Brian Jackson, *Untitled 6* Artwork from Reflections Art in Health

An Industry Perspective on the Utility of Systematic Reviews

Launch of the CAMARADES-NC3Rs Systematic Review Facility (SyRF), 30 March 2017

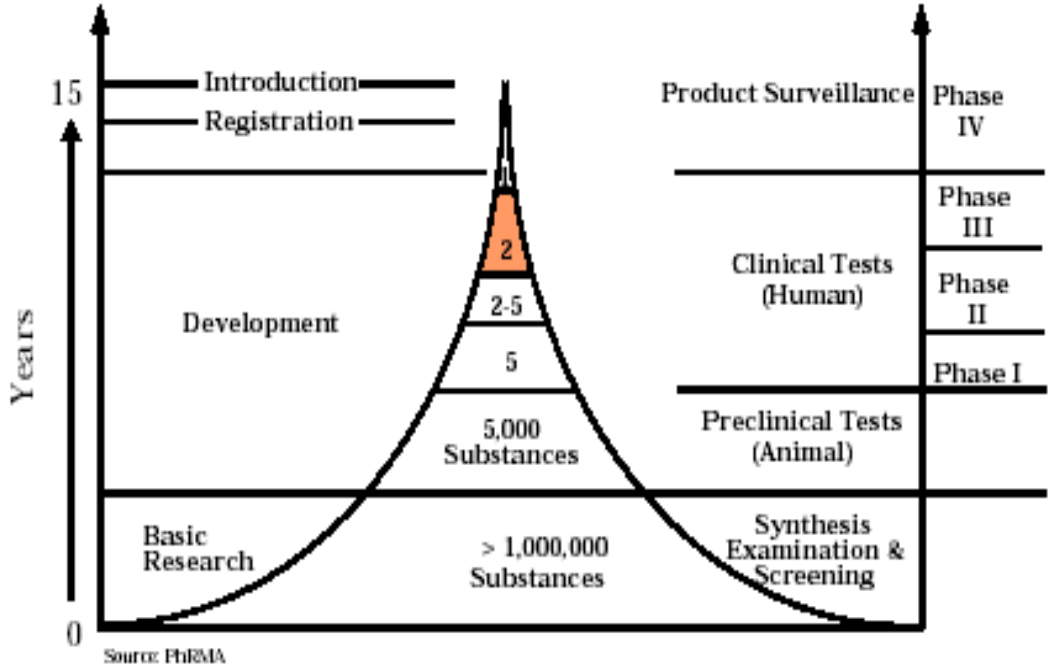
Thomas Steckler

The views expressed in this presentation are solely those of the individual authors, and do not necessarily reflect the views of their employers.

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Development of Drugs: Complex and Time Consuming

$ 2.6 billion to develop a drug*



Systematic Reviews: established at later stages

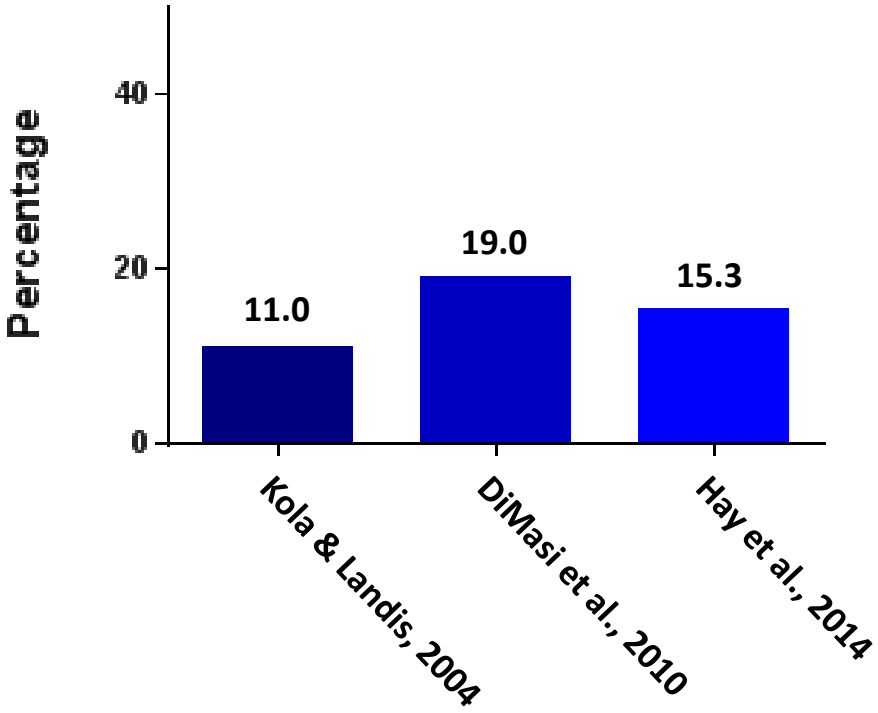
- **58 preclinical projects needed on average to achieve 1 launch**
- **93 preclinical projects needed to have 80% likelihood to achieve one launch**

(Decision Analysis & Portfolio Management, 2005)

*Tufts Center for the Study of Drug Development, 2015

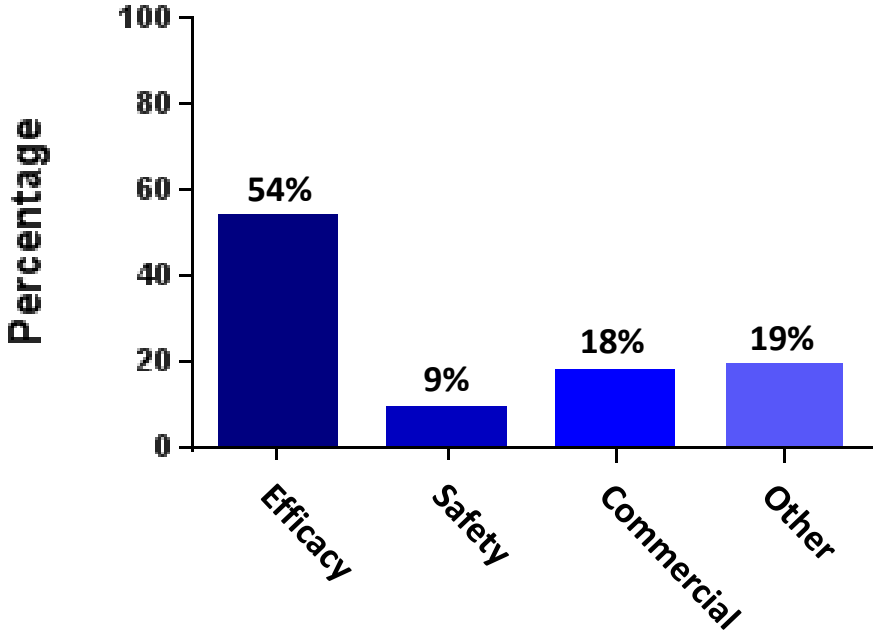
Probability of FDA Approval for Drugs in Phase 1

Low Probability for Lead Indication Across 3 Studies



Reason for Attrition in Phase 3

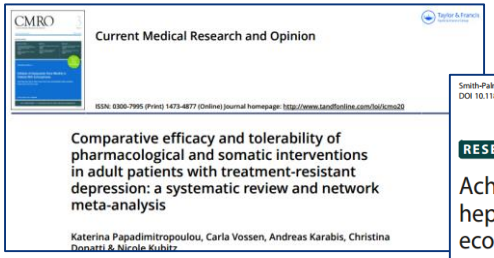
Hay et al., 2014

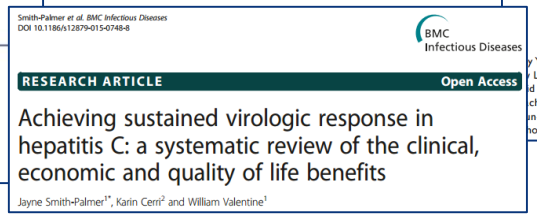


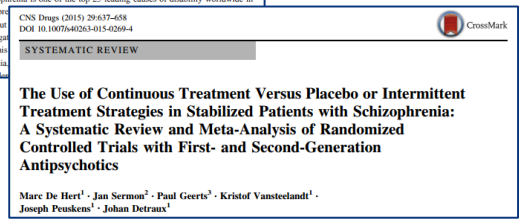

Can
Systematic
Reviews
help?

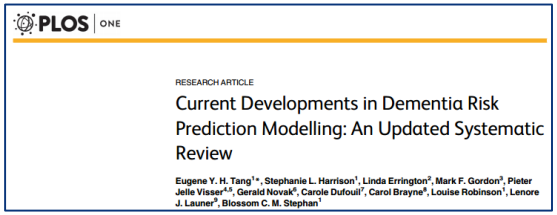
Systematic Reviews at Janssen

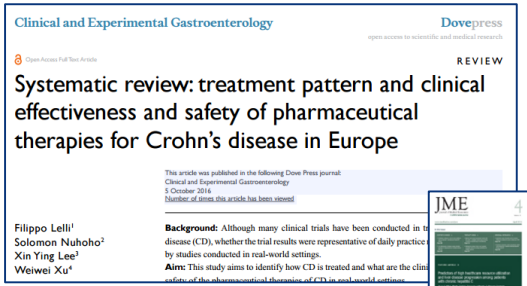
Established in Clinical Research and Health Economics

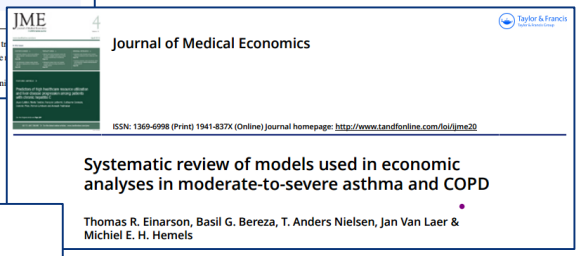


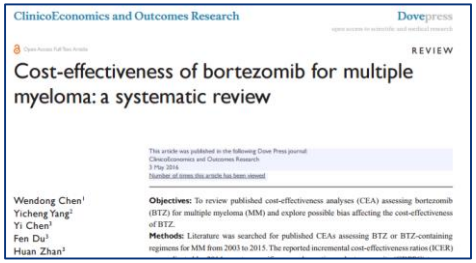


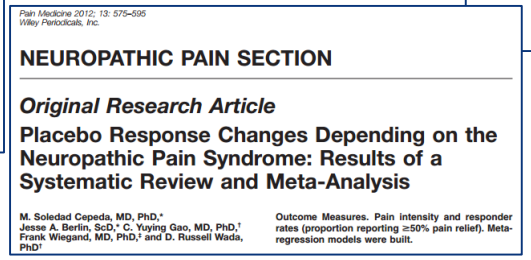












But Rather Limited Use in Other Areas Related to Drug Development

OXFORD SOT Society of Toxicology www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 152(1), 2016, 10–16

doi: 10.1093/toxsci/kfw059
Advance Access Publication Date: May 5, 2016
Forum Article

FORUM ARTICLE

The Emergence of Systematic Review in Toxicology

Martin L. Stephens,[a,1] Kellyn Betts,[b] Nancy B. Beck,[c] Vincent Cogliano,[d] Kay Dickersin,[e] Suzanne Fitzpatrick,[f] James Freeman,[g] George Gray,[h] Thomas Hartung,[a,i] Jennifer McPartland,[j] Andrew A. Rooney,[k] Roberta W. Scherer,[e] Didier Verloo,[l] and Sebastian Hoffmann[m]

Health Policy 100 (2011) 4–17

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journal homepage: www.elsevier.com/locate/healthpol

Review

The cost of drug development: A systematic review

Steve Morgan[a,b,*], Paul Grootendorst[c,d], Joel Lexchin[e,f], Colleen Cunningham[a], Devon Greyson[a]

Research BMJ

Comparison of treatment effects between animal experiments and clinical trials: systematic review

Pablo Perel, Ian Roberts, Emily Sena, Philipa Wheble, Catherine Briscoe, Peter Sandercock, Malcolm Macleod, Luciano E Mignini, Pradeep Jayaram, Khalid S Khan

Assessment of somatic *k-RAS* mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer

Helena Linardou, Issa J Dahabreh, Dimitra Kanaloupiti, Fotios Siannis, Dimitrios Bafaloukos, Paris Kosmidis, Christos A Papadimitriou, Samuel Murray

Lancet Oncol 2008; 9: 962-72

Summary

Background Somatic mutations of the *k-RAS* oncogene have been assessed as a mechanism of de-novo resistance to epidermal growth factor receptor (EGFR) tyrosine-kinase inhibition in patients with non-small-cell lung cancer (NSCLC), and to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer (mCRC). The aim of this systematic review and meta-analysis was to assess if *k-RAS* mutations represent a candidate predictive biomarker for anti-EGFR-targeted therapeutic strategies in mCRC and NSCLC.

Review | Clinician's Corner

August 15, 2007

High-Density Lipoprotein as a Therapeutic Target
A Systematic Review

Inder M. Singh, MD, MS; Mehdi H. Shishehbor, DO, MPH; Benjamin J. Ansell, MD

» Author Affiliations

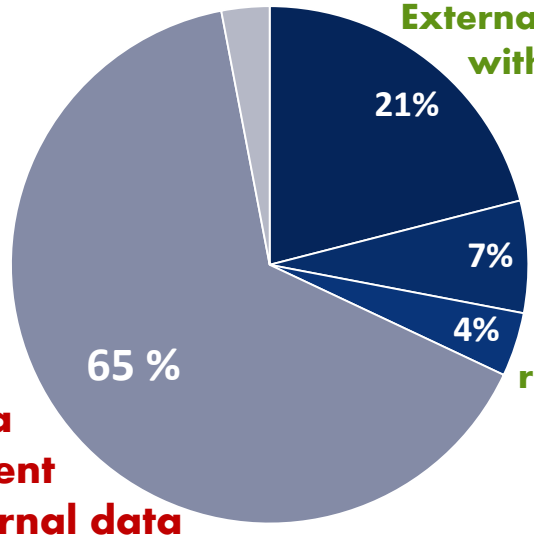
JAMA. 2007;298(7):786-798. doi:10.1001/jama.298.7.786

Unaware of any SR in drug discovery / preclinical development at Janssen

Despite Background of Poor Reproducibility of Published Preclinical Data

Majority of published studies not reproduced by Bayer

- Oncology
- Women's health
- Cardiovascular



External data consistent with internal data

Main external data reproducible internally

Some external data reproducible internally

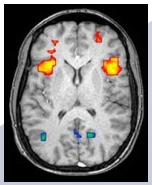
External data inconsistent with internal data

Prinz et al., Nature Rev Drug Disc, 2011

Aggregation of available information in a neutral manner reduces risk of bias and cherry picking

Should We Use Systematic Reviews Earlier? Example Target Validation

Tractability?
Viable starting points?
Freedom to operate?

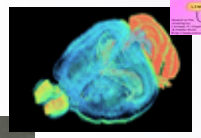


Medical Need? Supportive Clinical Data?
Evidence for efficacy and safety in patients?
Evidence for genetic association between target and disease?
Evidence for target linked to disease phenotype?

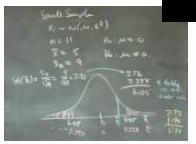
Market?

Supportive In Vivo Data?
Evidence for predictive validity of models?
Evidence for models with disease phenotype?
Evidence for efficacy of preclinical target manipulation?

Evidence for Conserved Cross-Species Characteristics?



Evidence for Relevant Expression Pattern?



Plausible Hypothesis?

What Prevents Systematic Review Early On for Target Validation?

Limited data and limited transparency

- Preference for new targets in the hope to develop first in class drugs
- Insufficient public data on novel target leaves review inconclusive

Limited availability of unbiased data

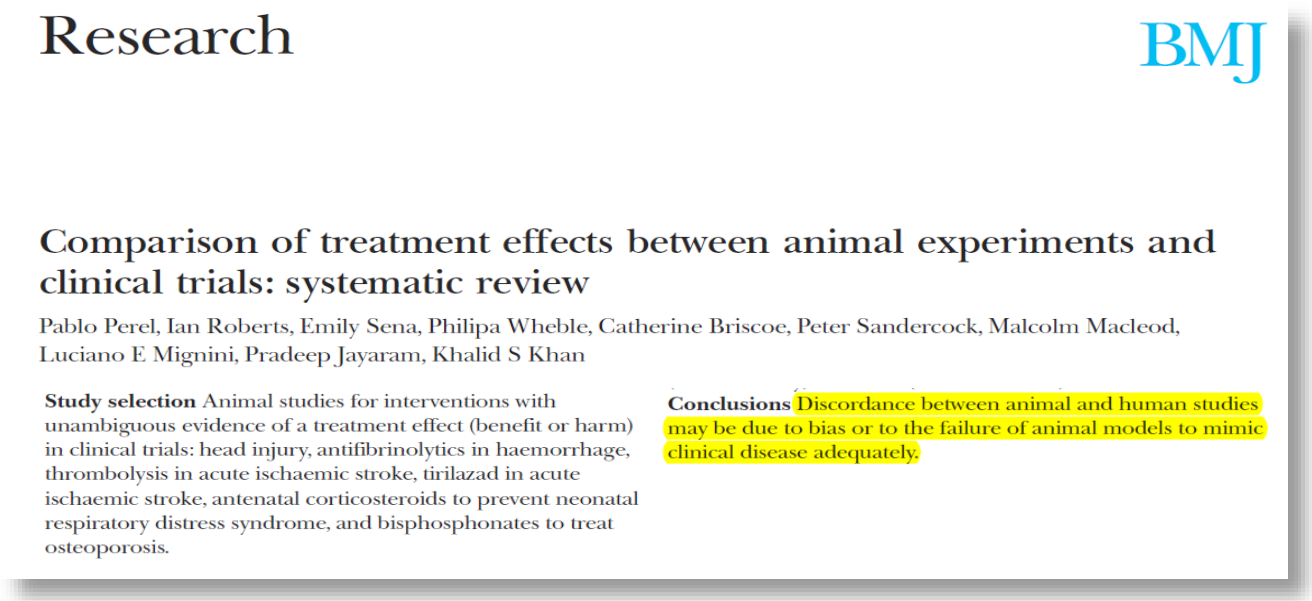
- Low likelihood of publication of negative data, especially for new findings on novel mechanism of action/target

➡ Leads to overestimation of the role of a target in a disease process

Long timelines to completion

- Often industry requires rapid decisions about the validity of a target
- Time required for a Systematic Review may be prohibitive

Where could Systematic Review be Enabling in Drug Discovery ? Example Assay Validation



Research

BMJ

Comparison of treatment effects between animal experiments and clinical trials: systematic review

Pablo Perel, Ian Roberts, Emily Sena, Philipa Wheble, Catherine Briscoe, Peter Sandercock, Malcolm Macleod, Luciano E Mignini, Pradeep Jayaram, Khalid S Khan

Study selection Animal studies for interventions with unambiguous evidence of a treatment effect (benefit or harm) in clinical trials: head injury, antifibrinolytics in haemorrhage, thrombolysis in acute ischaemic stroke, tirilazad in acute ischaemic stroke, antenatal corticosteroids to prevent neonatal respiratory distress syndrome, and bisphosphonates to treat osteoporosis.

Conclusions Discordance between animal and human studies may be due to bias or to the failure of animal models to mimic clinical disease adequately.

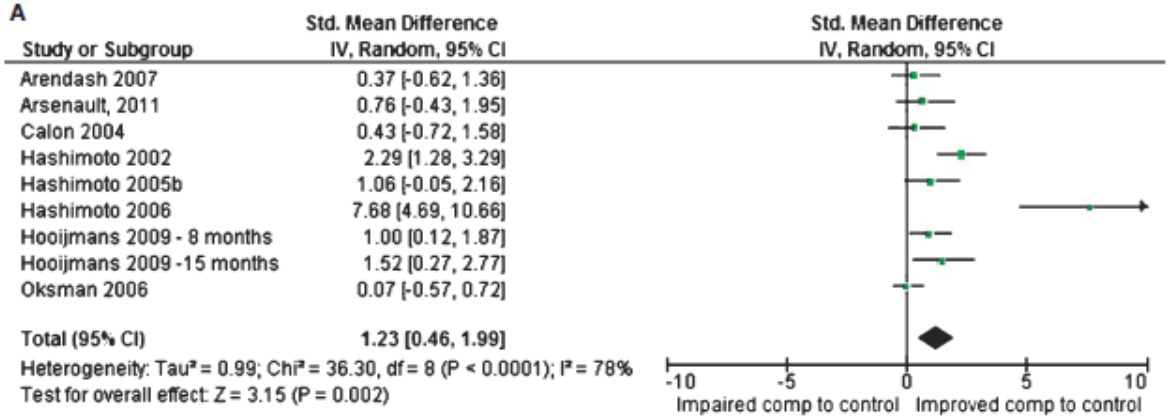
Potential Utilities:

- **Scientific tool**: *Phenotypic screening of compounds based on effects obtained in model systems*
  (Routine) efficacy / safety / tox models
- **Management tool**: *Decision-making based on predictions of clinical efficacy and absence of safety/tox issues of lead compounds*
- **Ethical tool**: *Animal study protocol approval by ethical committees*

The Problem: You Get Out What You Put In

Effects of Long-Term Omega-3 Fatty Acid Supplementation on Cognition in Animal Models of Alzheimer's Disease

A



B

Subgroups	n	Effect size and CI
Overall	9	1.23 [0.46, 1.99]
Male	6	1.72 [0.58, 2.86]
Female	0	ne
Mixed	3	0.50 [-0.14, 1.13]
Mice	6	0.56 [0.15, 0.98]
Rats	3	3.17 [0.77, 5.57]

Fig. 2. (a) Forest plot (effect size and 95% CI) and (b) subgroup analysis of individual studies of omega-3 FA supplementation on cognition in experimental animal models of Alzheimer's disease.

Hooijmans et al., J. Alzheimer's Disease 28, 2012

Included Cognition Studies

Study Characteristics (from Table 2 in Hooijmans et al., p. 195-195):

Study	Species	AD model	Sex	Supplement	Route of administration	Start supplementation	Amount of supplement (treated/control)	Duration of supplementation	Outcome measures
Arendash [43]	Mouse	AβPP/PS1 2×TgAD	?	*n*-3 fatty acids	Diet	2 months	13%/2.76	5.5 months	Cognition; MWM, circular platform
									platform recognition, Y-maze, RAWM
Arsenault [54]	Mouse	AβPP/PS1/tau; 3×TgAD	?	DHA	Diet	4 months	0.6%/0	8–10 months	Cognition: object recognition
Calon [45]	Mouse	tg2576	M+F	DHA	Diet	17 months	0.6%/<0.01%	103 days	Cognition: MWM
Hashimoto [48]	Rat	Aβ infused rats	M	DHA in gum arabic solution	Oral	25 weeks	300 mg/kgBW/day vs 0	15 weeks	Cognition: avoidance learning
Hashimoto [50]	Rat	Aβ infused rats	M	DHA in gum arabic solution	oral	26 weeks	300 mg/kgBW/day vs 0	12 weeks	Cognition: Radial Arm Maze
Hashimoto [46]	Rat	Aβ infused rats	M	DHA in gum arabic solution	oral	26 weeks	300mg/kgBW/day vs 0	12 weeks	Cognition: Radial Arm Maze
Hashimoto [47]	Rat	Aβ infused rats	M	DHA in gum arabic solution	oral	25 weeks	300mg/kgBW/day vs 0	12 weeks	Cognition: avoidance learning
Hooijmans [39]	Mouse	AβPP/PS1 2×TgAD	M	DHA + EPA	diet	2 months	0.4%/0%	6 or 13 months	Cognition: MWM, circular platform, reverse MWM
Oksman [53]	Mouse	AβPP/PS1 2×TgAD	M	DHA	diet	6 months	0.5%/0%	4 months	Cognition: MWM

No. tests truly predictive:

Tasks used (from Hooijmans et al., p. 198):

Task	Number of studies
M… wa… maze	5
Avo… …arning	2
Obj… …ition	1
Ra… …arm …aze	1

0

But: It doesn't work in patients!

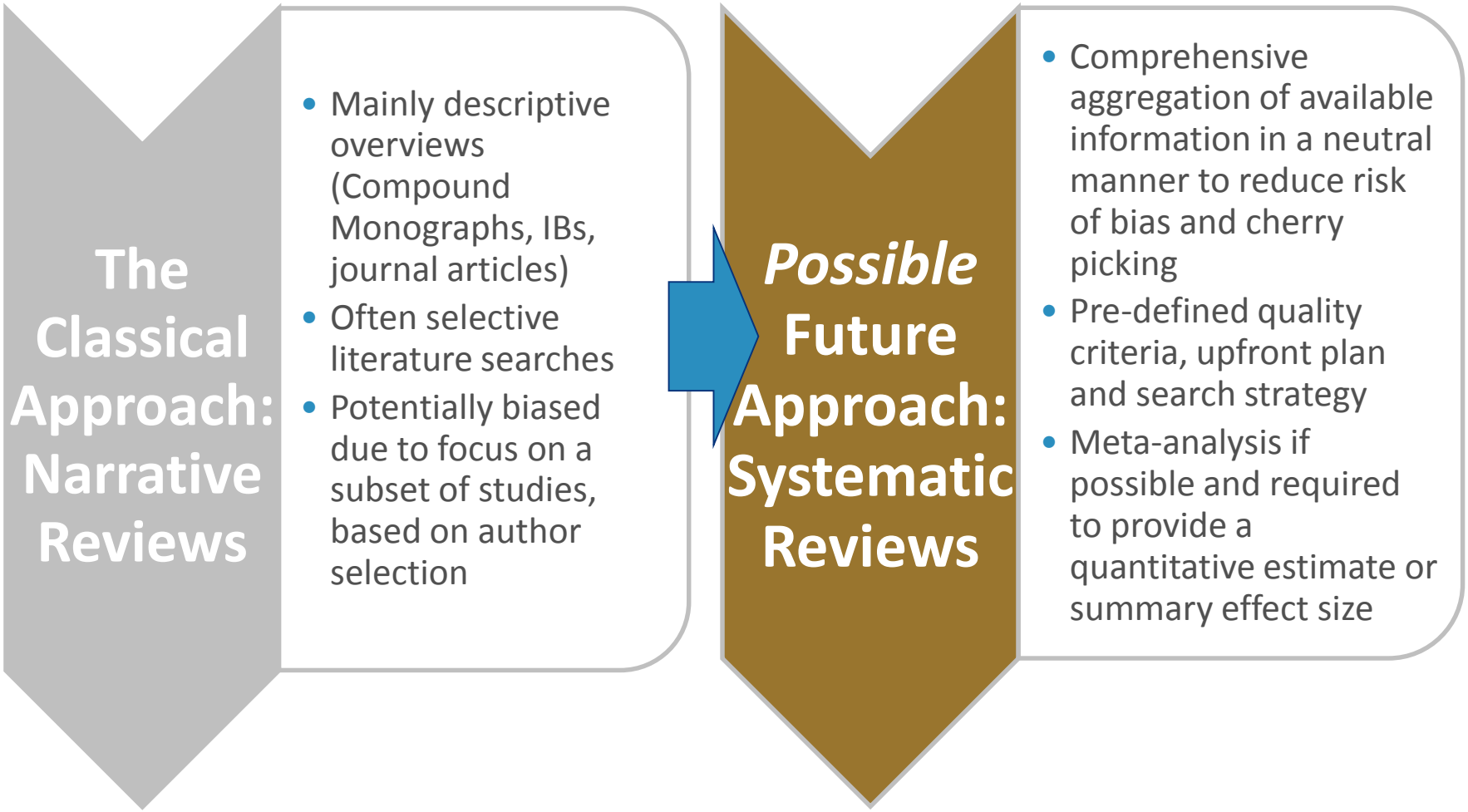
Authors' conclusions

We found no convincing evidence for the efficacy of omega-3 PUFA supplements in the treatment of mild to moderate AD. This result was consistent for all outcomes relevant for people with dementia. Adverse effects of omega-3 PUFAs seemed to be low, but based on the evidence synthesised in this review, we cannot make a final statement on tolerability. The effects on other populations remain unclear.

Cochrane Library

Burckhardt M, Herke M, Wustmann T, Watzke S, Langer G, Fink A.
Omega-3 fatty acids for the treatment of dementia.
Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD009002.
DOI: 10.1002/14651858.CD009002.pub3.

The Status Quo - Time to Change?



A Personal View on the Utility of Systematic Reviews in Industry

Data must be fit for purpose

- Availability of qualified data sets / publications
  - ➡ Not suited for all areas of drug development

Process must be fit for purpose

- Manageable workload
  - ➡ Graded approach: aggregate data analysis as default, individual data if required
  - ➡ Limited resource needs (<< 1 FTE), automated if possible
- Acceptable timelines
  - ➡ 3 months max.

Users must understand the limitations

- Overestimation of effect sizes due to biases in original reports
- Still requires judgement whether data are pertinent

Can SyRF offer solutions?

Meeting the conditions above, SRs would facilitate evidence-based decisions, also in the earlier stages of DD, and should be more widely employed !