The project is supported by

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of the European Union

Towards Evidence-Based Research

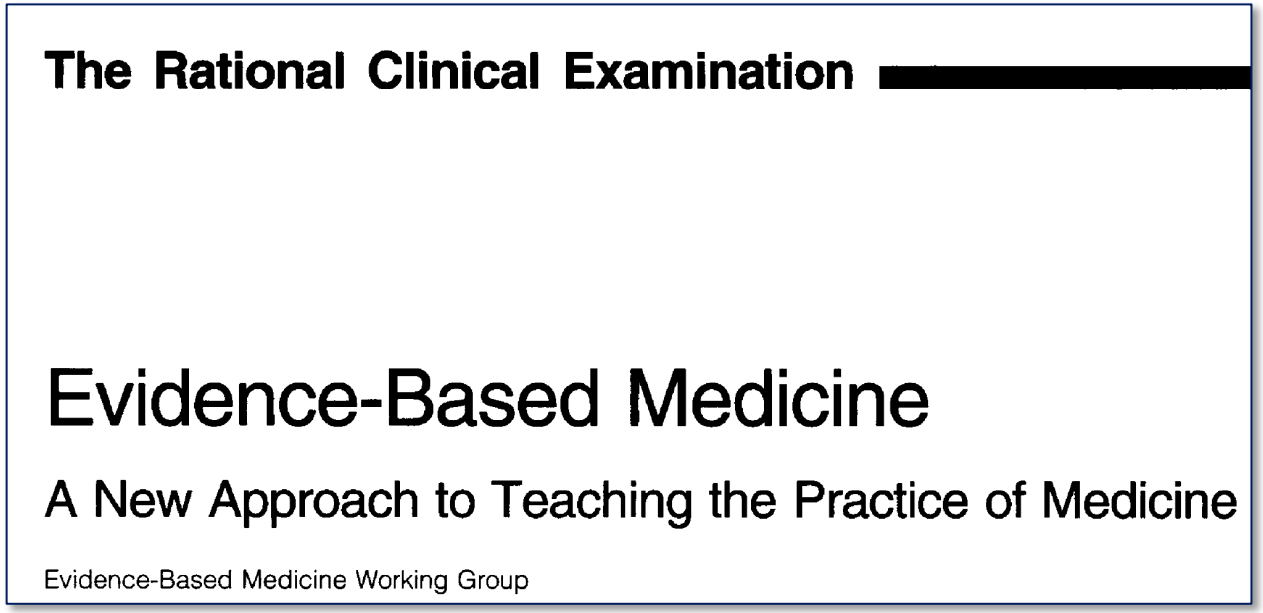
Hans Lund
Professor, Bergen, Norway
Chair of EVBRES

In 1992

"A NEW paradigm for medical practice is emerging.

Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and patho-physiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research.

Evidence-based medicine requires new skills of the physician, **including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature**"



The Evidence-Based Medicine Working Group. **Evidence-based medicine. A new approach to teaching the practice of medicine.** JAMA. 1992;268:2420-5.

This EBM approach ...

... argues that you can´t trust single studies. You need to perform a systematic approach to all earlier studies.

The concept of EBM was defined, and the Cochrane Collaboration was established – creating unique standards for systematic reviews.

... and so much more

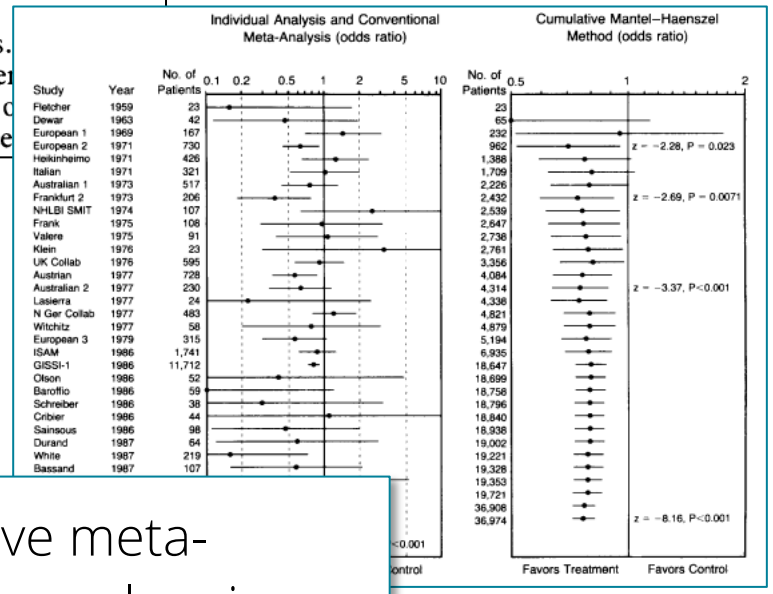
But almost simultaneously …

Getting to grips with Archie Cochrane's agenda

All randomised controlled trials should be registered and reported

…well local or national guidelines for
…ed.
…sses exist at all these steps.
…particular weakness, however
…l profession for not having
…g up to date reviews of the

Chalmers 1992: «… if systematic reviews, had been started at the beginning of a series of related trials … recommendations would have been made earlier.»



Lau 1992: «… Cumulative meta-analysis … may be helpful in … planning future trials, ..»

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Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability

Julian Savulescu, Iain Chalmers, Jennifer Blunt

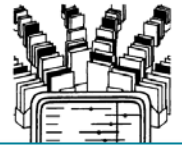
...ces of bias and methods of
...ecting against bias[11]
...blem formulation

Savulescu et al. 1996: «results of recent empirical investigations in research synthesis imply that research ethics committees are behaving unethically by endorsing new research which is unnecessary.»

Systematic Reviews

Rationale for systematic reviews

Cynthia D Mulrow



Systematic literature reviews including meta-analyses are invaluable scientific activities. The rationale for such reviews is well established. Health care providers, researchers, and policy makers are inundated with unmanageable amounts of information; they need systematic reviews to efficiently integrate existing information and provide data for rational decision making. Systematic reviews establish whether scientific findings are consistent and can be generalised across populations, settings, and treatment variations, or whether findings vary significantly by particular subsets. Meta-analyses in

Mulrow 1994: «Researchers use the review to identify, justify, and refine hypotheses;»


We may not only have a challenge in clinical practice – but also in doing research

A Scoping Review (under preparation) …

… have identified 98 meta-research studies evaluating if clinical researchers is **using existing evidence** when justifying and designing new studies, and if the results of the new study was placed in the context of all existing evidence.

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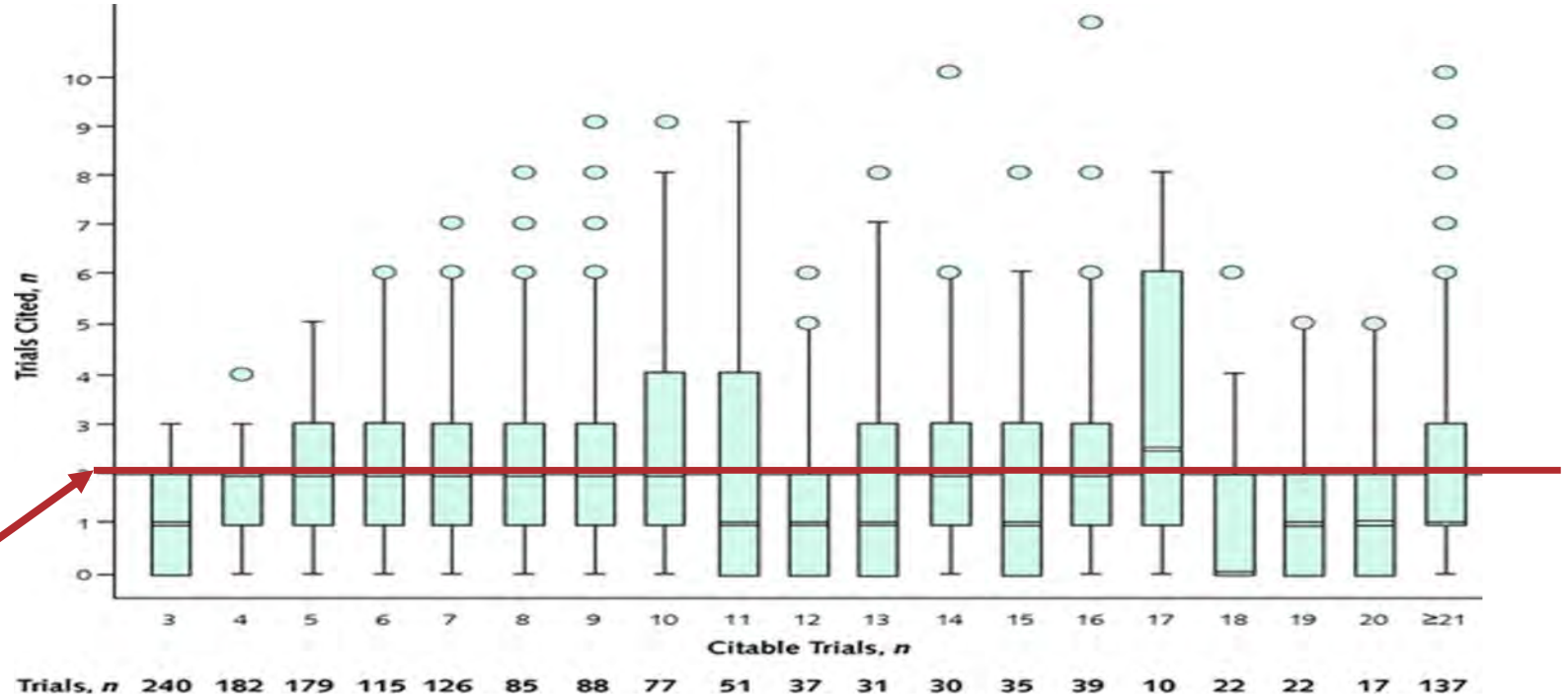
A Scoping …

… have ider… s evaluating
if clinical res… **ence** when
justifying ar… the results
of the new s… of all
existing evi…

… and the results shows (examples).

How often do scientific authors refer to the totality of earlier research?

- 55% cited no trials even though they could potentially refer to 3 or more studies within the same area
- the median number of references for earlier studies was consistently two.



Robinson KA, Goodman SN. **A systematic examination of the citation of prior research in reports of randomized, controlled trials**. Ann Intern Med. 2011;154(1):50-5.

How often ... refer to th... arch?

- 55% cited no tr... though they co... potentially refe... more studies w... same area
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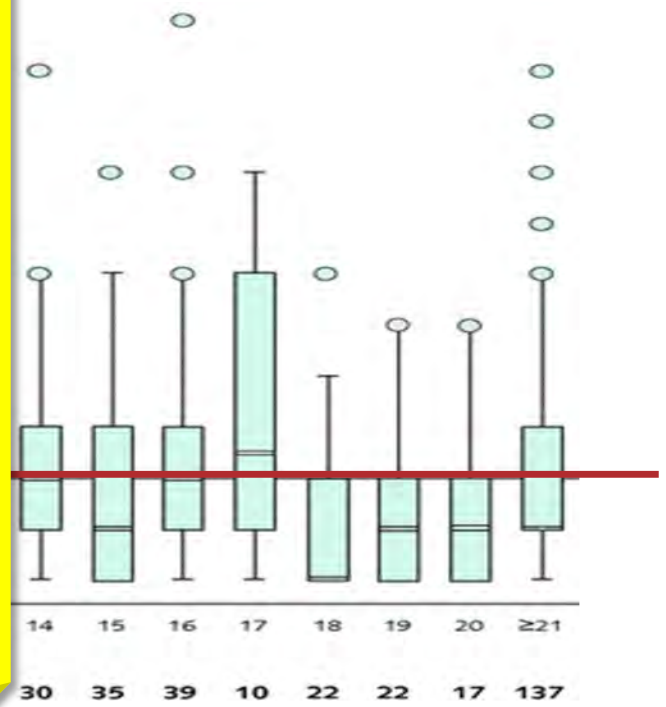
The problem:

systematic and transparent approach is rarely used when citing earlier similar trials



...amination of the citation of prior ...olled trials. Ann Intern Med. 2011;154(1):50-5.

Are systematic reviews used to justify a new study?

- Meta-epidemiological, descriptive cross-sectional study analysing RCTs published between 2014 and 2016.
- Less than 20% explicitly mentioned a systematic review as justification for the new study
- 44% did not cite a single systematic review

Section of the manuscript	SR cited, *N* (%)	Number of SRs cited, range	SR cited as a justification for conducting trial, *N* (%)
Introduction	278 (43)	1-10	76 (12)
Methods	51 (8)	1-4	2 (0.03)
Discussion	245 (39)	1-11	62 (10)
Entire manuscript	360 (56)[a]	1-19	126 (20)[a]

[a]In some of the trials, SR reported in multiple sections of a manuscript.

Engelking A, Cavar M, Puljak L. **The use of systematic reviews to justify anaesthesiology trials: A meta-epidemiological study.** Eur J Pain. 2018;22(10):1844-9.

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	2 (0.03)
	62 (10)
	126 (20)[a]

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e use of systematic reviews to justify -epidemiological study. Eur J Pain.

Do previous systematic reviews inform the design of a new study?

- Retrospective study using application for funding to see if a systematic review (SR) is used in the planning and design of new RCTs
- Cohort 2006-08: 42 of 46 (89%) referred to a SR
- Cohort 2013: 34 of 34 (100%) referred to a SR

Very few used SRs to inform the design of the trials (Besides to justify the treatment comparison: >90%)

Table 2 The use of systematic reviews in trial design

Reasons	Cohort I No. of applications (%) ($n = 42$)	Cohort II No. of applications (%) ($n = 34$)
Adverse events	7 (16.6)	1 (2.9)
Choice of frequency/dose	2 (4.7)	1 (2.9)
Duration of follow-up	1 (2.3)	2 (5.8)
Estimating the control group event rate	2 (4.7)	0 (0)
Estimating the difference to detect or margin of equivalence	2 (4.7)	1 (2.9)
Inform standard deviation	0 (0)	3 (8.8)
Intensity of interventions	1 (2.3)	1 (2.9)
Justification of prevalence	3 (7.1)	0 (0)
Justification of treatment comparison	38 (90.4)	32 (94.1)
Recruitment and consent	4 (9.5)	1 (2.9)
Route of intervention	0 (0)	1 (2.9)
Selection of definition or outcome	5 (11.9)	5 (16.1)
Withdrawal rate	1 (2.3)	0 (0)

2006-08 **2013**

Bhurke S, et al. **Using systematic reviews to inform NIHR HTA trial planning and design: a retrospective cohort**. BMC Med Res Methodol. 2015;15:108.

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inform the ?

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The problem:

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ws in trial design

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2006-08 **2013**

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Do authors put their results in the context of earlier similar research?

- Retrospective study showed that most randomised studies published in the month of May in the top 5 high impact journals made no systematic attempt to set their results in context with no improvement over time.

	1997 N=26	2001 N=33	2005 N=18	2009 N=29	2012 N=35
First trial addressing the question	1	3	3	5	2
Contained an updated systematic review integrating the new results	2	0	0	1	2
Discussed a previous systematic review in the topic area of the new trial but did not attempt to integrate their results	4	3	5	10	11
No apparent systematic attempt to set the results in the context of other trials	19	27	10	13	20

Classification of Discussion sections in reports of randomised studies published in May in Annals of Internal Medicine, BMJ, JAMA, Lancet and NEJM

Clarke M, Hopewell S. **Many reports of randomised trials still don't begin or end with a systematic review of the relevant evidence**. Journal of the Bahrain Medical Society. 2013;24(3):145-8.

Do autho… the conte…esearch?

- Retrospective s… showed that m… randomised stu… published in th… of May in the t… impact journals… systematic atte… their results in … with no improv… over time.

The problem:

systematic and transparent approach rarely used when placing new results in the context of existing results

2001 N=33	2005 N=18	2009 N=29	2012 N=35
3	3	5	2
0	0	1	2
3	5	10	11
27	10	13	20

…s of randomised studies published in …, JAMA, Lancet and NEJM

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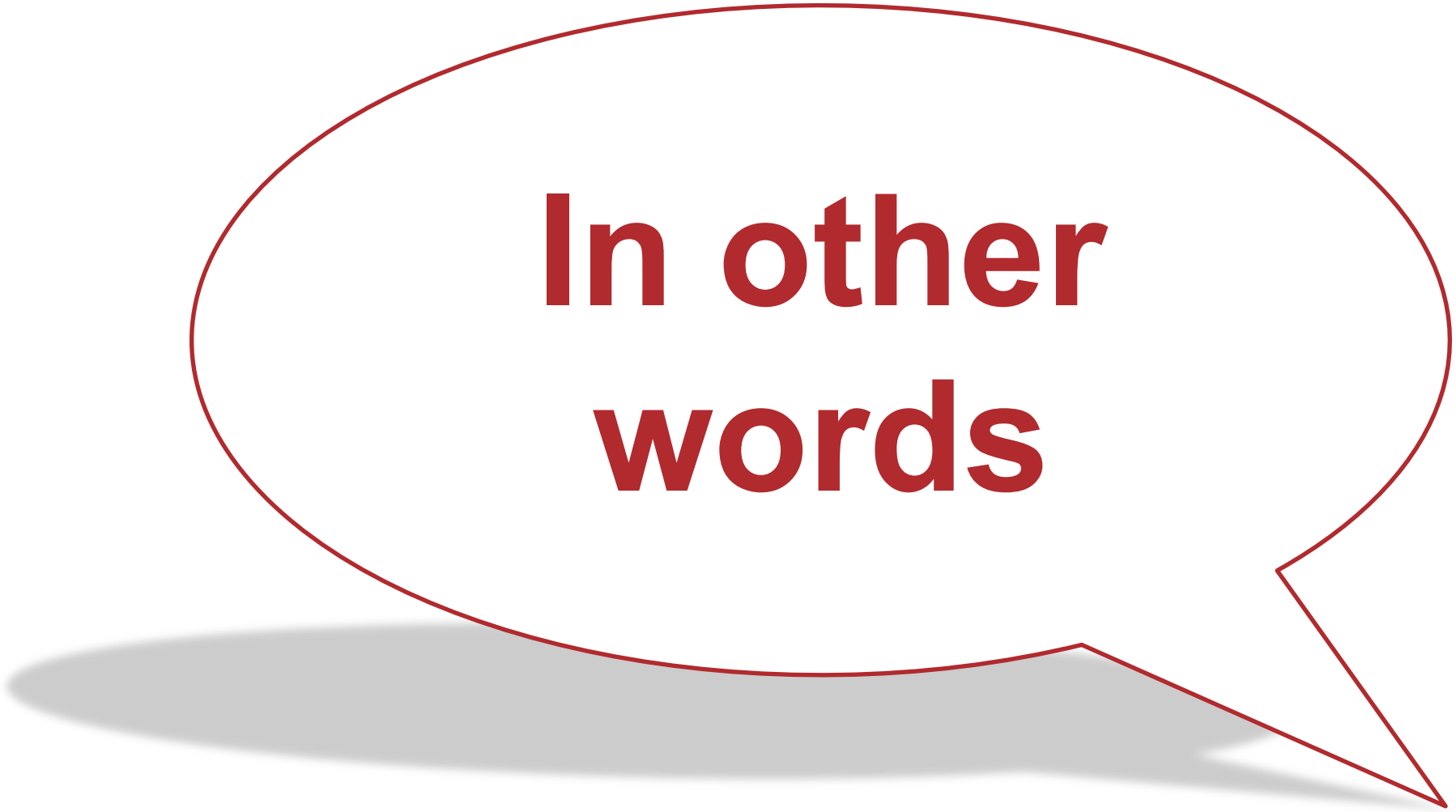
In other
words

When earlier studies are not considered in a systematic and transparent way when justifying and designing new studies:

- Too many redundant studies are performed and published – leading to the waste of time, resources and money
- Too many patients receive unnecessary placebo, or treatment which is incorrect or suboptimal – leading to the waste of health and life

When new results are not placed in the context of earlier similar trials in a systematic and transparent way:

- New results of a single study will bias the real results based upon all similar studies including the new study
- Medical reversal will happen as new interventions may be introduced in the clinic without real effect
- The recommendation that further studies are needed may be wrong and lead to new redundant studies.


This is an
ethical question!

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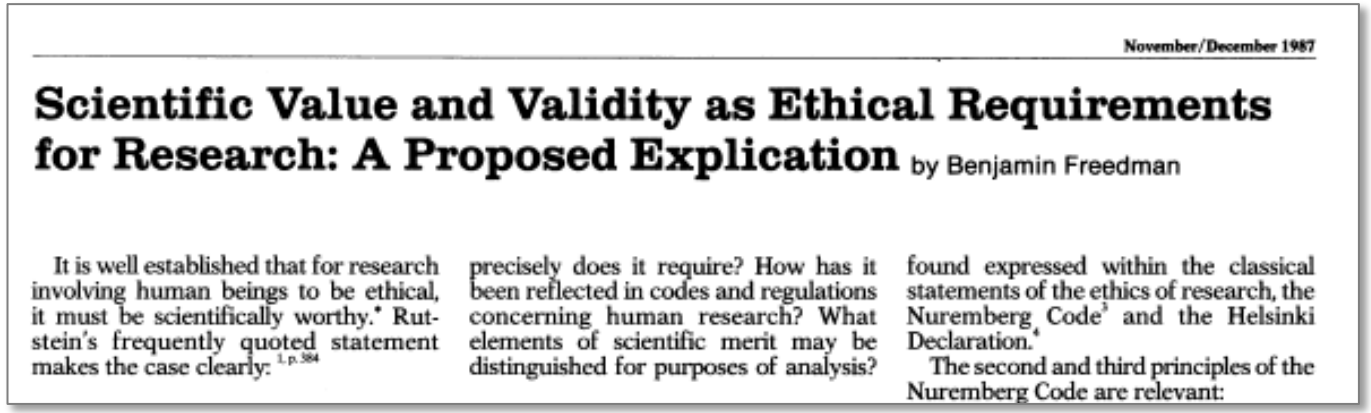
The first trial conducted under the **Nuremberg** Military Tribunals in **1947** became known as The **Doctors'** Trial, in which 23 physicians from the German Nazi Party were tried for crimes against humanity for the atrocious experiments they carried out on unwilling prisoners of war.

Nuremberg Code (1945-1946)

The experiment should be such as to yield fruitful results **for the good of society**, unprocurable by any other methods or means of study, and not random or unnecessary in nature.

The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study **that the anticipated results will justify the performance of the experiment**.

Freedman B. **Scientific Value and Validity as Ethical Requirements for Research: A Proposed Explication.** IRB: Ethics & Human Research. 1987;9(6):7-10.



November/December 1987

Scientific Value and Validity as Ethical Requirements for Research: A Proposed Explication by Benjamin Freedman

It is well established that for research involving human beings to be ethical, it must be scientifically worthy.* Rutstein's frequently quoted statement makes the case clearly: [1, p. 584]

precisely does it require? How has it been reflected in codes and regulations concerning human research? What elements of scientific merit may be distinguished for purposes of analysis?

found expressed within the classical statements of the ethics of research, the Nuremberg Code[3] and the Helsinki Declaration.[4]

The second and third principles of the Nuremberg Code are relevant:

Nuremberg

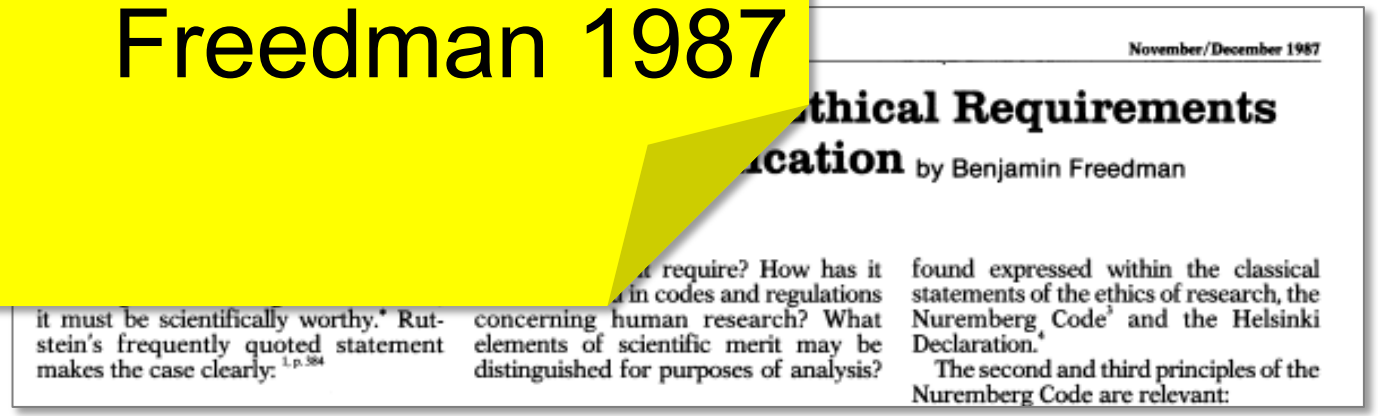
The experiment s **for the good of society**, unpro of study, and not random or ur

The experiment s results of animal experimen history of the disease or other p **ed results will justify the perfor**

"These principles seem to require as ethical preconditions that the study be of some **value**, and not simply be **valid**."

Freedman 1987

Freedman B. **Scientific Val as Ethical Requirements f Proposed Explication.** IRE Research. 1987;9(6):7-10.



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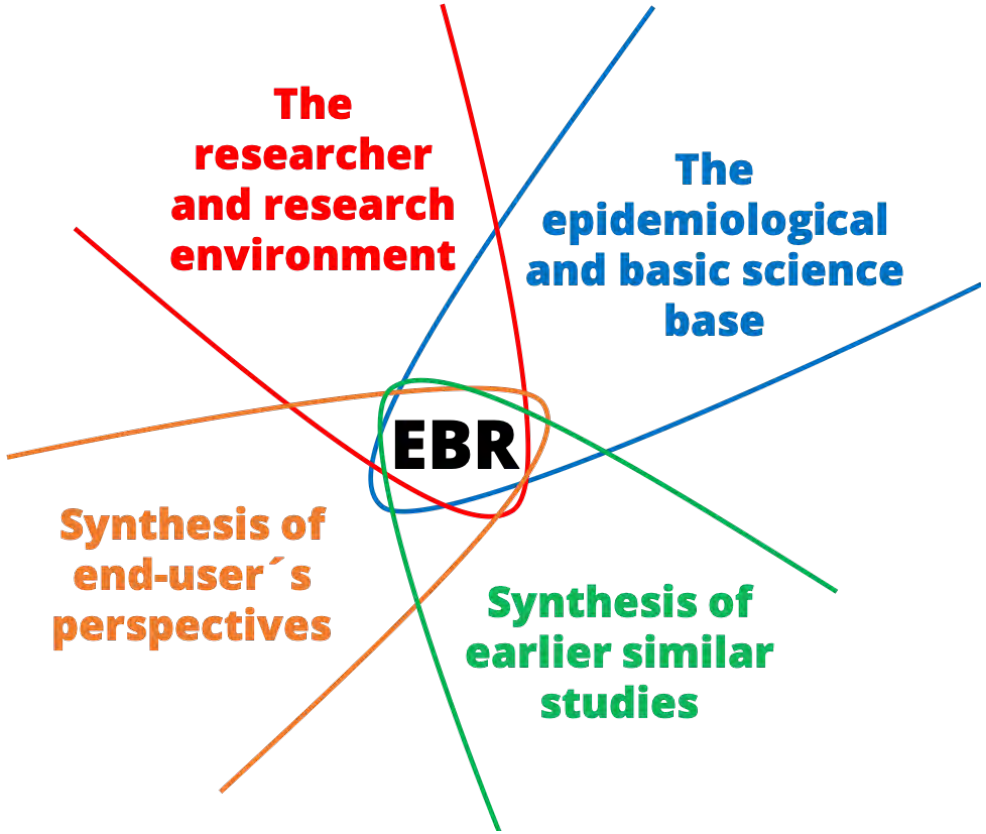
But even though the EBM has shown to be of great impact –
the use of systematic reviews in research is still lacking terrible behind!

To embark on research without ...

... systematically reviewing the evidence of what is already known, particularly when the research involves people or animals, is unethical, unscientific, and wasteful.

This systematic and transparent approach to research is called **"Evidence-Based Research" (EBR)**



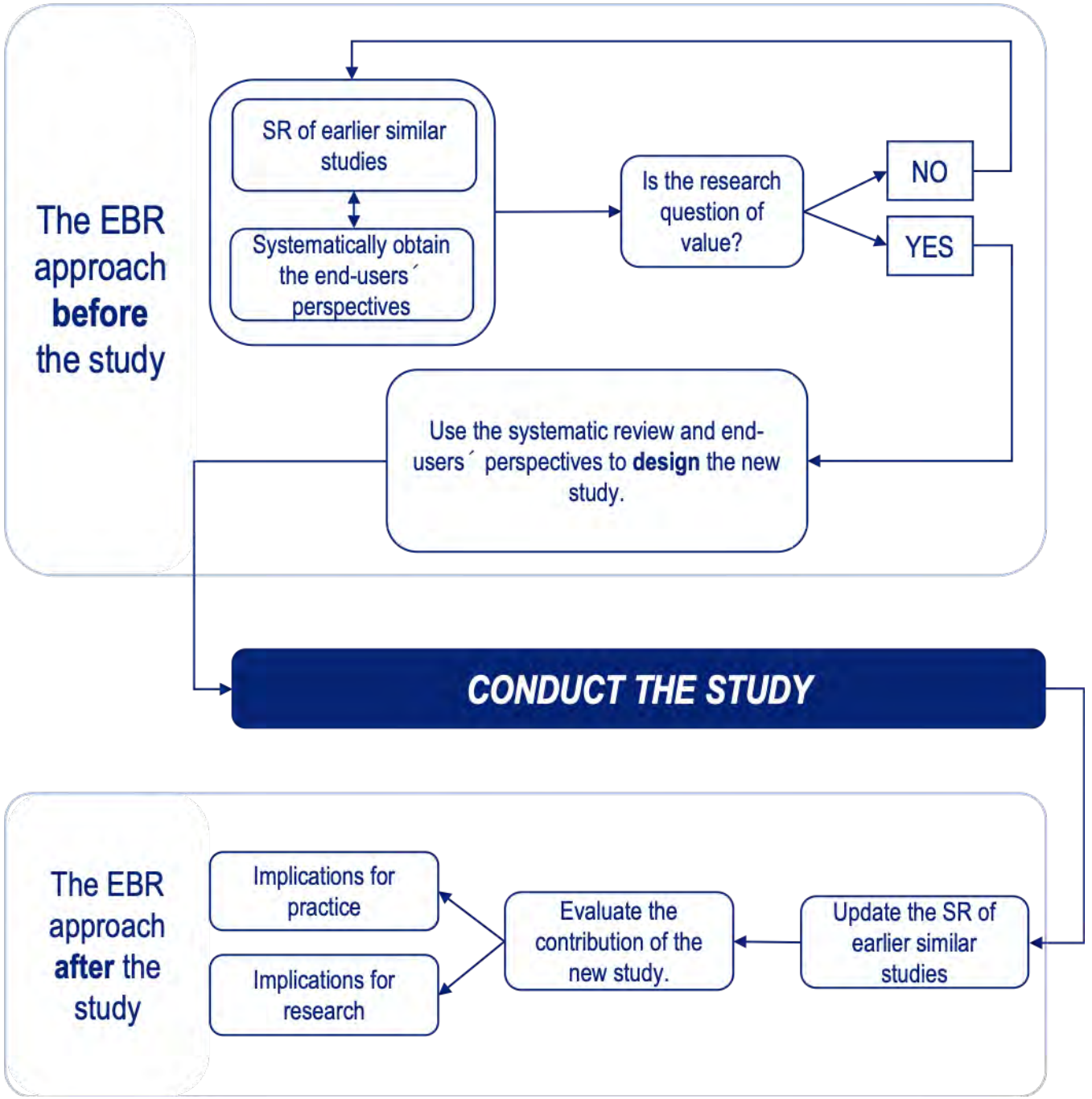
EBR can be defined as ...

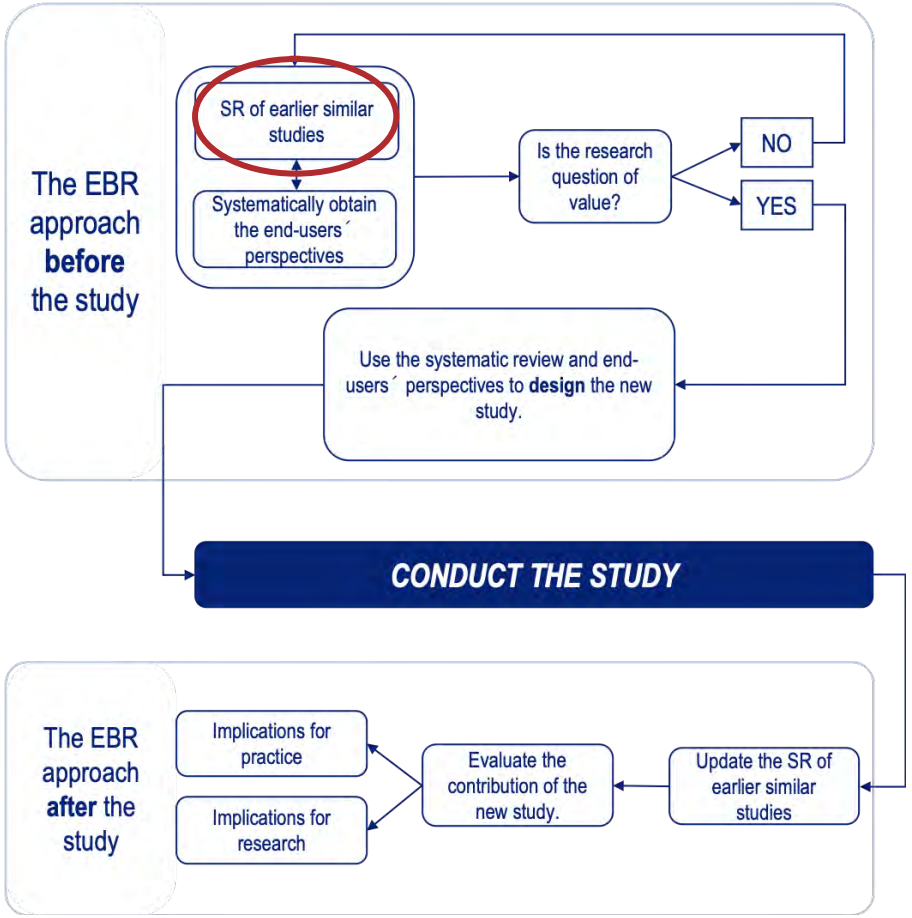
"... the use of prior research in a systematic and transparent way to inform a new study so that it is answering questions that matter in a valid, efficient and accessible manner."

IF I HAVE SEEN FARTHER, IT IS BY STANDING ON THE SHOULDERS OF GIANTS
- ISAAC NEWTON

The Evidence-Based Research Network


But
how?


The EBR approach **before** the study
SR of earlier similar studies
Systematically obtain the end-users´ perspectives
Is the research question of value?
NO
YES
Use the systematic review and end-users´ perspectives to **design** the new study.
CONDUCT THE STUDY
The EBR approach **after** the study
Implications for practice
Implications for research
Evaluate the contribution of the new study.
Update the SR of earlier similar studies



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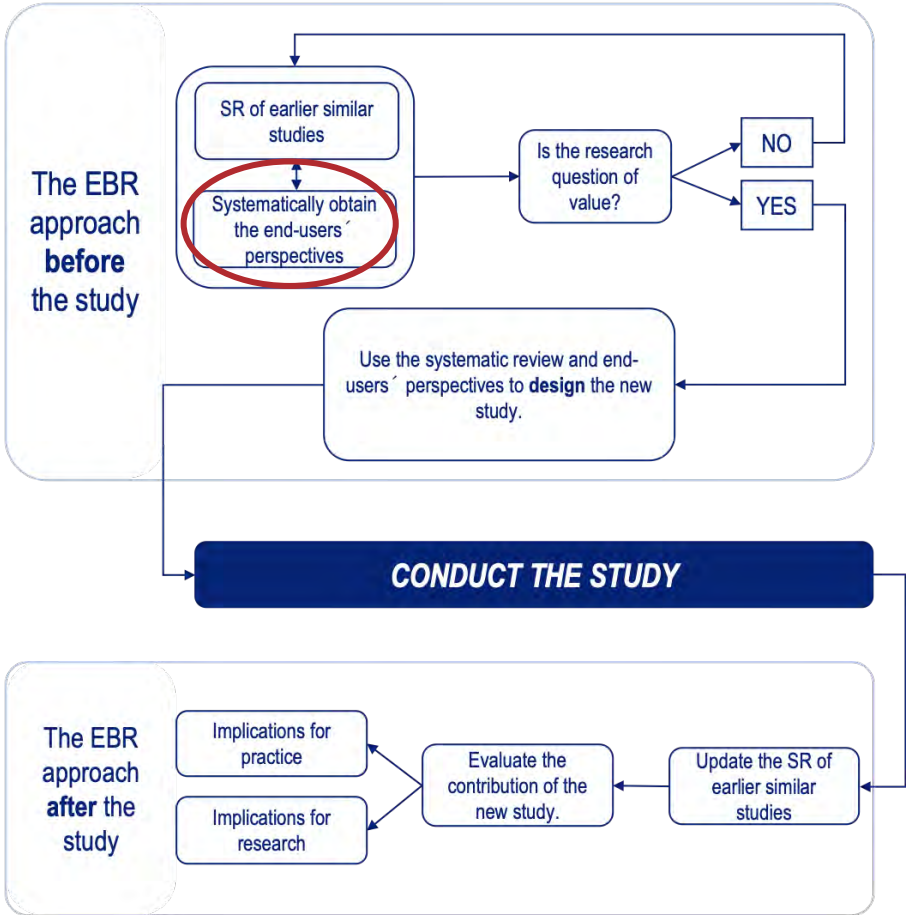
Identify a systematic review of earlier studies having tried to answer the same research question



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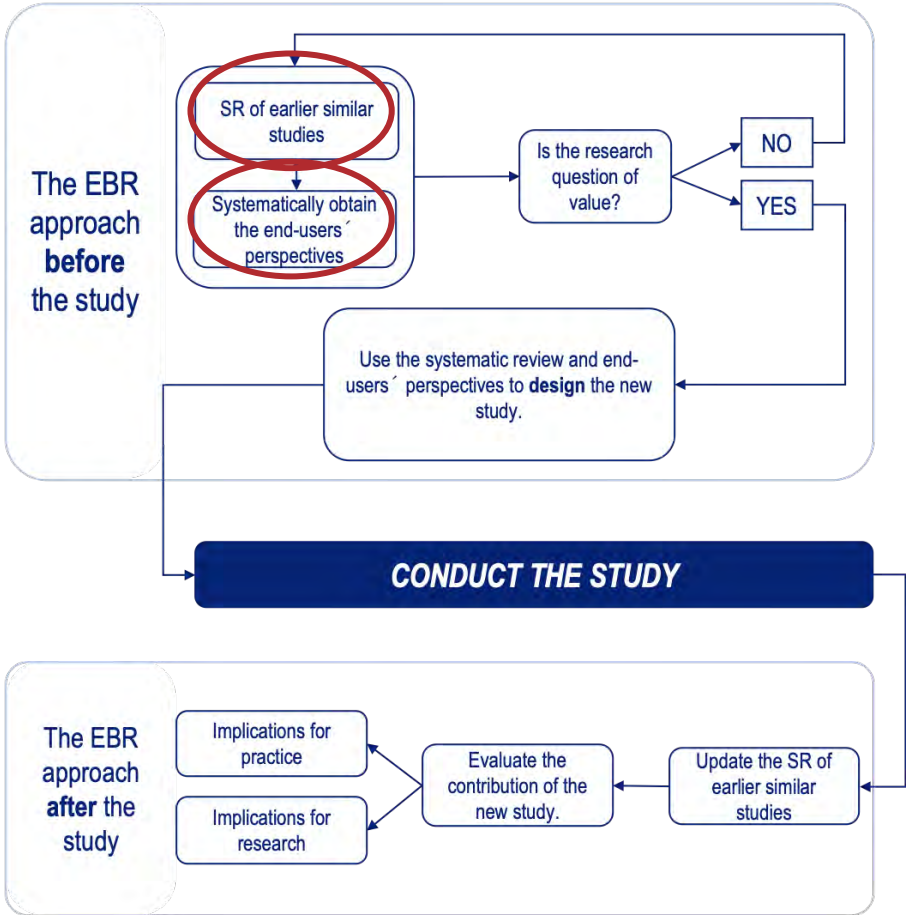
Identify a systematic review of qualitative studies obtaining the perspectives of the end-users that directly will be affected by this research

(Could be patients, next of kin, clinicians, managers, policy makers, other researchers and so on)



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Combine the results from these two systematic reviews in this matrix (Example from exercise and knee osteoarthritis (OA)):

EXAMPLE

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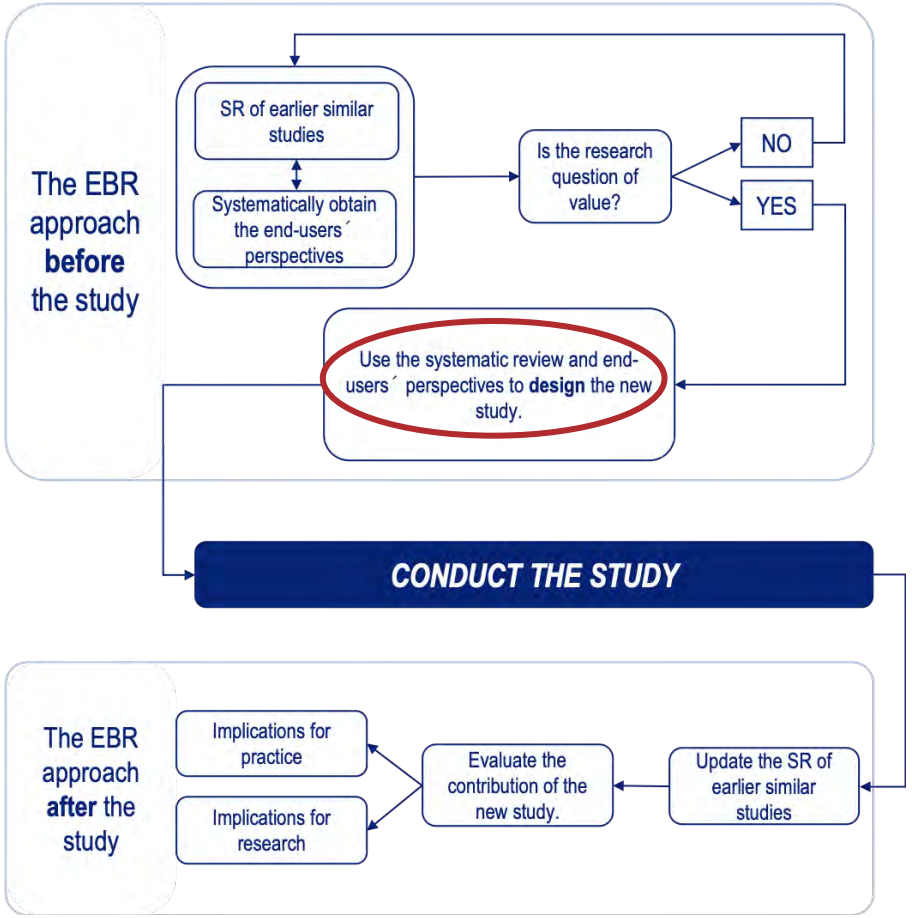
Results from earlier studies: SR Results from user perspective studies: SR-Q					
	P	I	C	O	T
SR	SR shows little knowledge about difference between short / long duration of OA	SR shows no knowledge about dose-response	SR shows few studies having compared to painkillers	**SR shows no studies measuring fatigue**	SR shows very few studies evaluating long-term
SR-Q			SR-Q shows need to compare to painkillers.	**SR-Q shows biggest problem not pain, but fatigue.**	SR-Q shows need to know long-term effect.



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Based upon the matrix it is also possible to decide upon design, i.e. if all aspects of the PICOT or just some of the aspects is needed to be adjusted related to earlier studies

Now the need for the new study is justified!

OR

you have realized that no further studies is needed.

Call to Action:

- Join EBRNetwork (All researchers)
- Join EVBRES and/or participate in the EBR Training School (Health researchers)
- Promote the concept of EBR in your own organisation and work
- Use an evidence-based research approach while planning new studies
- Use an evidence-based research approach when placing new results in the context of previous similar studies and when formulating recommendations for practice and future research

Thank you

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www.evbres.eu

@evbres

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