di Modena e Reggio Emilia**	**Efficacy, toxicity, duration and modalities of administration of anti-HER2 agents in HER-2 positive breast cancer: a prospective systematic review**	**concluso**
NN	**Università Federico II Napoli**	**Impact of antihypertensive therapy on mortality and cardiovascular events in hemodialysis patients: a sistematic review**	
XX	**AUSL Roma E di Roma**	**Cochrane systematic review to evaluate the efficacy, safety and cost effectiveness of Gamma-hydroxybutyric acid (GHB), acamprosate , benzodiazepines and anticonvulsants for the treatment of the Alcohol Withdrawal Syndrome (AWS)**	**concluso**
BB	**Istituto di Ricerche Farmacologiche Mario Negri**	**A systematic review on the novel targeted therapies in the treatment of advanced non small cell lung cancer (NSCLC)**	
UU	**Università di Torino**	**Systematic review of controlled clinical trials on pharmacologic treatments for acute nontubercolous pericarditis and its recurrences**	

Examples of SRs funded within the AIFA - 2008

BB	Consorzio Mario Negri Sud	**Chemotherapy alone or in combination with targeted drugs in advanced colorectal cancer. for how long should therapy be used? a systematic review and meta-analysis**
NN	Azienda AUSL di Modena	**Efficacy of human papillomavirus vaccines in prevention of cervical cancer. Comparison between results and conclusions of independent meta-analysis and those of industry funded meta-analyses.**
MM	Policlinico Universitario Campus Biomedico di Roma	**Systematic Review on Medical Treatments for Patients Affected by Dry Eye Disease**
PP	Istituto Superiore di Sanità	**Systematic review and metanalysis on safety and efficacy of pharmacological and non-pharmacological treatments for retinitis pigmentosa**
OO	IRCCS IFO - Istituto Regina Elena di Roma	**Vitamin D in Breast Cancer Treatment and/or Prevention: a series of Systematic Reviews of the Scientific Literature**
UU	Fondazione Ospedale S. Raffaele del Monte Tabor	**The effect of isoflurane on myocardial infarction and mortality in cardiac and non-cardiac surgery. a metanalysis of randomized controlled studies.**
YY	Consorzio Mario Negri Sud	**Biochemical targets (parathyroid hormone, phosphorus and calcium) for secondary hyperparathyroidism in CKD patients**
DD	A.O. Universitaria S. Martino di Genova	**Beta-2 agonists for prevention of exercise induced asthma (EIA): Cochrane systematic review and meta-analysis**
TT	Università Studi dell'Insubria	**Statins for acute ischemic stroke: a Cochrane systematic review**
TT	Istituto Superiore di Sanità	**Cochrane systematic review to evaluate the efficacy, safety and cost effectiveness of antidepressant, dopamine agonists and disulfiram for the treatment of cocaine dependence**

……e i rischi…..

The risks

- Fragmented (too narrow) questions
- Publication bias
- “Selective reporting”
- “Early stopping”
- “Non inferiority trials”
- Limitation in collaboration, transparency and data sharing

Conclusions

- SRs are a recognised and accepted tool to synthesize information and clarify the evidence profile in the natural history of the development of technologies
-
- If we try to answer the question that prompted this presentation empirical data are scant

Conclusions (II)

- The limitations of “spontaneous” SRs should be taken into account at least trying in the short term to improve their reporting (ie Checklist PRISMA)

- We must improve the commissioning process especially if SRs are to become an official tool for research prioritisation

Annals of Internal Medicine | Academia and Clinic

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher, PhD; Alessandro Liberati, MD, DrPH; Jennifer Tetzlaff, BSc; Douglas G. Altman, DSc; and the PRISMA Group*

Editor's Note: In order to encourage dissemination of the PRISMA Statement, this article is freely accessible on the Annals of Internal Medicine *Web site (www.annals.org) and will be also published in* PLOS Medicine, BMJ, Journal of Clinical Epidemiology, *and* Open Medicine. *The authors jointly hold the copyright of this article. For details on further use, see the PRISMA Web site (www.prisma-statement.org).*

Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field (1, 2), and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research (3), and some health care journals are moving in this direction (4). As with all research, the value of a systematic review depends on what was done, what was found, and changing the name from QUOROM to PRISMA was the desire to encompass both systematic reviews and meta-analyses. We have adopted the definitions used by the Cochrane Collaboration (9). A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies.

Developing the PRISMA Statement

A three-day meeting was held in Ottawa, Ontario, Canada, in June 2005 with 29 participants, including re-

Annals of Internal Medicine | ACADEMIA AND CLINIC

The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration

Alessandro Liberati, MD, DrPH; Douglas G. Altman, DSc; Jennifer Tetzlaff, BSc; Cynthia Mulrow, MD, MSc; Peter C. Gøtzsche, MD, DrMedSci, MSc; John P.A. Ioannidis, MD; Mike Clarke, BA, DPhil; P.J. Devereaux, MD, BSc, PhD; Jos Kleijnen, MD, PhD; and David Moher, PhD

Systematic reviews and meta-analyses are essential to summarize evidence relating to efficacy and safety of health care interventions accurately and reliably. The clarity and transparency of these reports, however, is not optimal. Poor reporting of systematic reviews diminishes their value to clinicians, policy makers, and other users.

Since the development of the QUOROM (*QU*ality *O*f *R*eporting *O*f *M*eta-analysis) Statement—a reporting guideline published in 1999—there have been several conceptual, methodological, and practical advances regarding the conduct and reporting of systematic reviews and meta-analyses. Also, reviews of published systematic reviews have found that key information about these studies is often poorly reported. Realizing these issues, an international group that included experienced authors and methodologists developed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) as an evolution of the original QUOROM guideline for systematic reviews and meta-analyses of evaluations of health care interventions.

The PRISMA Statement consists of a 27-item checklist and a four-phase flow diagram. The checklist includes items deemed essential for transparent reporting of a systematic review. In this Explanation and Elaboration document, we explain the meaning and rationale for each checklist item. For each item, we include an example of good reporting and, where possible, references to relevant empirical studies and methodological literature. The PRISMA Statement, this document, and the associated Web site (www.prisma-statement.org) should be helpful resources to improve reporting of systematic reviews and meta-analyses.

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For author affiliations, see end of text.

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