Cochrane France

Distorsion des résultats de la recherche clinique

Isabelle Boutron

Cochrane France

Centre de recherche en Épidémiologie et Statistiques

Université Paris Cité, Université Sorbonne Paris Nord, Inserm, INRAe

Université Paris Cité

Université Sorbonne Paris Nord

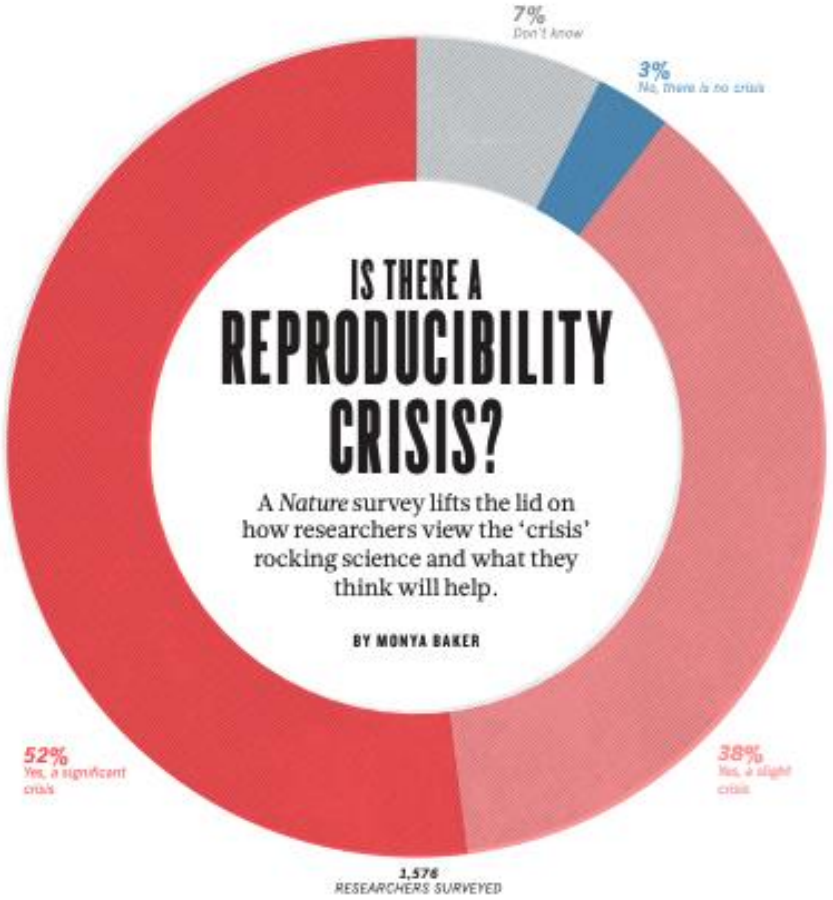
Inserm
La science pour la santé
From science to health

INRAE

Plan

- Crise de la reproductibilité
- Biais de publication
- Présentation sélective des résultats
- Spin

Crise de la reproductibilité



More than 70% of researchers have tried and failed to reproduce another scientist's experiments, and more than half have failed to reproduce their own experiments. Those are some of the telling figures that emerged from *Nature*'s survey of 1,576 researchers who took a brief online questionnaire on reproducibility in research.

The data reveal sometimes-contradictory attitudes towards reproducibility. Although 52% of those surveyed agree that there is a significant 'crisis' of reproducibility, less than 31% think that failure to reproduce published results means that the result is probably wrong, and most say that they still trust the published literature.

Data on how much of the scientific literature is reproducible are rare

Failing to reproduce results is a rite of passage, says Marcus Munafo, a biological psychologist at the University of Bristol, UK, who has a long-standing interest in scientific reproducibility. When he was a student, he says, "I tried to replicate what looked simple from the literature, and wasn't able to. Then I had a crisis of confidence, and then I learned that my experience wasn't uncommon."

The challenge is not to eliminate problems with reproducibility in published work. Being at the cutting edge of science means that sometimes results will not be robust, says Munafo. "We want to be discovering new things but not generating too many false leads."

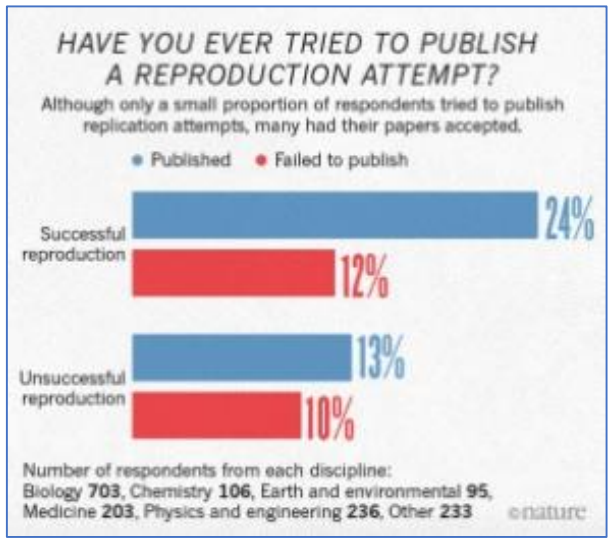
THE SCALE OF REPRODUCIBILITY

Nature 2016

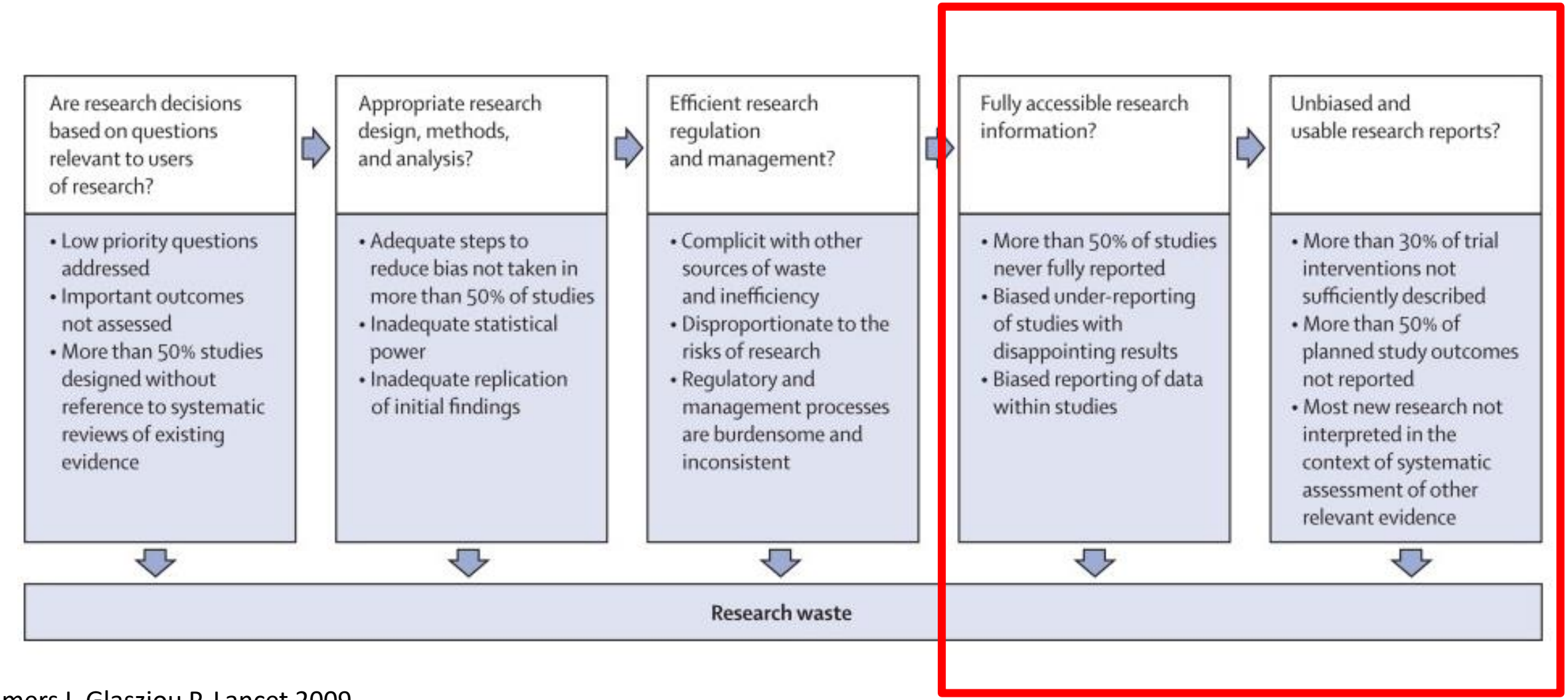
Nature's survey of 1,576 researchers

>70% of researchers have tried and failed to reproduce another scientist's experiments

>50% have failed to reproduce their own experiments.



Research quality and reproducibility is being questioned



Chalmers I, Glasziou P. Lancet 2009
Lancet series 2014
Lancet 2016

Ethique et Législation

DÉCLARATION D'HELSINKI
PRINCIPES ÉTHIQUES APPLICABLES À LA RECHERCHE MÉDICALE IMPLIQUANT DES ÊTRES HUMAINS

- 35. Toute recherche impliquant des êtres humains doit être **enregistrée** dans une banque de données accessible au public **avant que ne soit recrutée** la première personne impliquée dans la recherche.
- 36. Les chercheurs, auteurs, promoteurs, rédacteurs et éditeurs ont tous des obligations éthiques concernant la **publication et la dissémination des résultats de la recherche**. Les chercheurs ont le devoir de mettre à la disposition du public les résultats de leurs recherches impliquant des êtres humains. (..)

Legislation

FDA Amendment Act
(FDAAA 2007)

ClinicalTrials.gov

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014

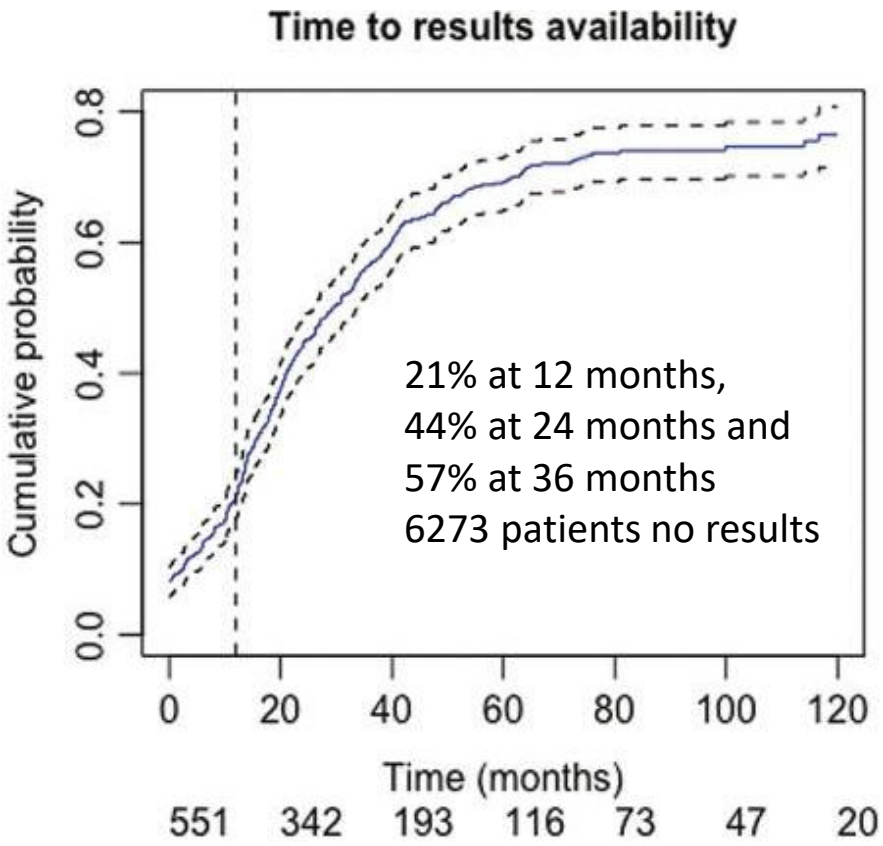
EU Clinical Trials Register

Pour les études qui débutent après 2022 -> possibilité d'avoir des sanctions financières
Responsabilité = Etats membres

Les résultats de la recherche ne sont pas disponibles

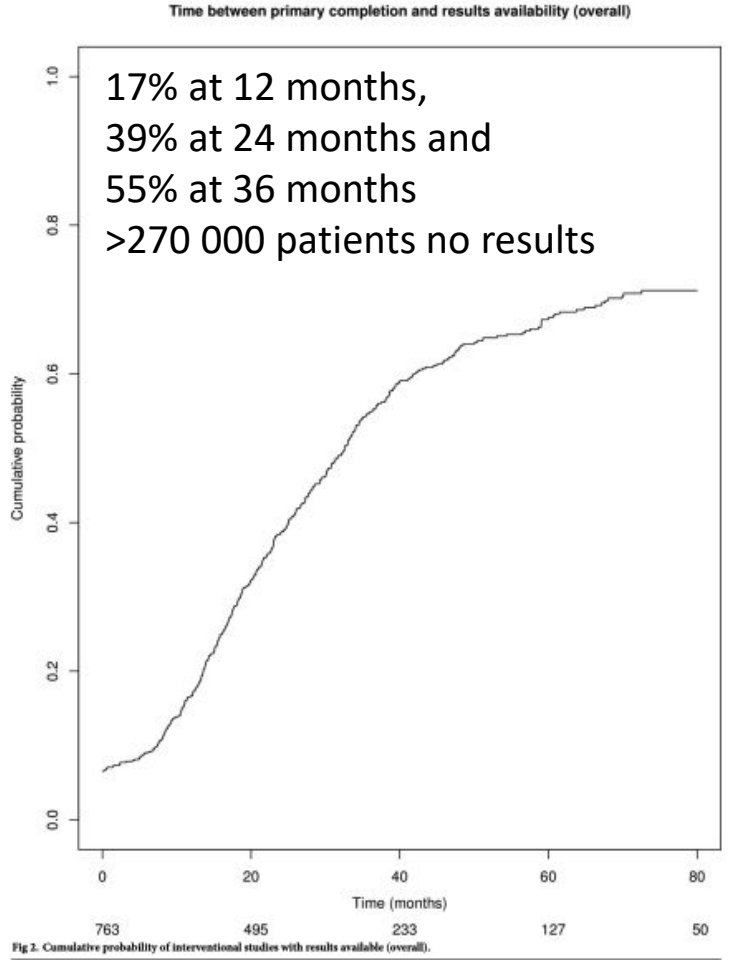
Cochrane France

Pancreatic Adenocarcinoma; 2010-2020
551 studies



Pellat, Boutron, Ravaud. The Oncologist. 2022

Colorectal cancer; 2013-2020
763 studies



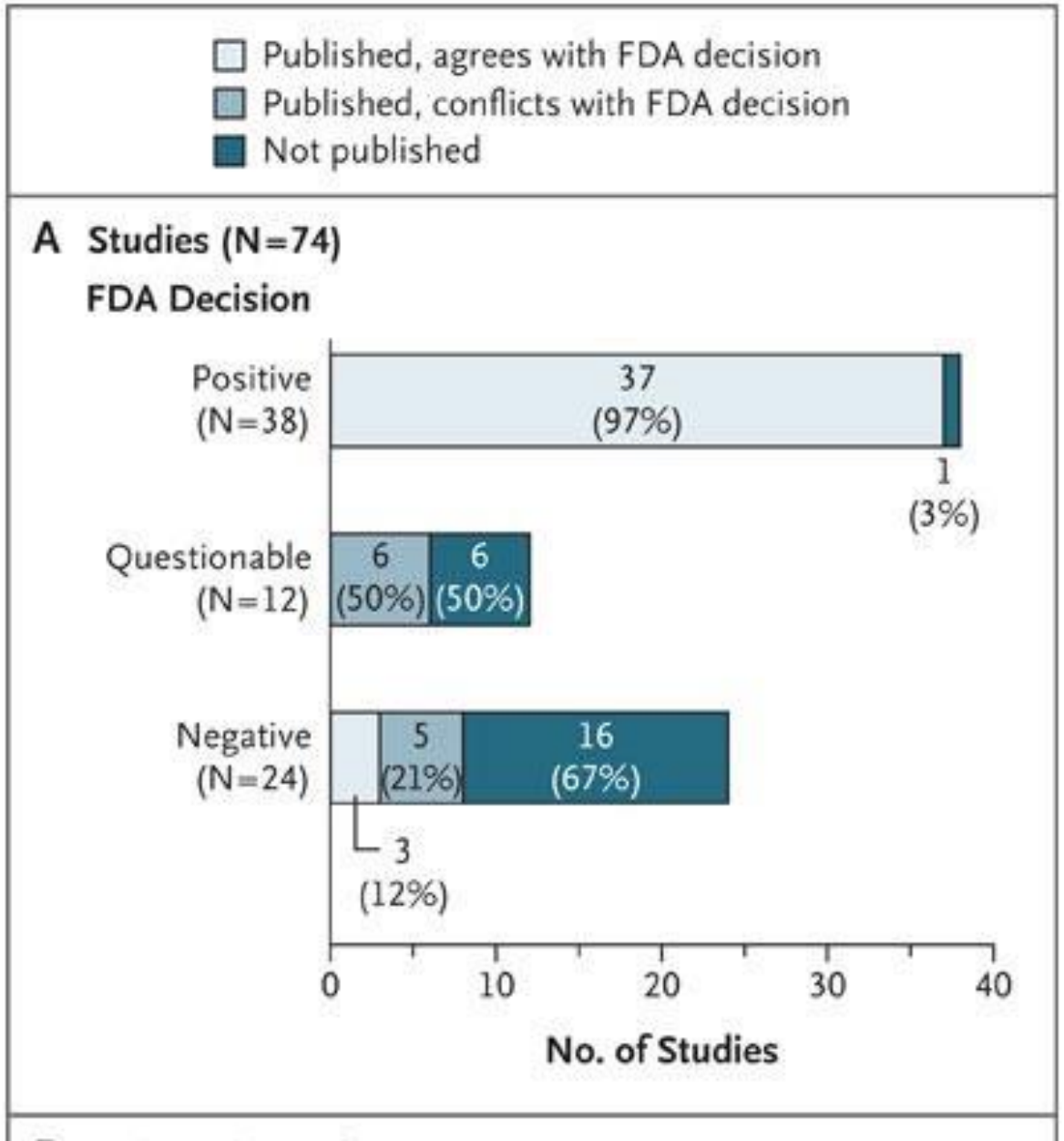
Pellat, Boutron, Ravaud. Plos One. 2022


A Published Trial
JOURNAL ARTICLES
PUBLISHED TRIAL
Conference Abstracts
clinical study report
An unpublished trial
clinical study report
!
?

L'accès aux résultats de la recherche est biaisé

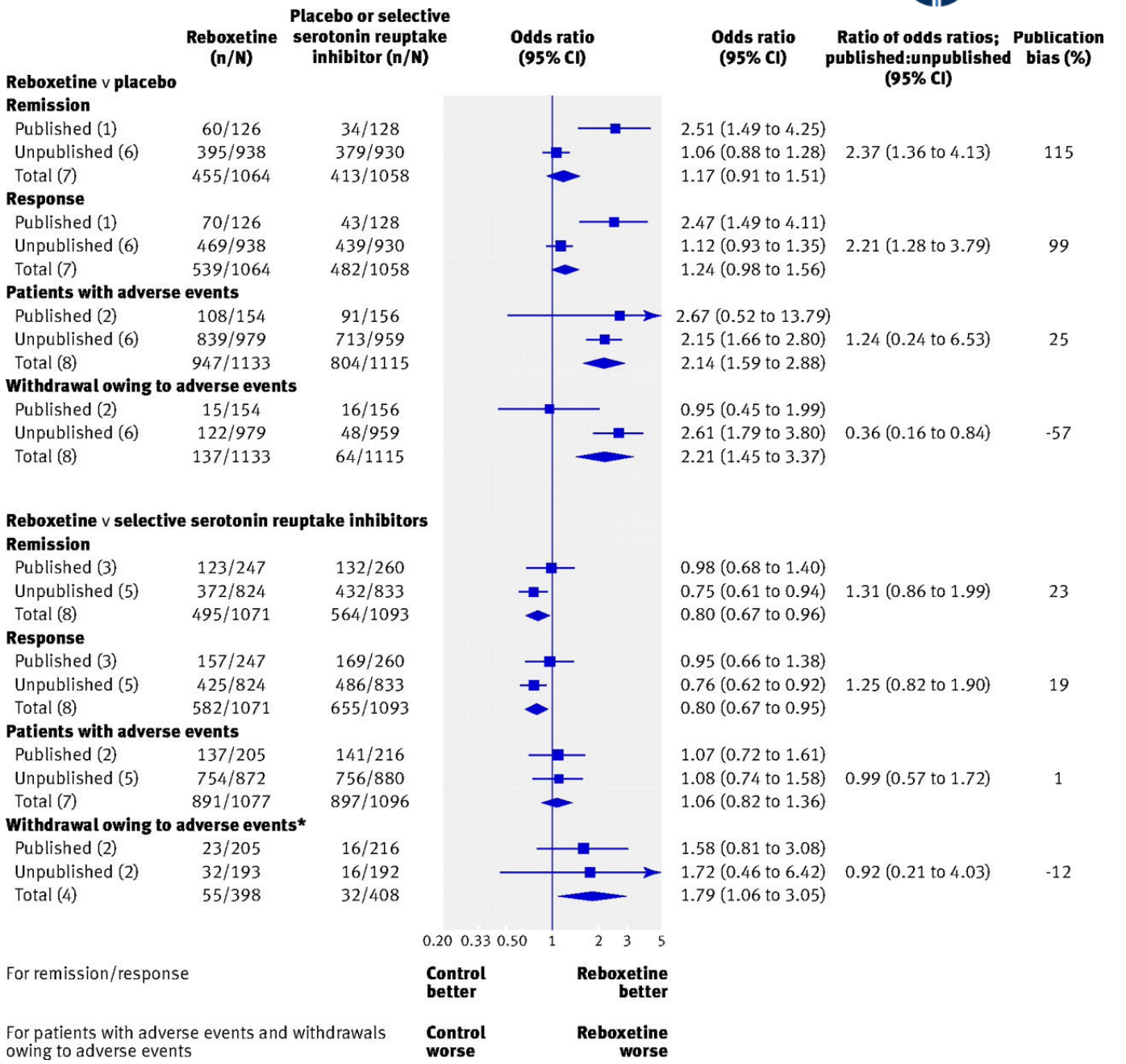
- 74 FDA-registered antidepressant trials
  - 31% were not published
  - Statistically significant results were more likely to be published
- Meta-analyses of journal data sets compared to FDA dataset showed an increase in effect size of 32% overall
  - from 11% to 69% for individual drugs

Turner, NEJM, 2008



Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials

BMJ 2010



RESEARCH ARTICLE

Extent of Non-Publication in Cohorts of Studies Approved by Research Ethics Committees or Included in Trial Registries

Christine Schmucker[1], Lisa K. Schell[1], Susan Portalupi[1], Patrick Oeller[1], Laura Cabrera[1], Dirk Bassler[3], Guido Schwarzer[2], Roberta W. Scherer[5], Gerd Antes[1], Erik von Elm[4], Joerg J. Meerpohl[1]* on behalf of the OPEN consortium[1]

rg, Berliner Allee 29, 79110 Freiburg, enter – University of Freiburg, Freiburg, , Zurich, Switzerland, **4.** Cochrane niversity Hospital Lausanne, Biopôle 2, rane Center, John Hopkins Bloomberg rica

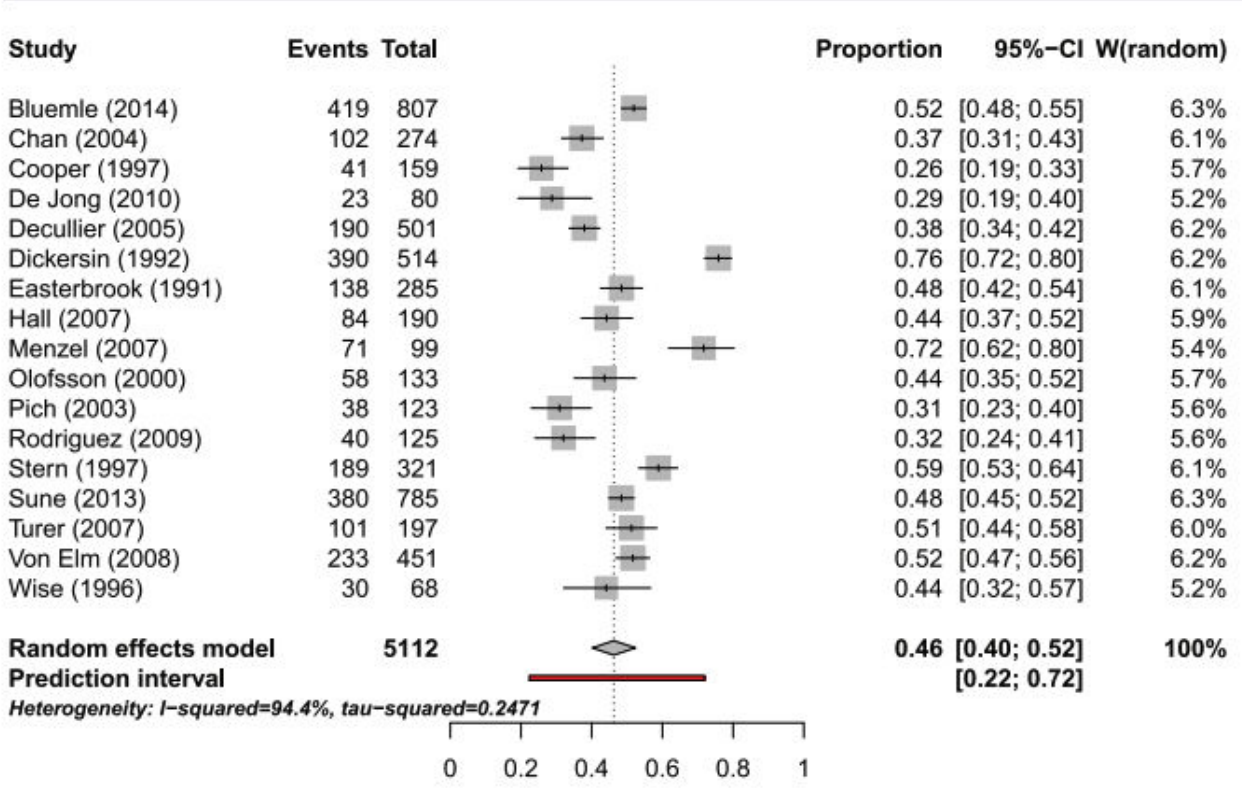


Fig. 2. Weighted proportion of published studies for 17 MRPs following studies after REC approval.

About **3 times** more likely to be published if results were statistically significant

Schmucker et al. Plos One 2014

Présentation selective des résultats et des analyses

- Selective outcome reporting :
  1. Omitting outcomes which are deemed to be unfavourable or not statistically significant.
  2. Adding new outcomes based on collected data to favour statistical significance.
  3. Including only a subset of the analysed data in the published study.
  4. Failing to report data that was analysed in the trial (such as adverse effects).
  5. Changing outcomes of interest (from primary outcomes to secondary outcomes if they do not yield significant results or the desired direction and magnitude of effect).

- In comparing published articles with protocols for clinical trials, **62% of trials had at least 1 primary outcome that was changed, introduced, or omitted**

- Statistically significant outcomes had a higher odds of being fully reported for efficacy (OR=2.4[1.4-4.0] and harm (OR, 4.7;[1.8-12.0]) data.

AW Chan JAMA 2004

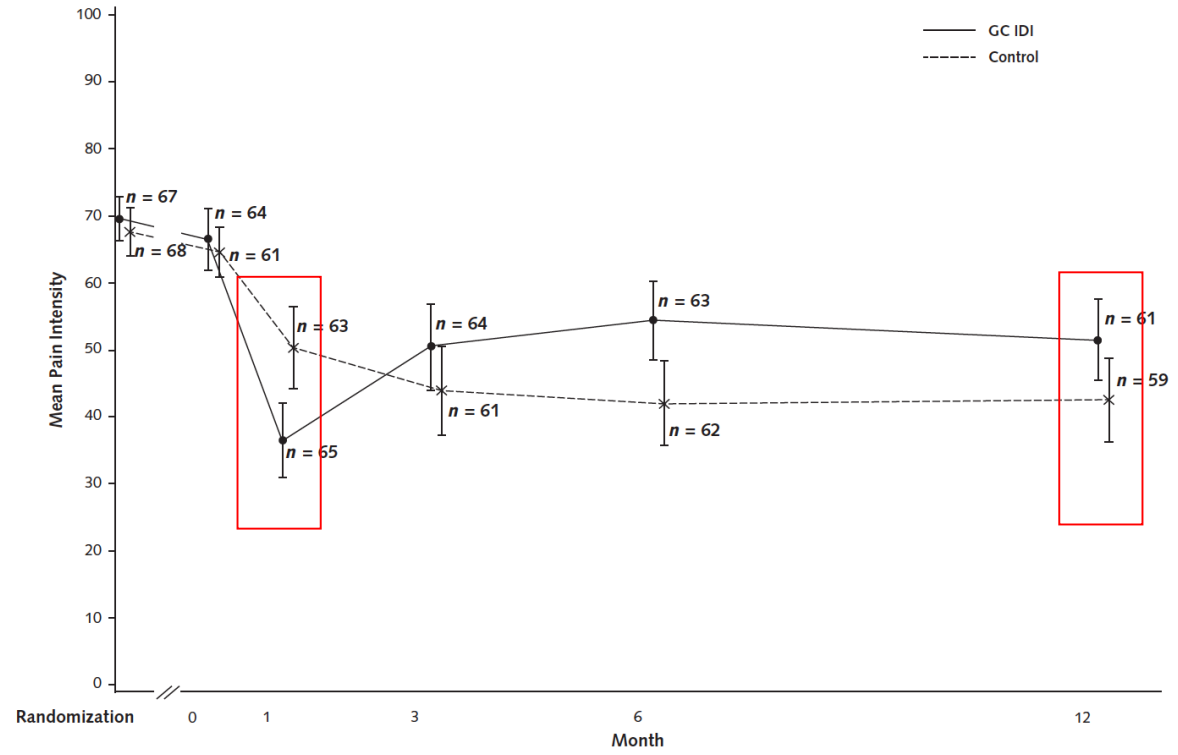
Randomized controlled trial evaluating intradiscal injection of steroid in patients with low back pain

Different possible ways to report the results?

- Mean at M1
- Mean at M6
- Mean at M12

- Mean change from baseline at M1
- Mean change from baseline at M6
- Mean change from baseline at M12

Figure 2. Mean lumbar pain intensity in previous 48 h, by intervention group.



Dichotomization

- Success is defined as less than 40/100 on pain numeric scale
- Success is defined as less than 35/100 on pain numeric scale
- Success is defined as less than 30/100 on pain numeric scale
- Etc…

Outcome in the publication

The primary outcome was the percentage of patients with LBP intensity less than 40 on an 11-point numerical rating scale (0 [no pain] to 100 [maximum pain] in 10-point increments) in the previous 48 hours at 1 month after the intervention. The main secondary outcomes were LBP intensity and

Outcome in the registry/Protocol/SAP (blinded and before the analysis)

Primary Outcome Measures : Back pain level assessed on a 11-point numeric scale (0-100) at 1 month. Success is defined as less than 40 on pain numeric scale at 1 month [Time Frame: 1 month] CT.gov

Pas de biais

Primary outcome: Back pain level assessed on a 11-point numeric scale (0-100) at 12 month

Biais de reporting

Role des registres

Tracking switched outcomes in clinical trials

Outcome switching in clinical trials is a serious problem. Between October
COMPare team systematically checked every trial published in the top five
they misreported their findings. We are now submitting the first set of findi
academic paper, summarising the quantitative results, and the themes of res
editors and trialists in collaboration with a qualitative researcher. Prior to p
and methods as per the reference at the bottom of this page. This is our wor

1. We compared each clinical trial report with its protocol or registry entr
their outcomes perfectly. For the others, we counted how many of the c
the protocol or registry were never reported. We also counted how mar
silently added.
2. When we detected unreported or added outcomes, we wrote a letter to
them out. We tracked which journals published our letters – and which

Here's what we found.

Here's what we found.

67	9	354	357
TRIALS CHECKED	TRIALS WERE PERFECT	OUTCOMES NOT REPORTED	NEW OUTCOMES SILENTLY ADDED

On average, each trial reported just 58.2% of its specified outcomes. And on average, each trial silently added 5.3 new outcomes.

58	18	8	32
LETTERS SENT	LETTERS PUBLISHED	LETTERS UNPUBLISHED AFTER 4 WEEKS	LETTERS REJECTED BY EDITOR

Learn why we did this this, more about our methodology, or see the full results for every trial.

Le concept de 'spin'

PNAS

Misrepresentation and distortion of research in biomedical literature

Isabelle Boutron[a,b,c,1] and Philippe Ravaud[a,b,c,d]

[a]Methods of Therapeutic Evaluation Of Chronic Diseases (METHODS) team, INSERM, UMR 1153, Epidemiology and Biostatistics Sorbonne Paris Cité Research Center (CRESS), F-75014 Paris, France; [b]Faculté de Médicine, Paris Descartes University, 75006 Paris, France; [c]Centre d'Épidémiologie Clinique, Hôpital Hôtel Dieu, Assistance Publique des Hôpitaux de Paris, 75004 Paris, France; and [d]Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY 10032

Edited by David B. Allison, Indiana University Bloomington, Bloomington, IN, and accepted by Editorial Board Member Susan T. Fiske November 14, 2017 (received for review June 14, 2017)

PLOS BIOLOGY

META-RESEARCH ARTICLE

'Spin' in published biomedical literature: A methodological systematic review

Kellia Chiu, Quinn Grundy, Lisa Bero*

Charles Perkins Centre, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

* lisa.bero@sydney.edu.au

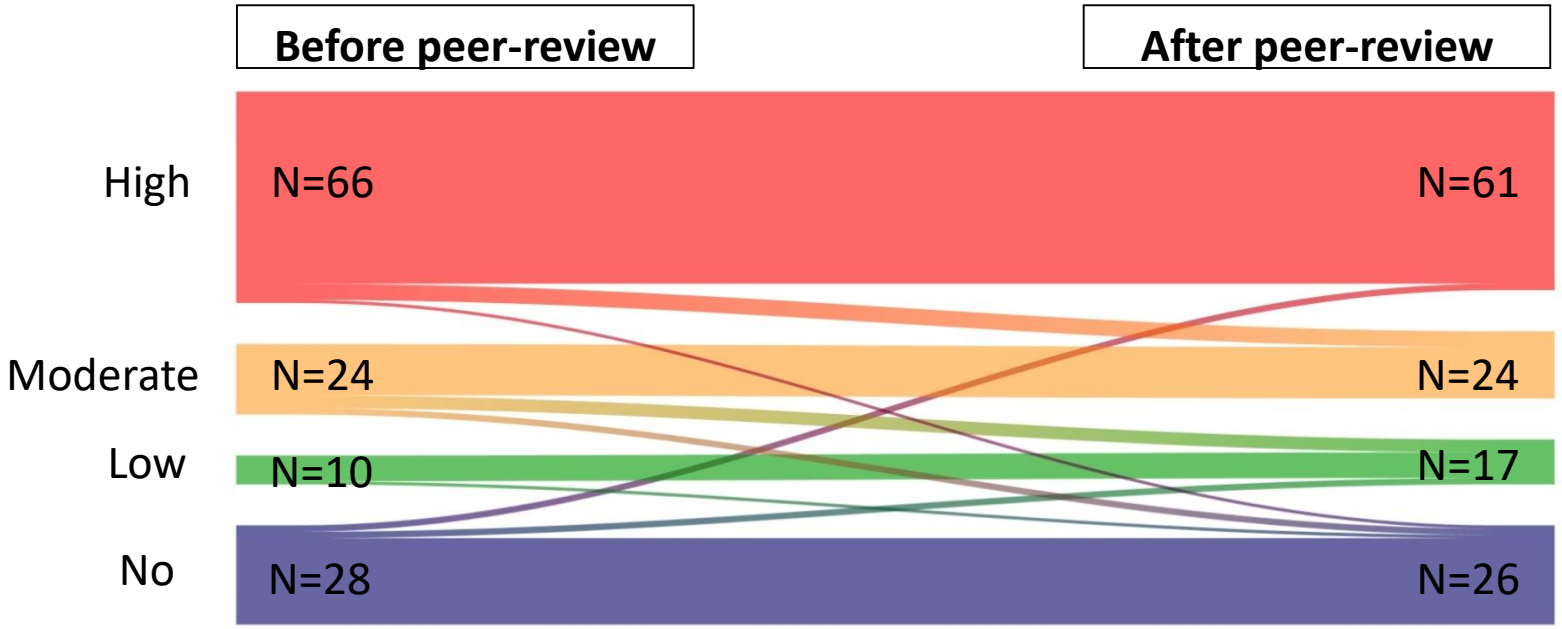
Abstract

- A **specific reporting** that **fails to faithfully reflect the findings** and that could affect the impression that the results produce in readers
- **Prevalence of spin in the conclusion: 50% of negative trials**
- Empirical evidence shows that spin can **impact** readers' interpretation

Boutron , Ravaud. PNAS 2018
Boutron et al. J Clinical Oncology 2014
Boutron et al. BMC Med 2019

Role de la peer-review

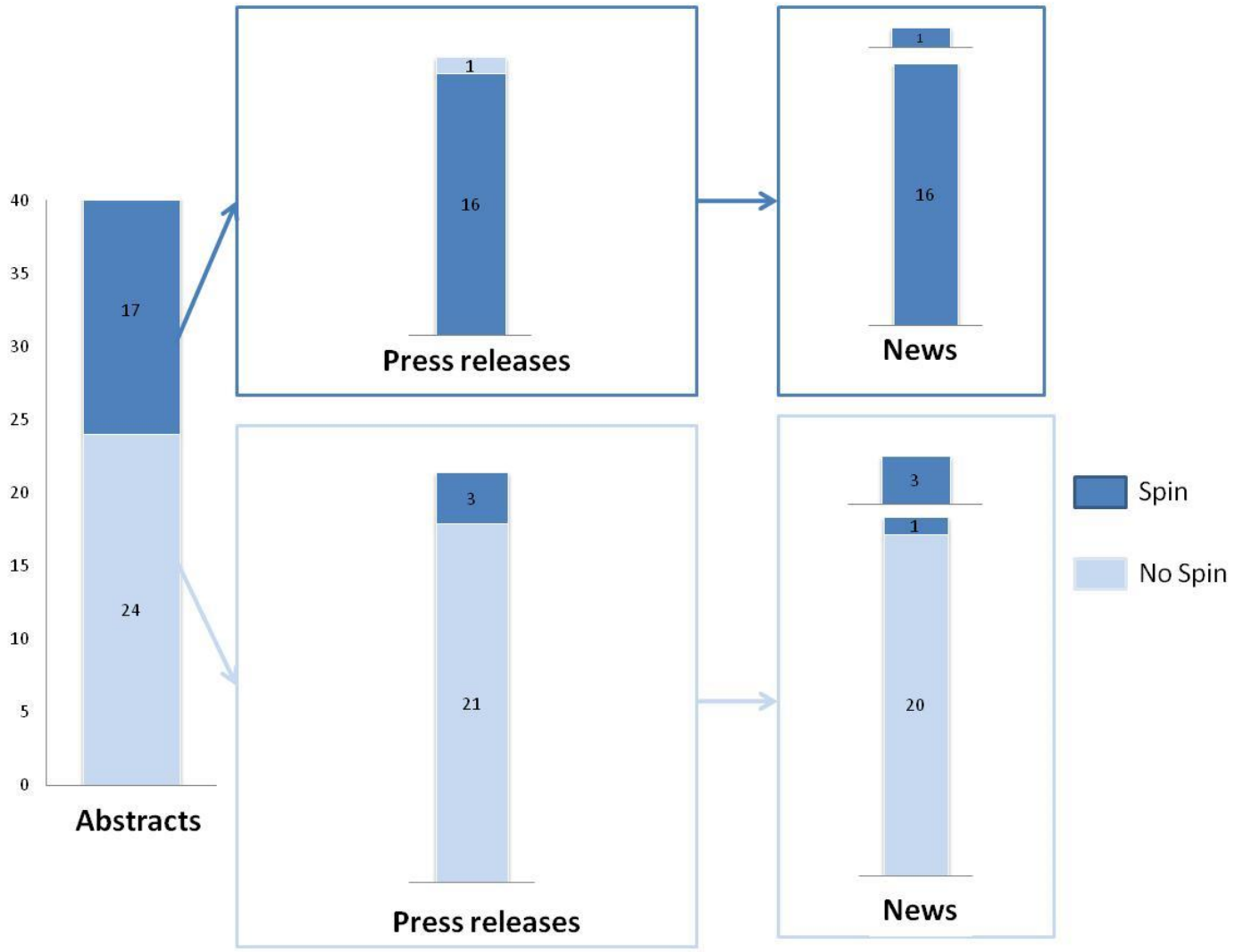
Level of spin before and after peer review in the abstract conclusion



76% Peer reviewers failed to identify spin in abstract conclusions

Lazarus, J Clin Epidemiol. 2016

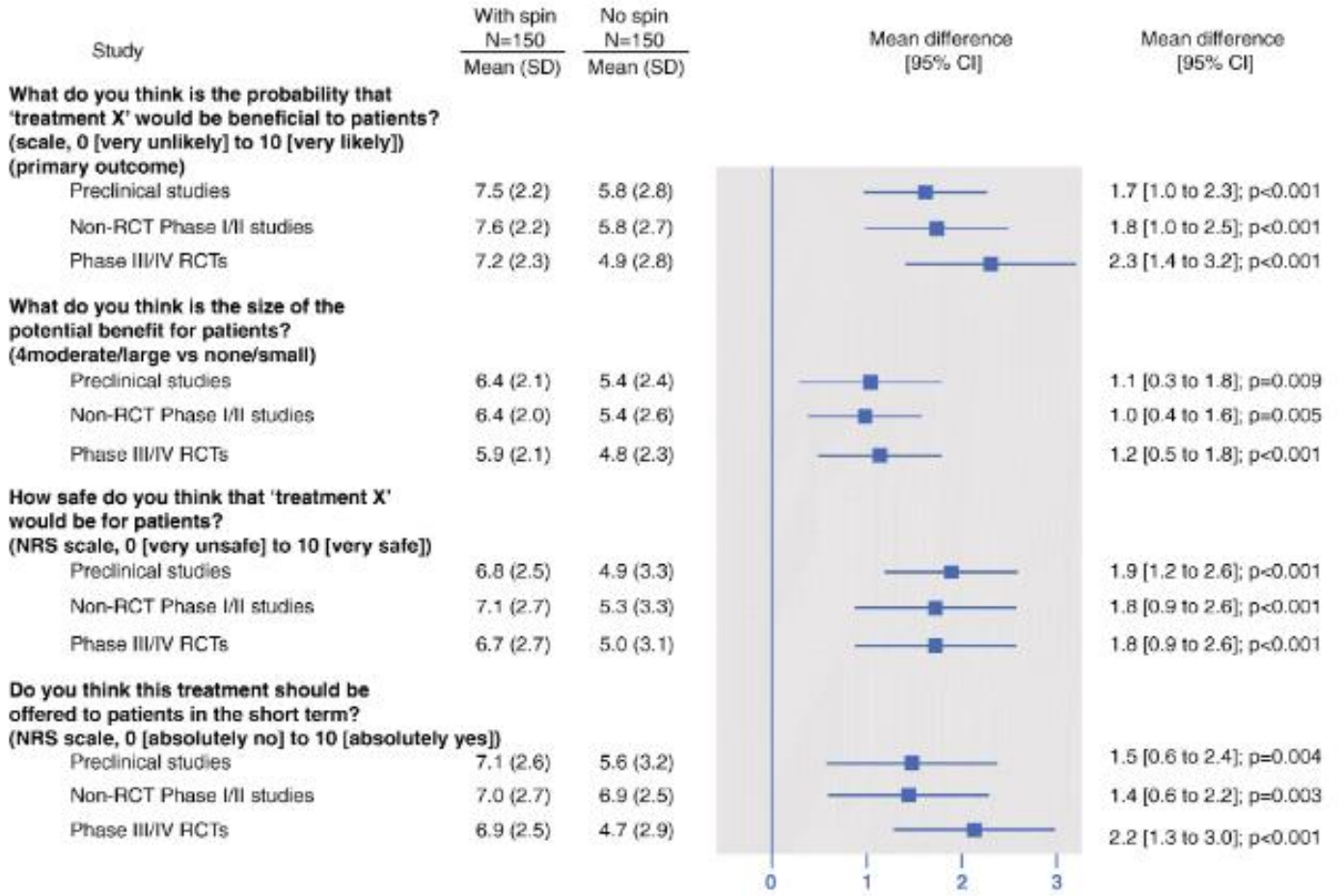
Spin et communiqué de presse et média



Impact des spin dans les articles de presse sur la comprehension par le lecteur

- **Identification of news items** reporting studies pharmacological treatments **with spin**
  1) Preclinical studies (n=10)
  2) Non randomized comparative trials (n=10)
  3) RCTs (n=10)
- **Rewriting news items without spin**
  1) Deletion of spin
  2) Addition of cautions
- **Participants**
  - 900 patients or carers (300 in each trial)
- **Outcome**
  - Probability that treatment X would be beneficial to patients (0 – very unlikely to 10 very likely)

BMC Med 2019



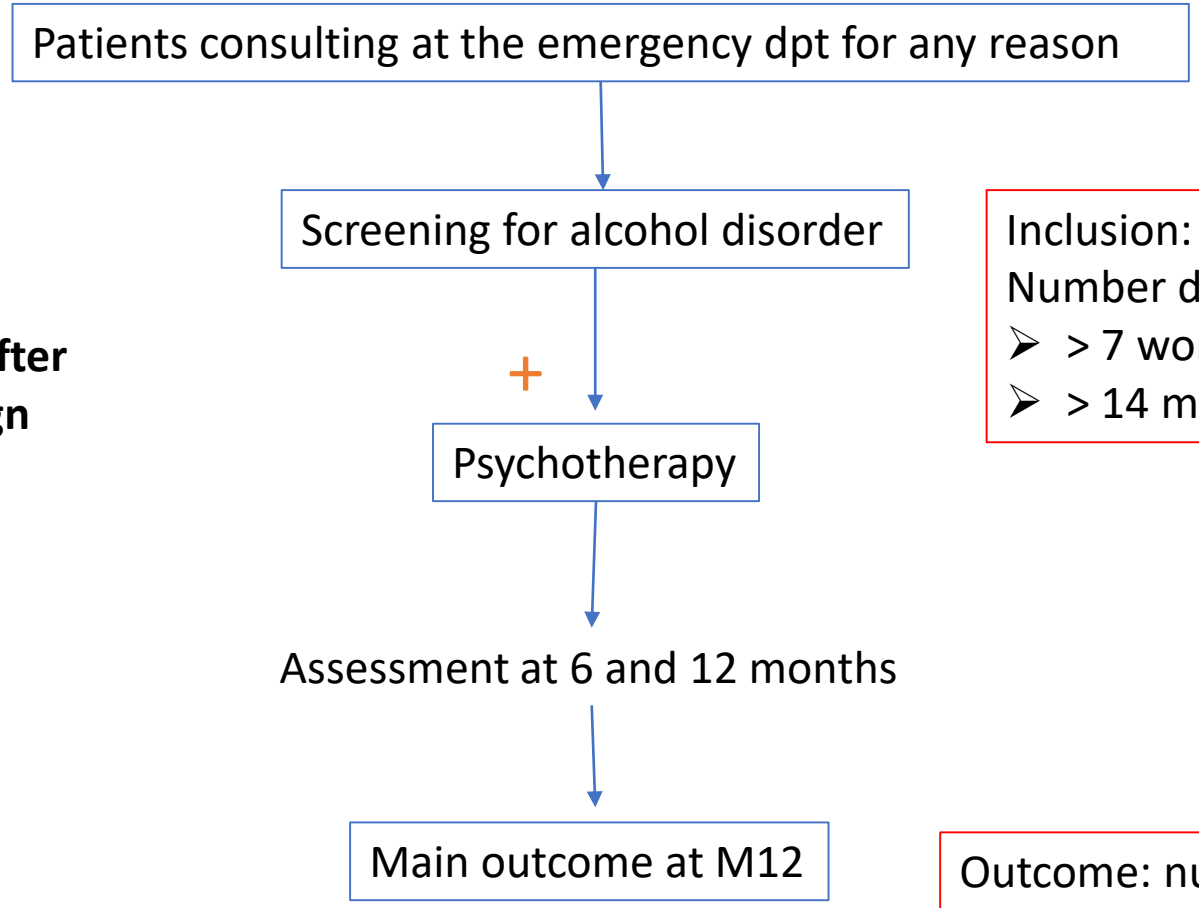
Forest plot of the results for primary and secondary outcomes

Examples à partir d'articles d'essais randomisés

Examples

Impact of a psychotherapy program on alcohol use

Before and after study design



Inclusion:
Number drinks/week
- > 7 women
- > 14 men

Outcome: number of daily alcohol drinks

Example

Impact of a psychotherapy program on alcohol use

Before and after study design

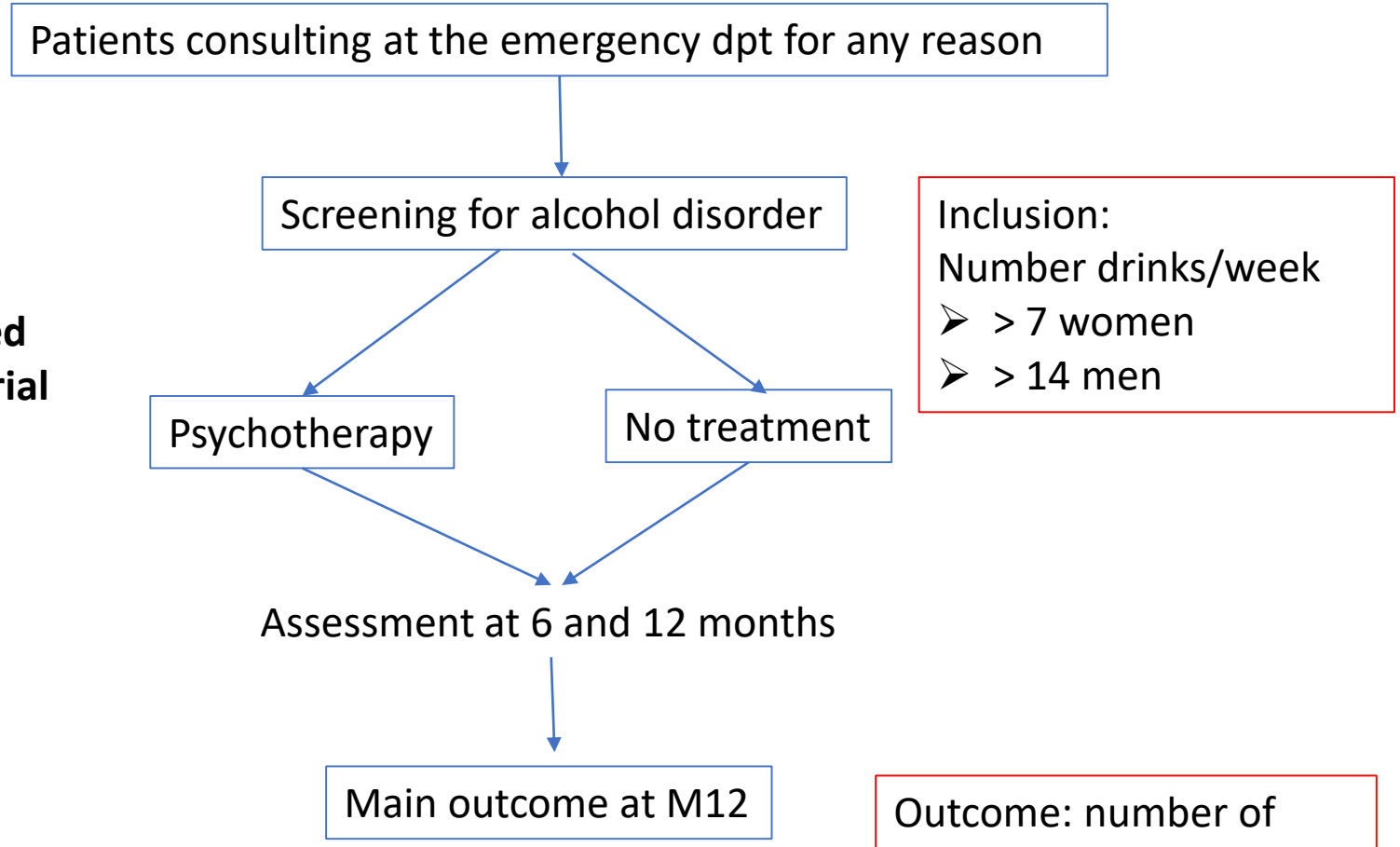
	Program (n=286) Mean (SD)	P value
Number of daily alcohol drinks		
M0	**6.17 (4.99)**	
M6	4.27 (3.97)	**<0.05**
M12	**4.16 (4.54)**	

What is you conclusion?

Example

Impact of a psychotherapy program on alcohol use

Randomized controlled trial (RCT)



Inclusion:
Number drinks/week
- > 7 women
- > 14 men

Outcome: number of daily alcohol drinks

Example

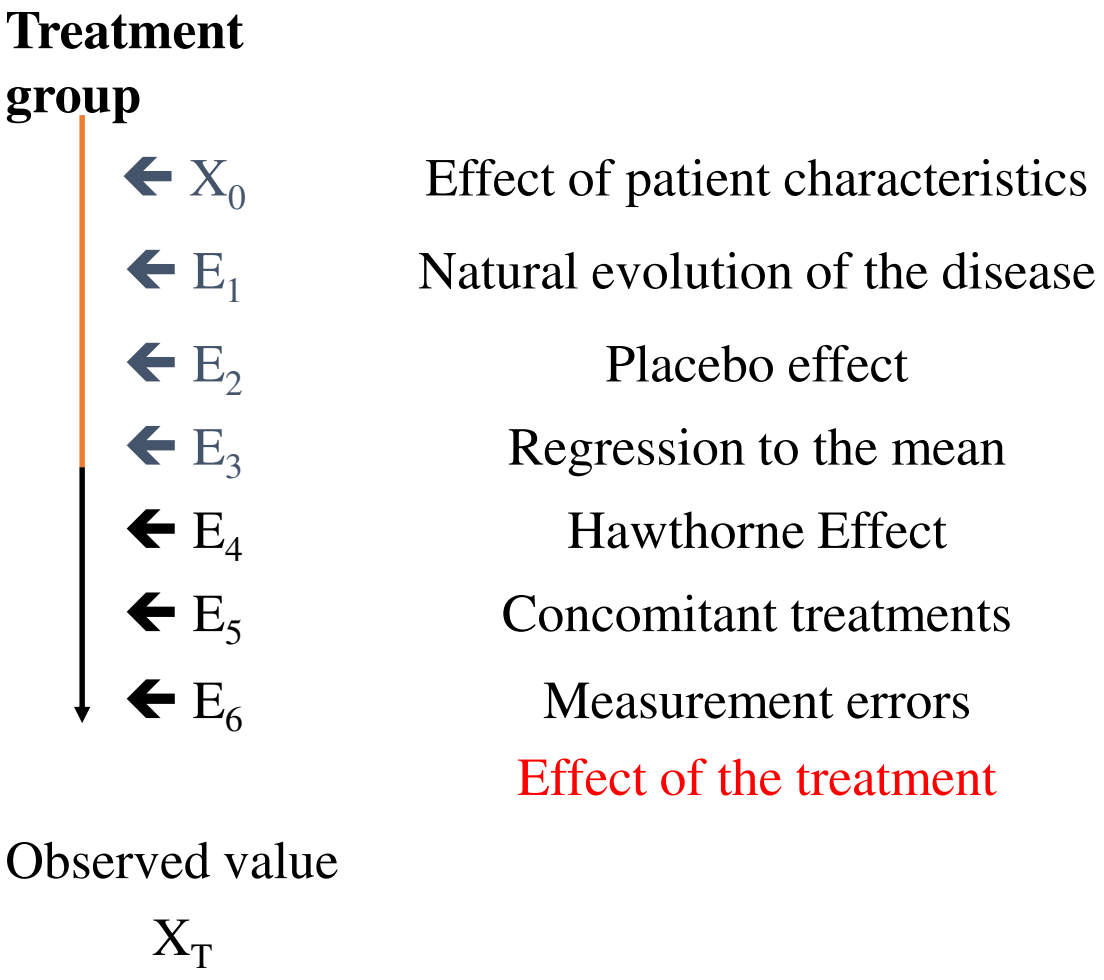
Impact of a psychotherapy program on alcohol use

Study design: randomized controlled trial

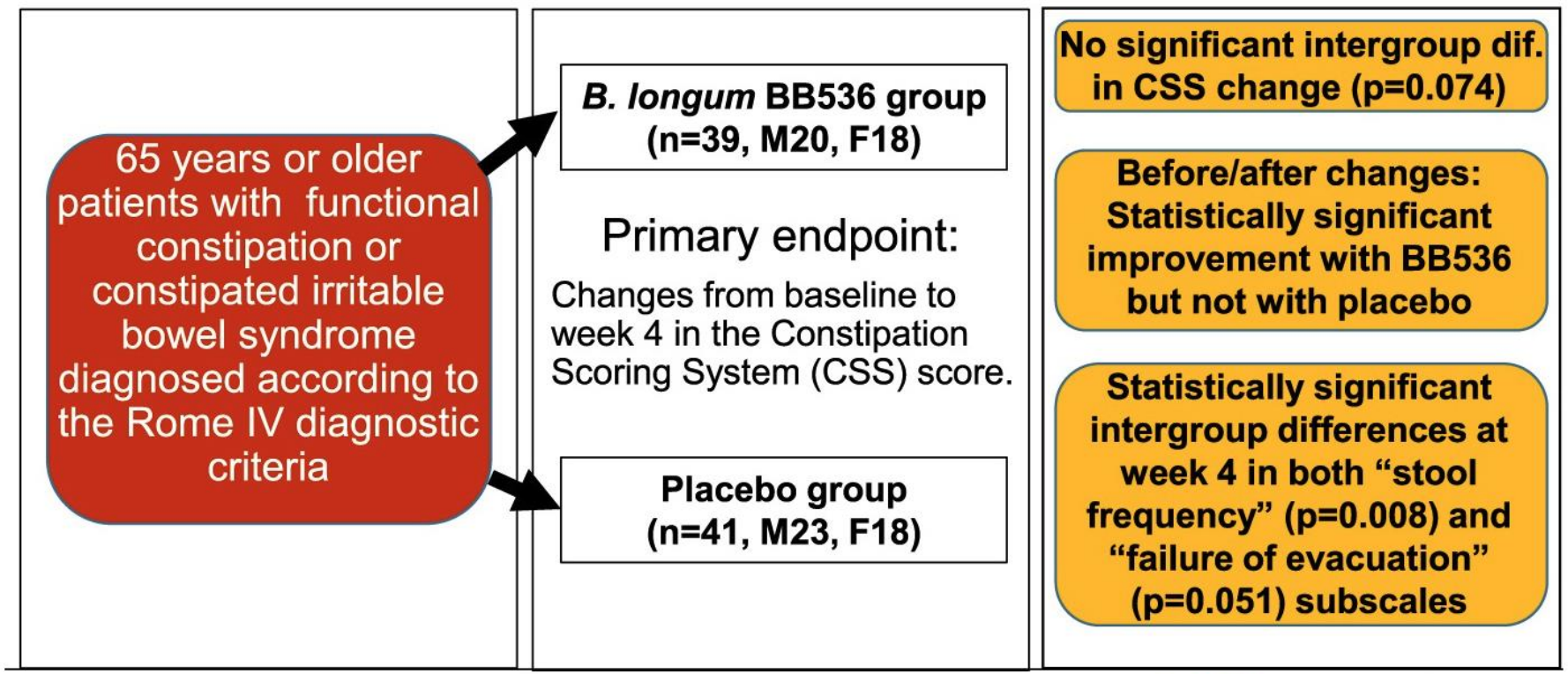
	Intervention (n=286) Mean (SD)	Control (n=286) Mean (SD)	Adjusted mean change from baseline difference/OR (95% CI)	P value
Primary outcome				
Number of daily alcohol drinks **M0** **M6** **M12**	 6.17 (4.99) 4.27 (3.97) 4.16 (4.54)	 6.42 (4.76) 4.33 (4.3) 4.28 (3.67)	 0.12 (-0.88; 1.11)	 0.81

What is your conclusion?

Factors that may explain the response to a treatment



Usefulness of *Bifidobacterium longum* BB536 in Elderly Individuals with Chronic Constipation: A Randomized Controlled Trial



Takeda et al. *Am J Gastroenterol. 2022*. [doi:10.14309/ajg.0000000000002028]

AJG The American Journal of GASTROENTEROLOGY

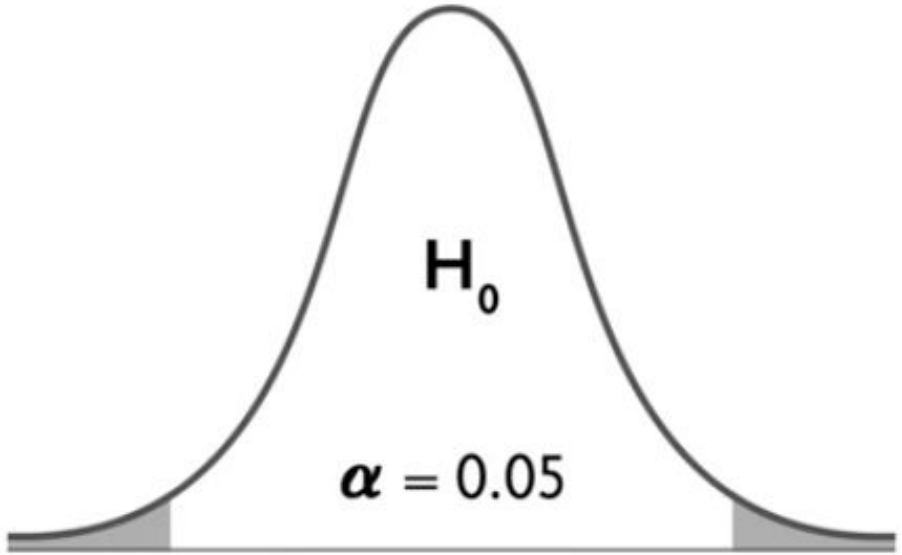
Usefulness of Bifidobacterium longum BB536 in Elderly Individuals With Chronic Constipation: A Randomized Controlled Trial

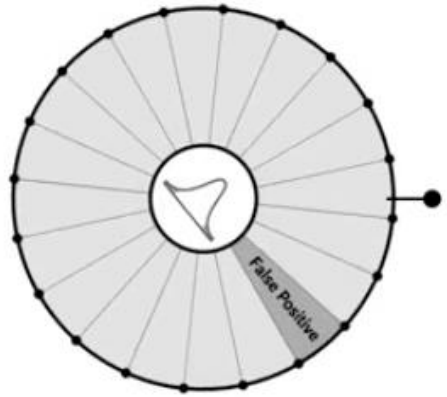
Introduction: Few reports exist regarding the therapeutic effects of probiotics on chronic constipation in elderly individuals. This study evaluated the effects of Bifidobacterium longum BB536 in elderly individuals with chronic constipation.

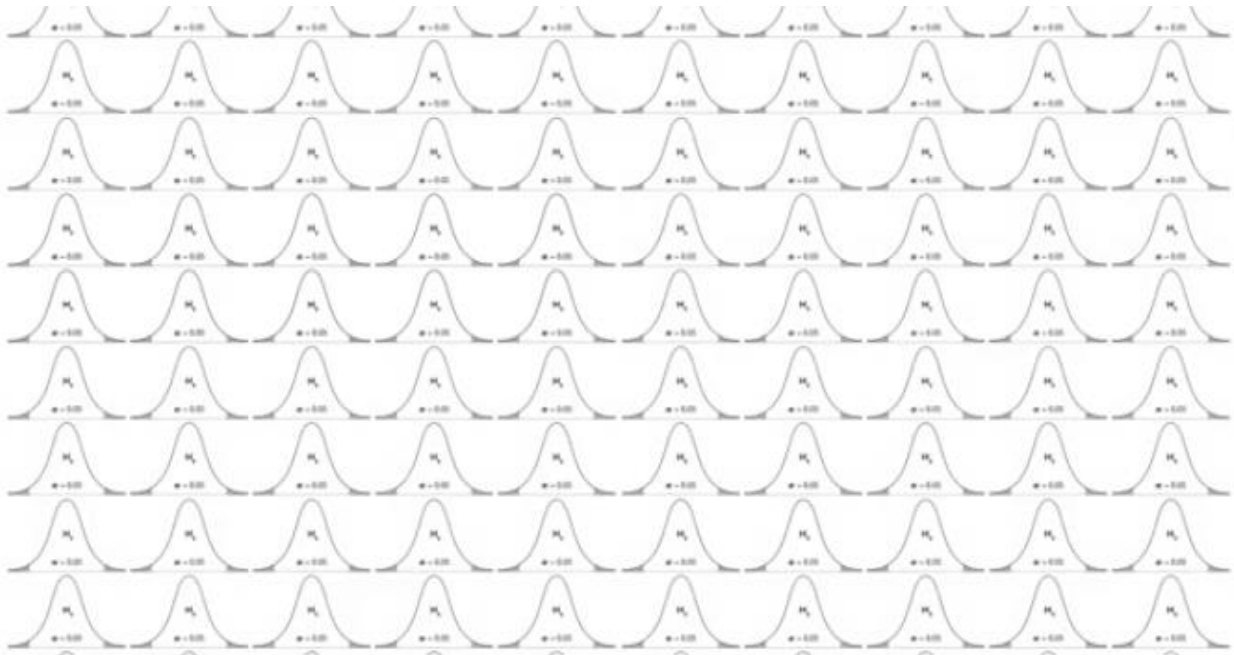
Methods: This was a randomized, double-blind placebo-controlled, parallel-group superiority trial in Japan (UMIN 000033031). Eighty older adults diagnosed with chronic constipation were randomly assigned (1:1) to receive either probiotics (B. longum BB536, 5 × 10 10 colony-forming unit, n = 39) or placebo (n = 41) once daily for up to 4 weeks. The severity of constipation was evaluated using the Constipation Scoring System. The primary end point was the difference in the changes from baseline in the constipation scoring system total score between the 2 groups at week 4.

Results: A total of 79 patients (mean age of 77.9 years), including 38 patients in the BB536 group and 41 in the placebo group, completed the study. The primary end point was not significant (P = 0.074), although there was significant improvement (P < 0.01) in the BB536 group from baseline to week 4, but there were no significant changes in the placebo group. There was a significant difference and a tendency toward a difference in the changes from baseline on the stool frequency (P = 0.008) and failure of evacuation (P = 0.051) subscales, respectively, at week 4 between the 2 groups. Few adverse events related to the probiotics were observed.

Discussion: The primary end points were not significant. However, probiotic supplementation significantly improved bowel movements. These results suggest that B. longum BB536 supplementation is safe and partially effective for improving chronic constipation in elderly individuals.

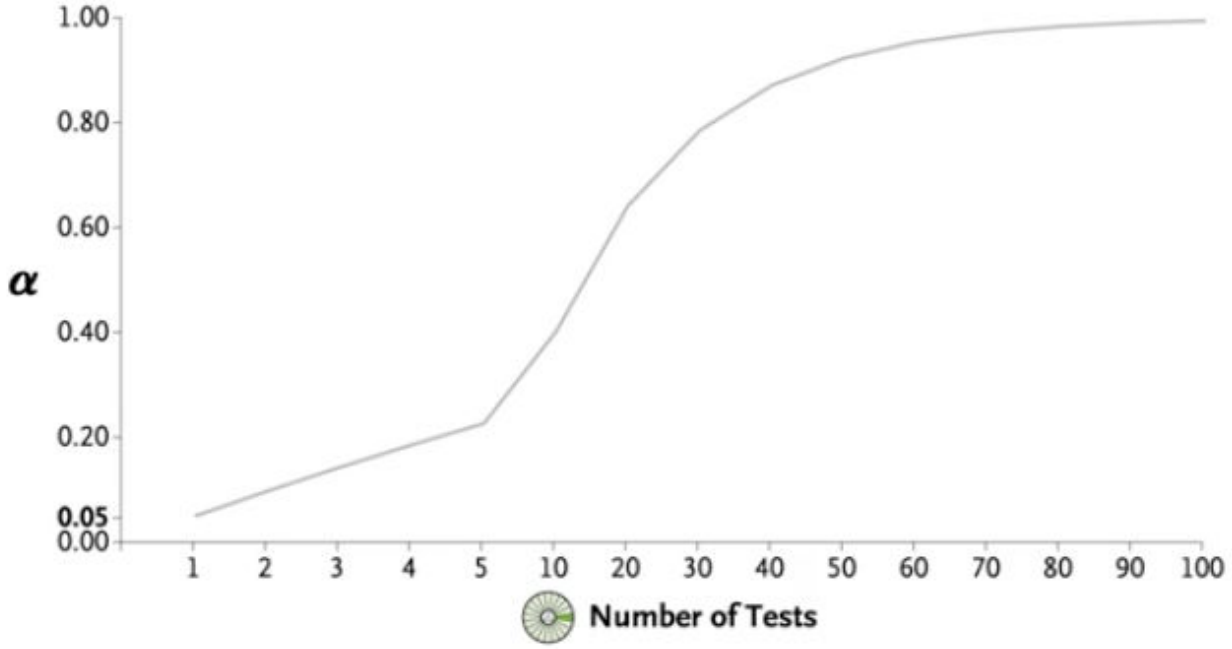

H_0
$\alpha = 0.05$

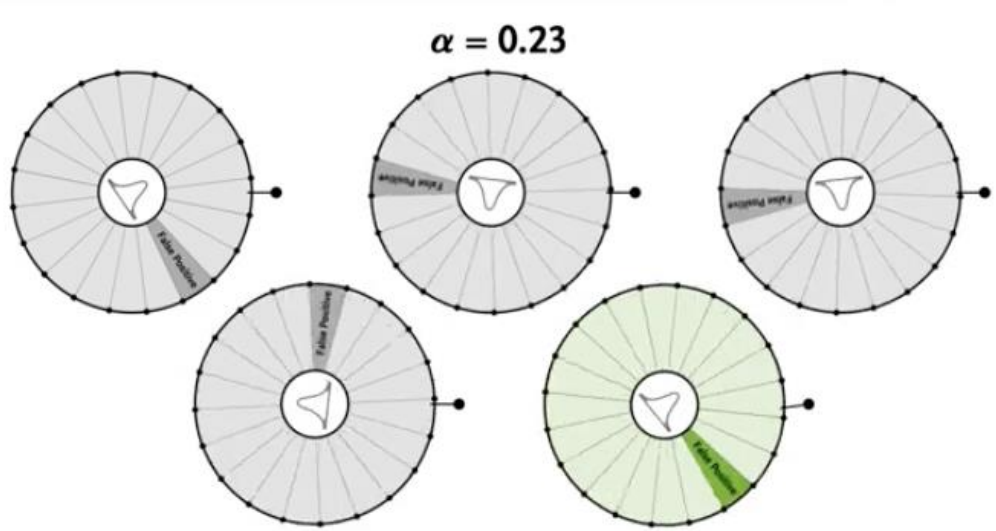

False Positive

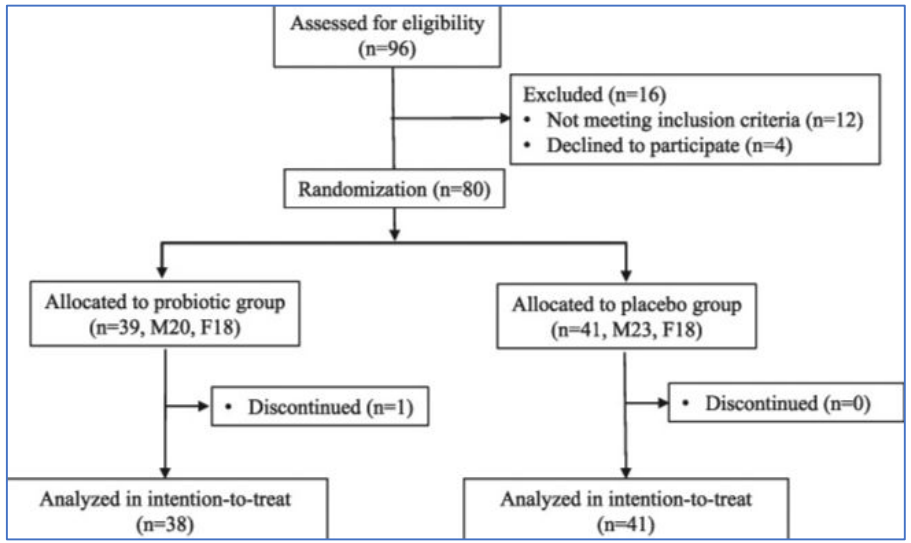


P-value et multiplicité

- Probabilité d'avoir un résultats statistiquement significatif P = 1-(1-0,05)^k, k = nombre de tests.
- 5 tests => 23%







52 tests

Risque de faux positif: 93%

Table 2. Results of CSS

	Probiotic			Placebo			Intergroup comparison	
	Baseline (wk 0)	After ingestion (wk 4)	4 wk postingestion (wk 8)	Baseline (wk 0)	After ingestion (wk 4)	4 wk postingestion (wk 8)	*P* value for Δ wk 4	*P* value for Δ wk 8
Frequency of bowel movements	0.89 ± 0.88	0.47 ± 0.94[b]	0.69 ± 1.02	0.54 ± 0.71	0.53 ± 0.73	0.50 ± 0.75	0.008	0.1761
Difficulty: painful evacuation effort	2.00 ± 1.29	1.53 ± 1.25	1.39 ± 1.13[b]	1.76 ± 1.02	1.38 ± 1.05	1.32 ± 1.11	0.719	0.6700
Completeness: feeling incomplete evacuation	1.95 ± 1.00	1.31 ± 1.12[b]	1.44 ± 1.03[b]	2.05 ± 0.84	1.56 ± 0.92[b]	1.51 ± 0.95[b]	0.498	0.8356
Pain: abdominal pain	0.76 ± 0.95	0.47 ± 0.66	0.66 ± 0.87	0.80 ± 0.87	0.93 ± 1.13	0.88 ± 0.99	0.222	0.4363
Time: minutes in lavatory per attempt	1.23 ± 0.94	0.78 ± 0.72[b]	0.86 ± 0.87[a]	1.24 ± 0.92	1.00 ± 0.88[b]	1.03 ± 0.90[a]	0.116	0.3399
Assistance: type of assistance (laxatives, enemas, or manual maneuvers)	0.39 ± 0.69	0.33 ± 0.53	0.42 ± 0.65	0.28 ± 0.56	0.33 ± 0.57	0.37 ± 0.62	0.380	0.2615
Failure of evacuation: unsuccessful attempts for evacuation per 24 hr	0.83 ± 0.45	0.61 ± 0.96[c]	0.72 ± 0.74	0.85 ± 0.42	0.83 ± 0.59	0.88 ± 0.64	0.051	0.1821
History: duration of constipation	2.22 ± 1.42	2.22 ± 1.42	2.22 ± 1.42	2.02 ± 1.11	2.02 ± 1.11	2.02 ± 1.11	—	—
CSS total score	10.26 ± 3.29	7.78 ± 4.30[b]	8.43 ± 3.52[a]	9.62 ± 2.68	8.57 ± 3.41	8.45 ± 3.88	0.074	0.1648

Data represent means (with SDs).
CSS, Constipation Scoring System.
[a] $P < 0.05$.
[b] $P < 0.01$, significant difference from baseline (Wilcoxon signed-rank test).
[c] $P < 0.05$, significant difference from the placebo group (Wilcoxon rank-sum test); *P* value, based on the difference from baseline (Wilcoxon rank-sum test).

Abstract

Background & aims: Conventional endoscopic mucosal resection (CEMR) with submucosal injection is the current standard for the resection of large, nonmalignant colorectal polyps. We investigated whether underwater endoscopic mucosal resection (UEMR) is superior to CEMR for large (20-40mm) sessile or flat colorectal polyps.

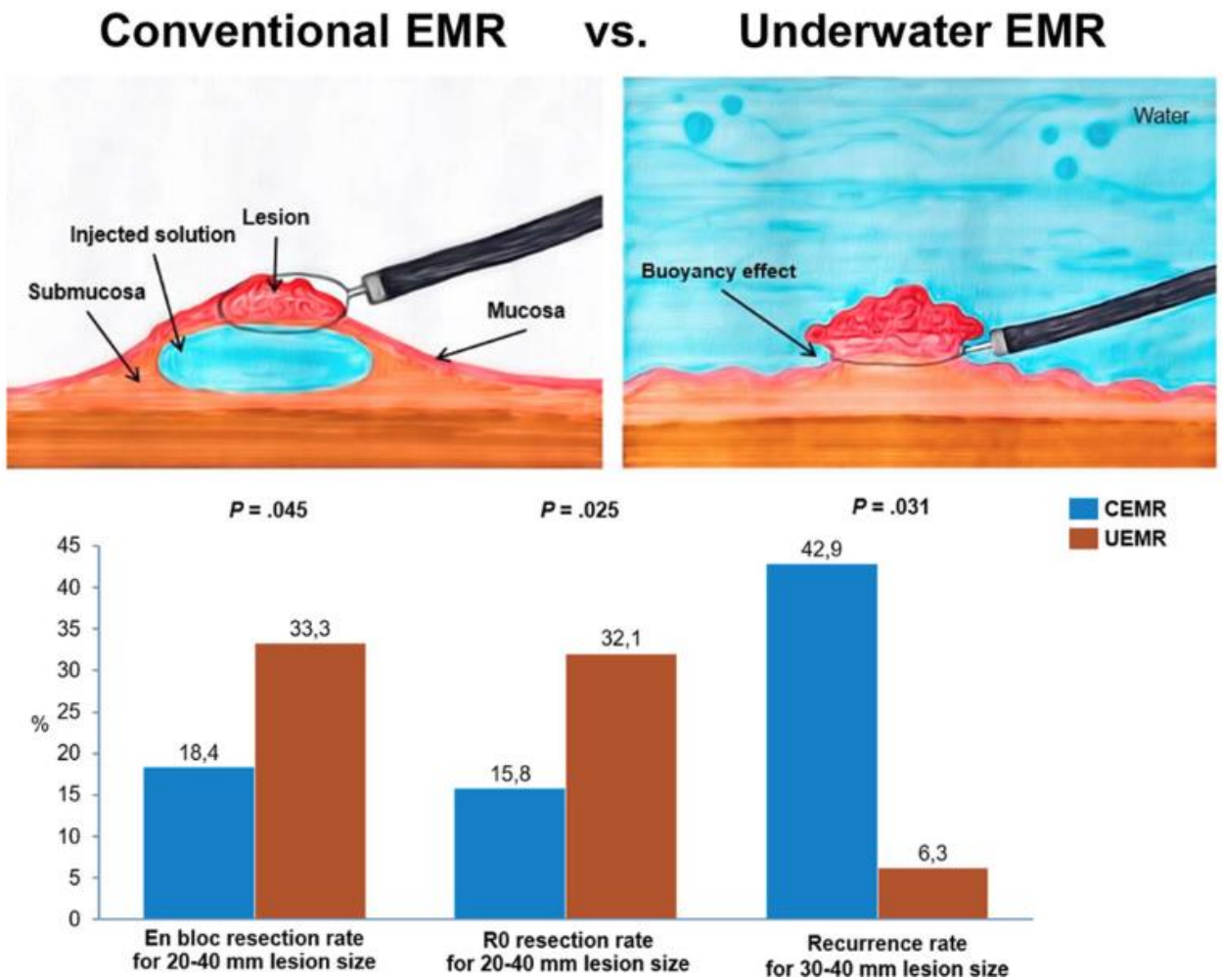
Methods: In this prospective randomized controlled study, patients with sessile or flat colorectal polyps between 20 and 40 mm in size were randomly assigned to UEMR or CEMR. The primary outcome was the recurrence rate after 6 months. Secondary outcomes included en bloc and R0 resection rates, number of resected pieces, procedure time, and adverse events.

Results: En bloc resection rates were 33.3% in the UEMR group and 18.4% in the CEMR group (P = .045); R0 resection rates were 32.1% and 15.8% for UEMR vs CEMR, respectively (P = .025). UEMR was performed with significantly fewer pieces compared to CEMR (2 pieces: 45.5% UEMR vs 17.7% CEMR; P = .001). The overall recurrence rate did not differ between both groups (P = .253); however, subgroup analysis showed a significant difference in favor of UEMR for lesions of >30 mm to ≤40 mm in size (P = .031). The resection time was significantly shorter in the UEMR group (8 vs 14 minutes; P < .001). Adverse events did not differ between both groups (P = .611).

Conclusions: UEMR is superior to CEMR regarding en bloc resection, R0 resection, and procedure time for large colorectal lesions and shows significantly lower recurrence rates for lesions >30 mm to ≤40 mm in size. UEMR should be considered for the endoscopic resection of large colorectal polyps.

Gastroenterology 2021

Is UEMR superior to CEMR for lesions 20 – 40 mm in size?



Gastroenterology

Analyses en sous groupe

Cochrane France

Risque

- Faux positif
- Manque de puissance

Analyse en sous groupe

- Pre-spécifiée dans le protocole
- Stratification de la randomisation
- Nombre limité (<5)
- Testée par un test d'intéraction
- Sur une variable mesuréeau début de l'étude avant de prendre le traitement

Observation	Refutation
Aspirin is ineffective in secondary prevention of stroke in women[29,30]	31
Antihypertensive treatment for primary prevention is ineffective in women[32,33]	34
Antihypertensive treatment is ineffective or harmful in elderly people[35]	36
Angiotensin-converting enzyme inhibitors do not reduce mortality and hospital admission in patients with heart failure who are also taking aspirin[37]	38
β blockers are ineffective after acute myocardial infarction in elderly people,[39] and in patients with inferior myocardial infarction[41]	40
Thrombolysis is ineffective >6 hours after acute myocardial infarction[42]	43
Thrombolysis for acute myocardial infarction is ineffective or harmful in patients with a previous myocardial infarction[42]	44
Tamoxifen citrate is ineffective in women with breast cancer aged <50 years[45]	46
Benefit from carotid endarterectomy for symptomatic stenosis is reduced in patients taking only low-dose aspirin due to an increased operative risk[47]	48
Amlodipine reduces mortality in patients with chronic heart failure due to non-ischaemic cardiomyopathy but not in patients with ischaemic cardiomyopathy[49]	50

Table 1: Examples of subgroup analyses that have shown apparently clinically important heterogeneity of treatment effect which has subsequently been shown to be false

BMJ 2012
BMJ 2015

Erreur fréquente

Day of birth	Events/patients: Surgical	Events/patients: Medical	ARR (%)	95% CI	p value
Sunday	7/56	6/41	3·1	−11·3 to 17·5	0·34
Monday	4/66	10/44	16·7	3·0 to 30·3	0·008
Tuesday	8/76	6/28	10·5	−6·9 to 27·9	0·12
Wednesday	8/67	13/47	18·3	2·3 to 34·2	0·01
Thursday	9/75	9/36	12·8	−3·8 to 29·4	0·07
Friday	1/56	6/37	15·1	2·3 to 27·9	0·01
Saturday	6/51	8/41	9·5	−6·6 to 25·6	0·12
Total	43/447	58/274	12·3	6·5 to 18·1	<0·001

Heterogeneity: p=0·83

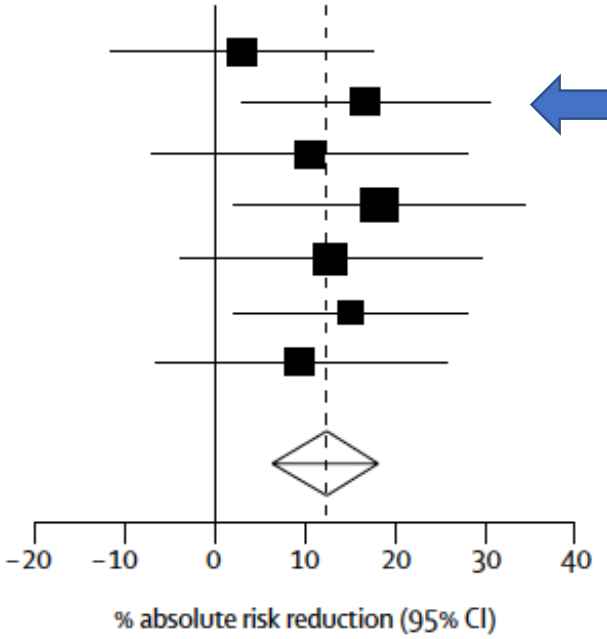
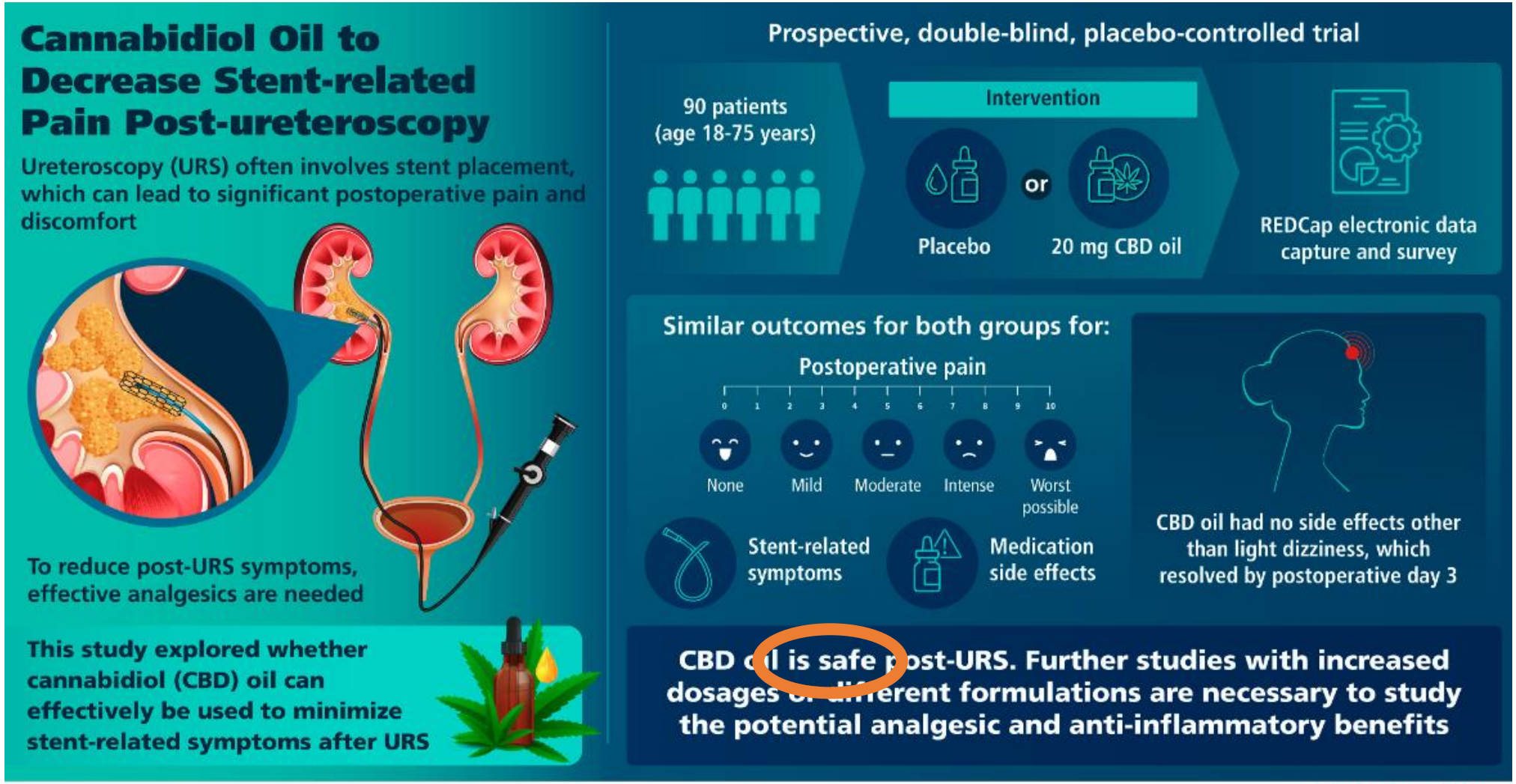


Figure 2: **Effect of carotid endarterectomy in patients with ⩾70% symptomatic stenosis in ECST[126] according to day of week on which patients were born**

Tolérance

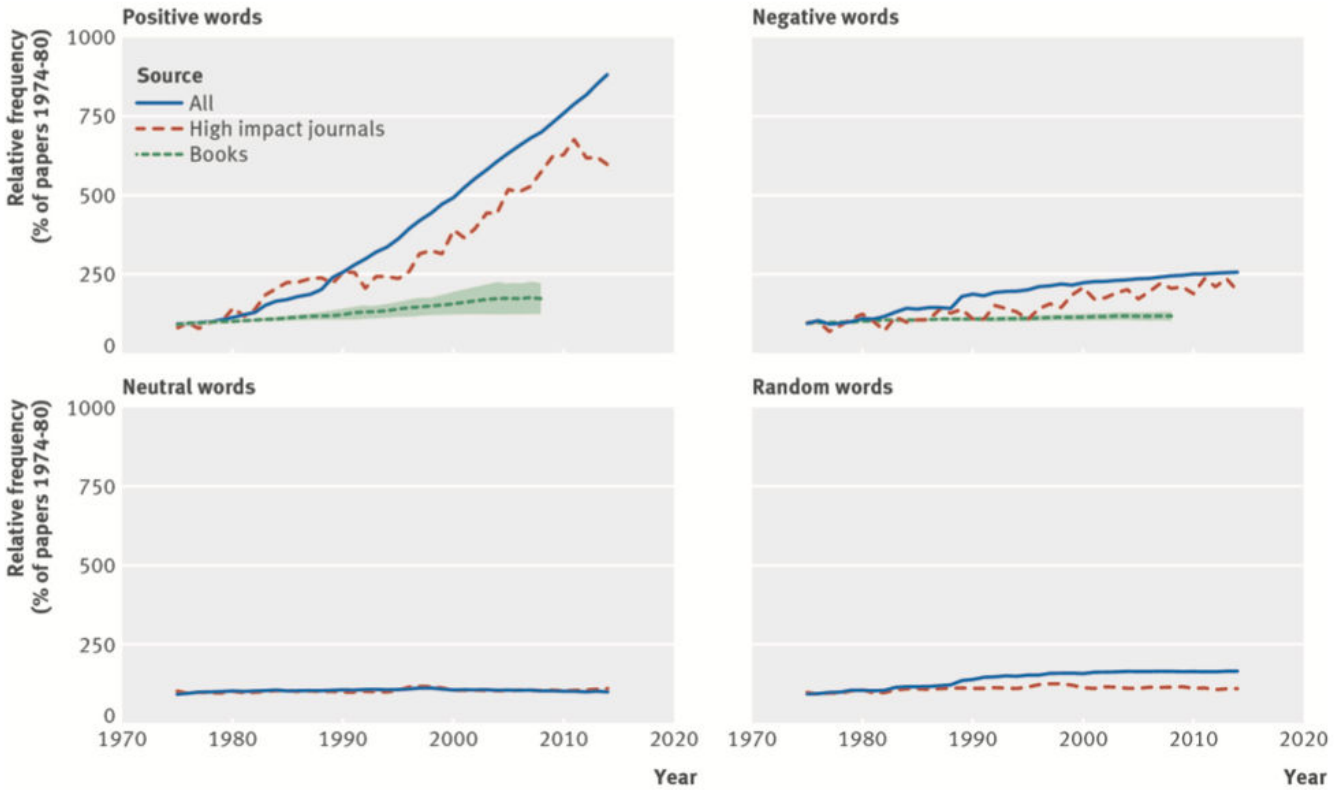


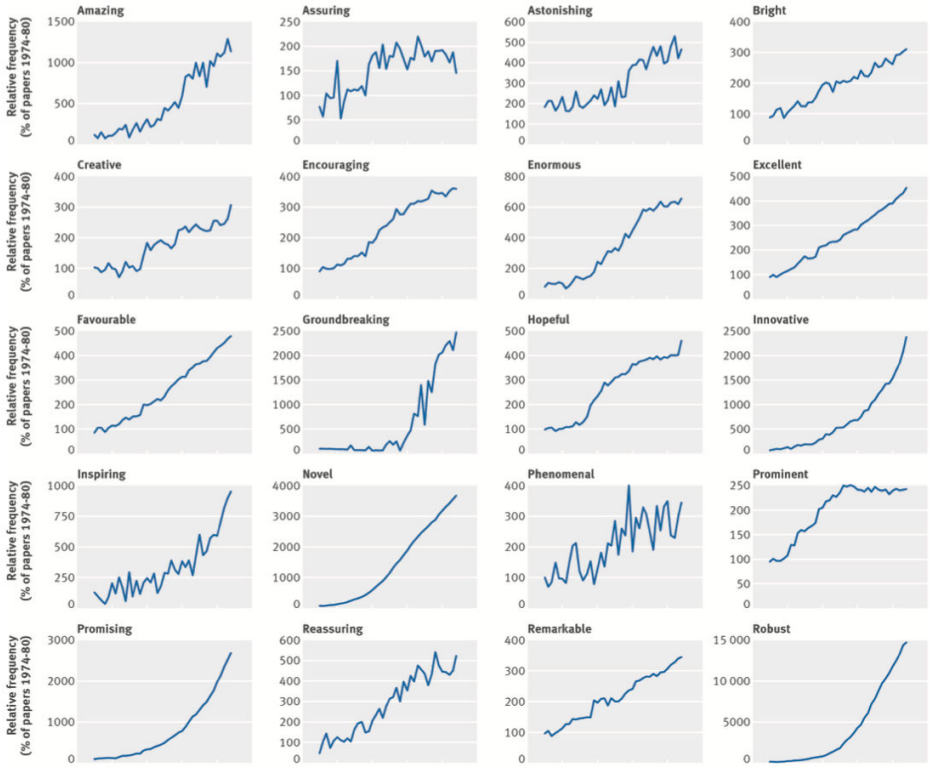
Effect of Cannabidiol Oil on Post-ureteroscopy Pain for Urinary Calculi: A Randomized Double-blind Placebo-controlled Trial
Narang *et al.* (2022) | DOI: 10.1097/JU.0000000000002670.01

THE JOURNAL of UROLOGY®

Lexicographic analysis – linguistic spin

- To investigate whether language used in science abstracts can skew towards the use of strikingly positive and negative words over time.





Vinkers et al. BMJ 2015

Extrapolation d'une expérience individuelle

« PROSTATE cancer patient Bob McGregor ***is living proof*** that a new treatment regime for the disease is ***as good as gold*** »

Prostate cancer gold treatment

By ALISON BRANLEY, Health reporter Sept. 1, 2013, 10:30 p.m.

PRECIOUS: Bob McGregor has received some of the latest prostate cancer treatment available, using gold granules. Picture: Simone De Peak

Points d’attention

- Evaluation d’une intervention/traitement: Il faut un groupe contrôle
- Les analyses crédibles sont les analyses pre-spécifiées
- Attention à la multiplicité des tests (groups multiples, critères de jugement secondaire, analyses en sous groupe)
- La conclusion doit s’appuyer sur le critère de jugement principal tel que pré-spécifié dans le protocole

Points d’attention

- On ne fait pas des recommandations à partir d’une seule étude
- 1 étude = experimentation et donc les résultats peuvent être liés
  - à la chance,
  - au choix de la population,
  - Aux modalité d’administration du traitement
  - À l’organization de la recherche
  - aux risque de biai

- => la synthèse de l’evidence est necessaire (revues systématique, méta-analyses) pour aider à la prise de décision

Points d’attention

- **Incertitude** en recherche +++

- Connaissance **à un temps donné,** les connaissances vont évoluer dans le temps

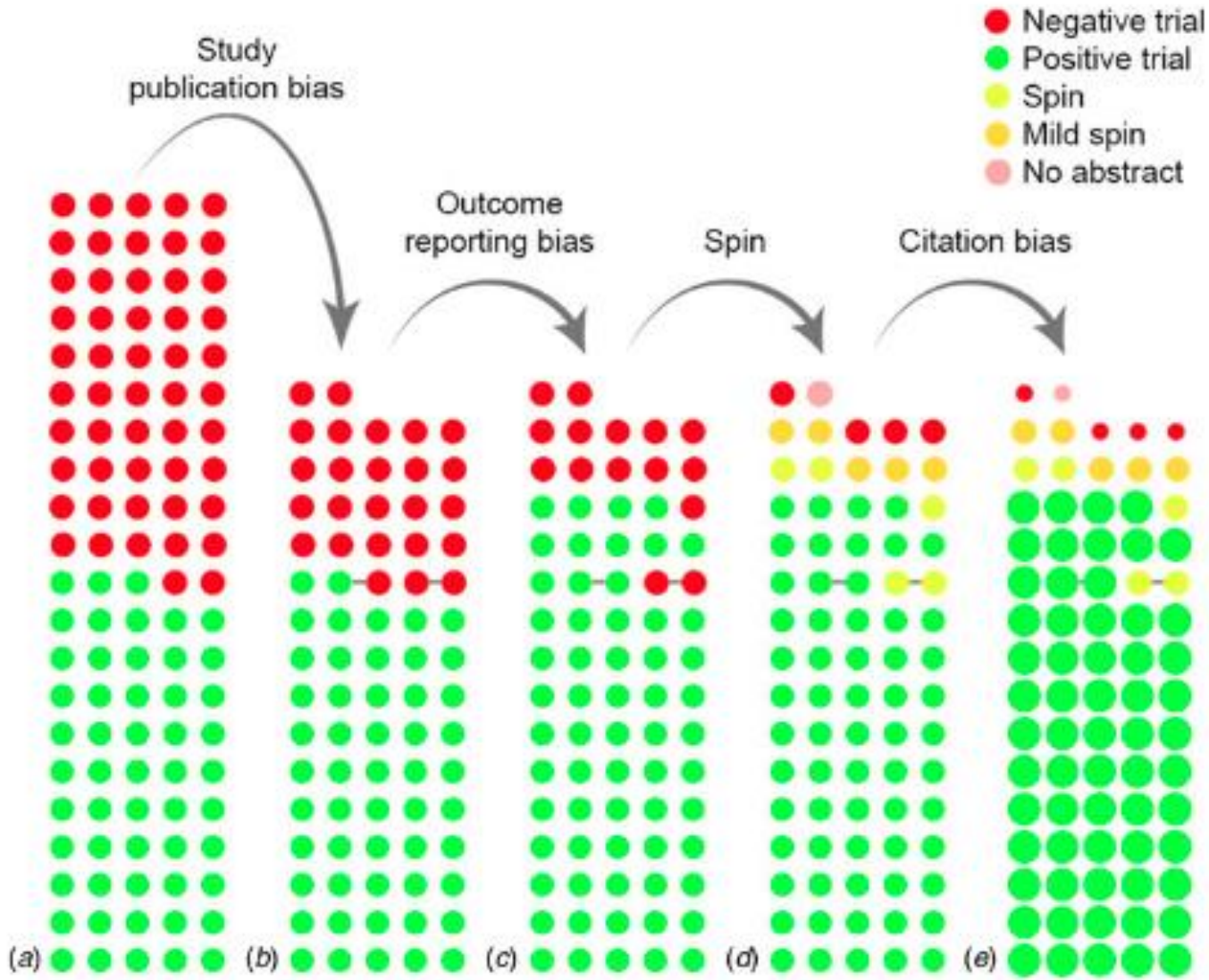
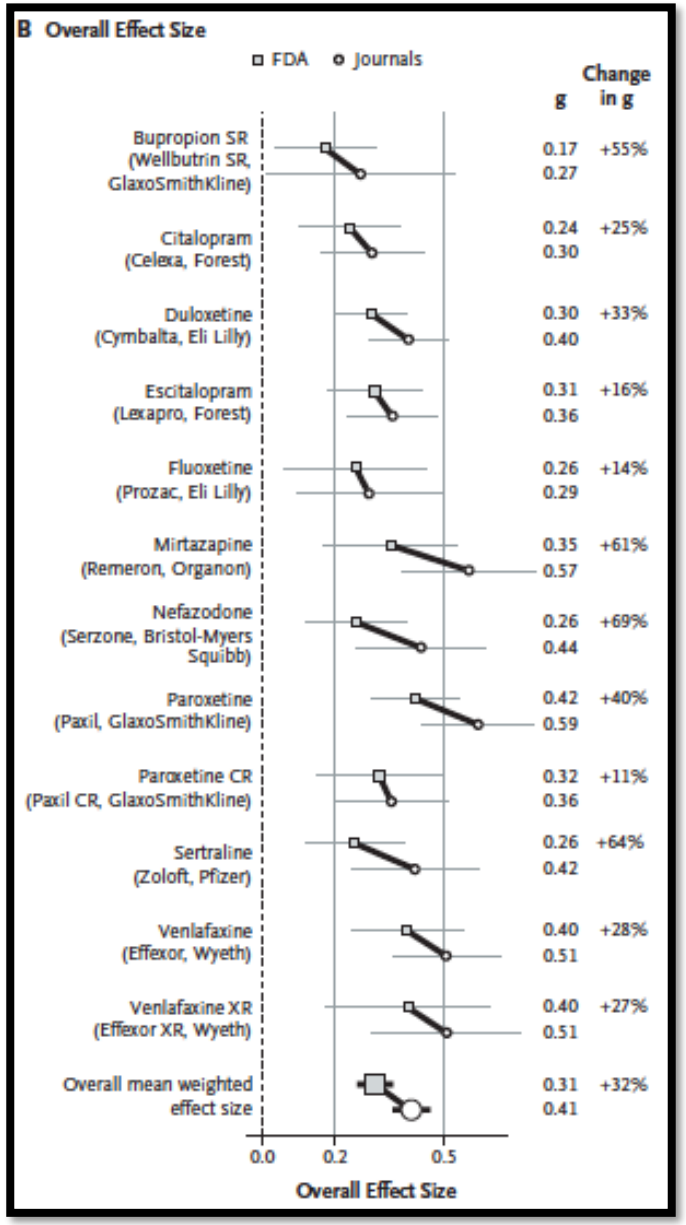
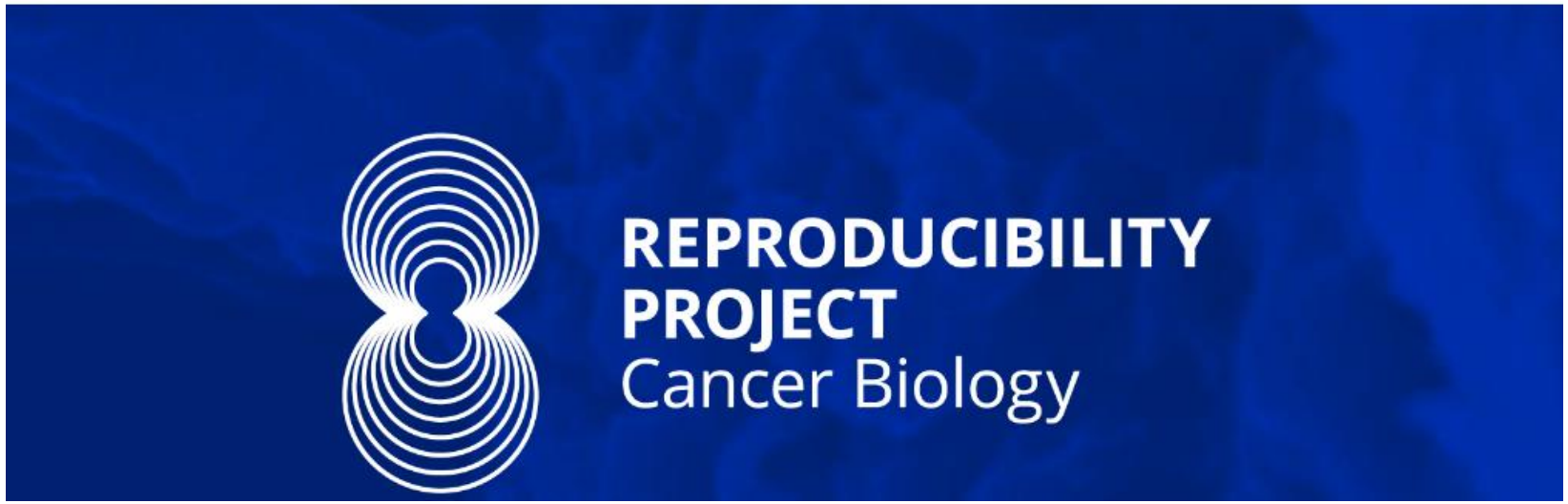


Fig. 1. The cumulative impact of reporting and citation biases on the evidence base for antidepressants. (*a*) displays the initial, complete cohort of trials, while (*b*) through (*e*) show the cumulative effect of biases. Each circle indicates a trial, while the color indicates the results or the presence of spin. Circles connected by a grey line indicate trials that were published together in a pooled publication. In (*e*), the size of the circle indicates the (relative) number of citations received by that category of studies.

L'accès aux résultats de la recherche est biaisé



Turner, NEJM, 2008



- To investigate the replicability of preclinical research in cancer biology
- The goal was to repeat 193 experiments from 53 papers published in high-impact journals between 2010 and 2012
- 200 individuals contributed in some way to complete this project
- Project duration: 8 years

The Reproducibility Project: Cancer Biology

Feasibility of the replication

- 0% protocol completely described the experiment
- 2% had open data

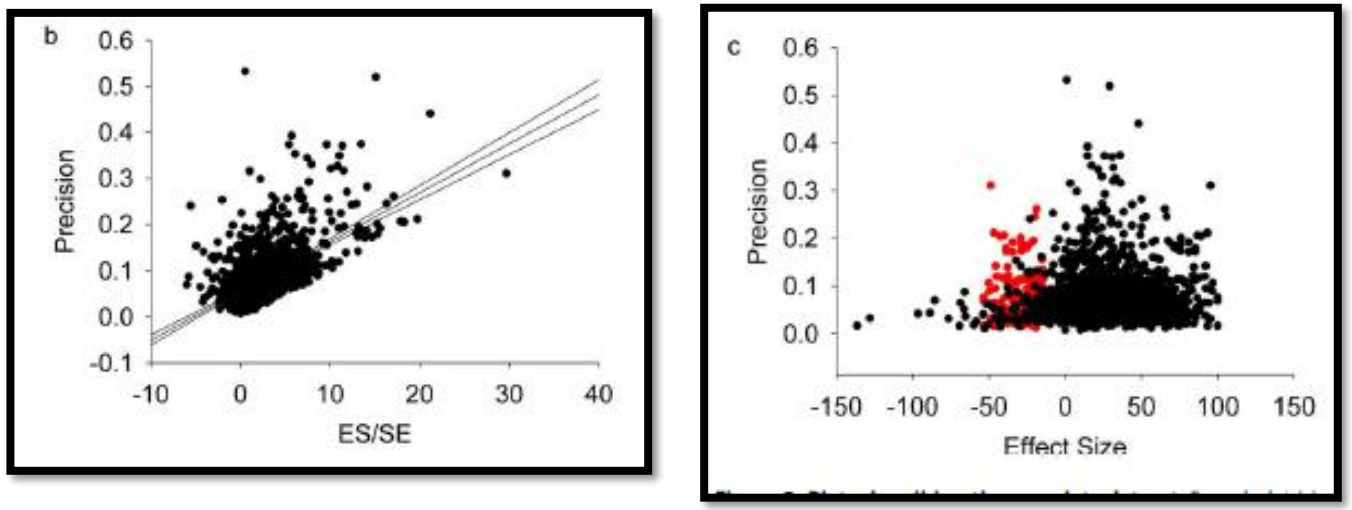
➔ Only 50 (25%) experiments from 23 papers were repeated

Results of the replication

- **46% of effects replicated successfully** on more criteria than they failed
- Original positive results were half as likely to replicate successfully (**40%**) than original null results (**80%)**
- Replication effect sizes were **85% smaller** on average than the original findings

Biais de publication et études animales

- 16 systematic reviews (525 publications) of interventions tested in animal studies of acute ischaemic stroke
- Egger regression and trim-and-fill analysis suggested that **publication bias was highly prevalent**
- **Overestimation of treatment effect 30%**



a) Egger regression showing precision plotted against the standardised effect size. In the absence of publication bias the regression line should pass through the origin.
b) Funnel plots showing the data in black, and the additional missing studies imputed by trim-and-fill in red.

Sena ES, PLoS Biol 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D.,

BACKGROUND

Nitrates are commonly prescribed to enhance activity tolerance in patients with heart failure and a preserved ejection fraction. We compared the effect of isosorbide mononitrate or placebo on daily activity in such patients.

METHODS

In this multicenter, double-blind, crossover study, 110 patients with heart failure and a preserved ejection fraction were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate (from 30 mg to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. The primary end point was the daily activity level, quantified as the average daily accelerometer units during the 120-mg phase, as assessed by patient-worn accelerometers. Secondary end points included hours of activity per day during the 120-mg phase, daily accelerometer units during all three dose regimens, quality-of-life scores, 6-minute walk distance, and levels of N-terminal pro–brain natriuretic peptide (NT-proBNP).

RESULTS

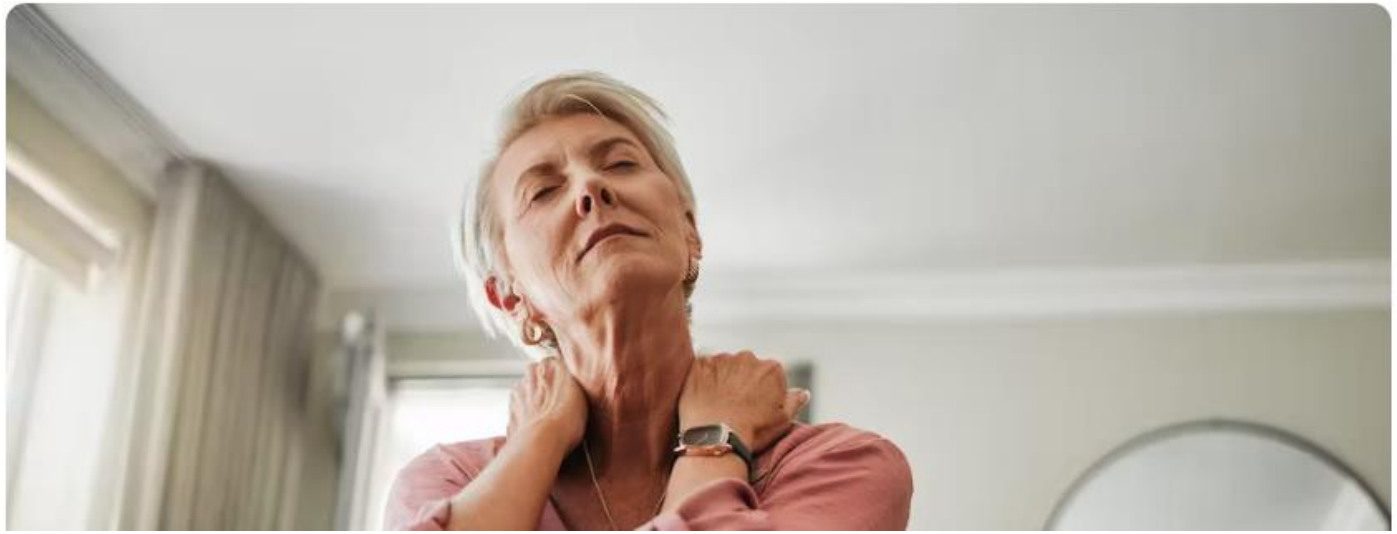
In the group receiving the 120-mg dose of isosorbide mononitrate, as compared with the placebo group, there was a nonsignificant trend toward lower daily activity (−381 accelerometer units; 95% confidence interval [CI], −780 to 17; P=0.06) and a significant decrease in hours of activity per day (−0.30 hours; 95% CI, −0.55 to −0.05; P=0.02). During all dose regimens, activity in the isosorbide mononitrate group was lower than that in the placebo group (−439 accelerometer units; 95% CI, −792 to −86; P=0.02). Activity levels decreased progressively and significantly with increased doses of isosorbide mononitrate (but not placebo). There were no significant

Outcome Measures

Change History		See all versions of this study
Primary (Current) **(Submitted: 2016-10-07)**	ICMJE	• Arbitrary Accelerometry Units (AAU) (Phase I) [Time Frame: 5-6 weeks] ◦ To evaluate whether isosorbide mononitrate increases daily activity as assessed by 14-day averaged arbitrary accelerometry units in comparison to placebo. An arbitrary accelerometer unit is calculated within the accelerometer device that is worn by the patient and represents level of activity based on patient movement. Higher values indicate more movement. 0 indicates no movement. • Arbitrary Accelerometry Units (AAU) (Phase II) [Time Frame: 11-12 weeks] ◦ To evaluate whether isosorbide mononitrate increases daily activity as assessed by 14-day averaged arbitrary accelerometry units in comparison to placebo. An arbitrary accelerometer unit is calculated within the accelerometer device that is worn by the patient and represents level of activity based on patient movement. Higher values indicate more movement. 0 indicates no movement.
Primary (Original) **(Submitted: 2014-01-31)**	ICMJE	• Change in arbitrary accelerometry units [Time Frame: 12 weeks] ◦ To evaluate whether isosorbide mononitrate increases daily activity as assessed by 14-day averaged arbitrary accelerometry units in comparison to placebo. Participants will be assessed at weeks 5-6 and weeks 11-12 Comparison of weeks 5/6 and weeks 11/12

Example

Fibromyalgie : ce nouveau traitement améliore l'état de santé de 8 patients sur 10



L'intensité de la maladie a été réduite pour 53 % des patients, qui « sont passés d'une intensité de la fibromyalgie dite sévère à modérée », et ce **pendant 6 mois**. Selon l'étude, **75 % des patients ont noté une amélioration de leur état de santé** après 3 mois d'utilisation du bracelet.

Source 1 : « 1ère solution technologique dédiée à la fibromyalgie dont les bénéfices ont été validés cliniquement », Remedee Labs, 13 novembre 2023.

Une amélioration chez

6 patients sur 10

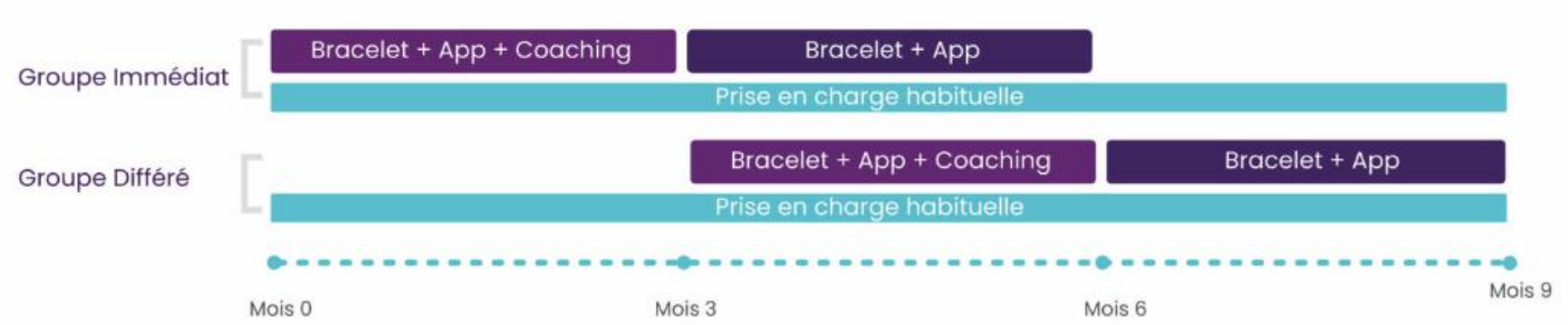
52.7% des patients passent d'une intensité sévère (FIQ ≥ 59/100) à modérée (39 ≤ FIQ < 59)

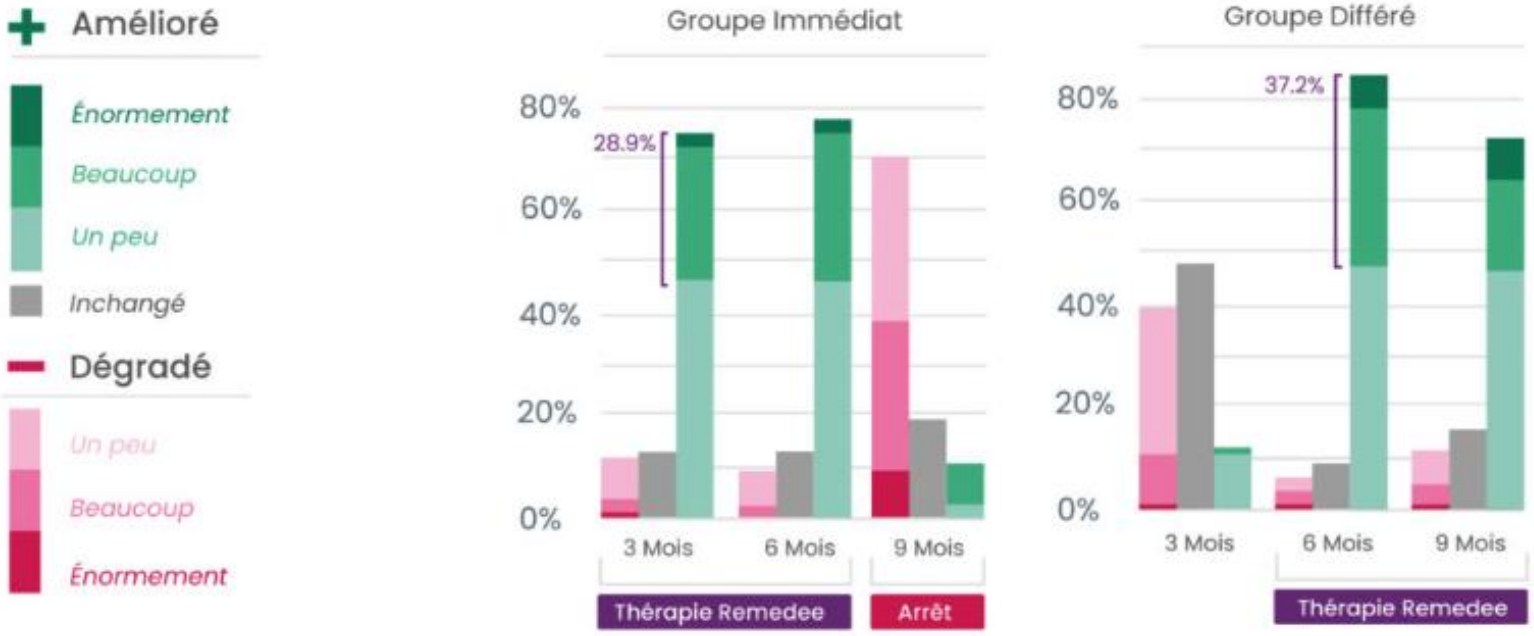
8 patients sur 10

déclarent une amélioration de leur état de santé après 3 mois

Cochrane France

Procédure : 2 Groupes





- 5 patients sur 10 déclarent une amélioration à 3 mois sans traitement

L'abstract de la présentation "Therapy Combining Millimeter Wave-based Neuromodulation with Coaching for the Improvement in Quality of Life of Patients with Fibromyalgia: A Prospective, Multicenter, Randomized, Controlled Trial "

Efficacy of intervention was assessed by comparing the number of patients in both groups whose quality of life measurement on the FIQ significantly improved between inclusion and M3. A decrease in FIQ score of ≥14% is considered clinically significant (Bennett et al., 2009). FIQ scores of the 2 groups were also measured at 6 months (M6).

Results: At M3, 55.1% patients of IG improved their quality of life beyond 14%, compared with 35.9% in the DG, and this difference between the groups was statistically significant (p=0.021). On average, patients in the IG improved their FIQ score by 21.7%, versus 7.2% in the DG. Benefits observed in the IG were preserved at M6, patients in this group having used their device autonomously between M3 & M6.

- Intervention: Succès 55%
- Control: succès 35,9%
- RR: 0,65
- RAR : 19,1

Outcome Measures

Change History		See all versions of this study
Primary (Current) **(Submitted: 2021-09-16)**	ICMJE	• Percentage of patients who significantly improve their fibromyalgia-specific quality of life on the FIQ questionnaire between the inclusion visit at D0 and the 3-month visit (M3). [Time Frame: 3 months] ◦ A decrease in FIQ score ≥ 14% is considered clinically meaningful (Bennett et al., 2009)
Primary (Original)	ICMJE	Same as current

Conclusion

Role des registres

Résultats publiés en décembre 2015

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

- PO prespecified "daily accelerometer units during the 120-mg phase"
  - non-significant result
- SO: "No of hours of activity"
  - Significant result
- Post hoc secondary outcome:
  - "Blood pressure" Significant result.

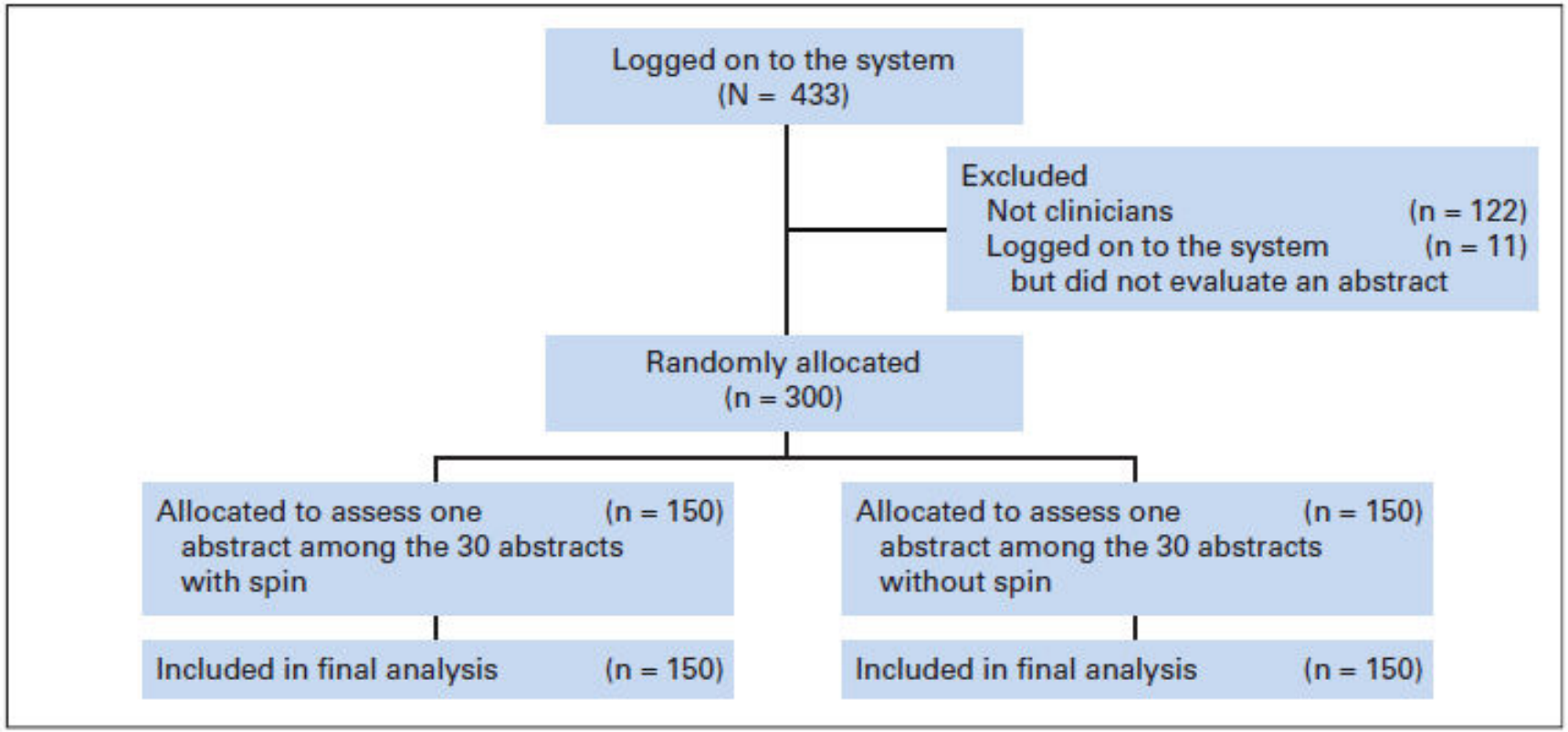
"Our post hoc analysis indicated decreases in blood pressure with isosorbide mononitrate."

- " In conclusion, in patients with heart failure with a preserved ejection fraction, the receipt of isosorbide mononitrate, as compared with placebo, **decreased daily activity levels**"

Table 2. Efficacy and Safety End Points.

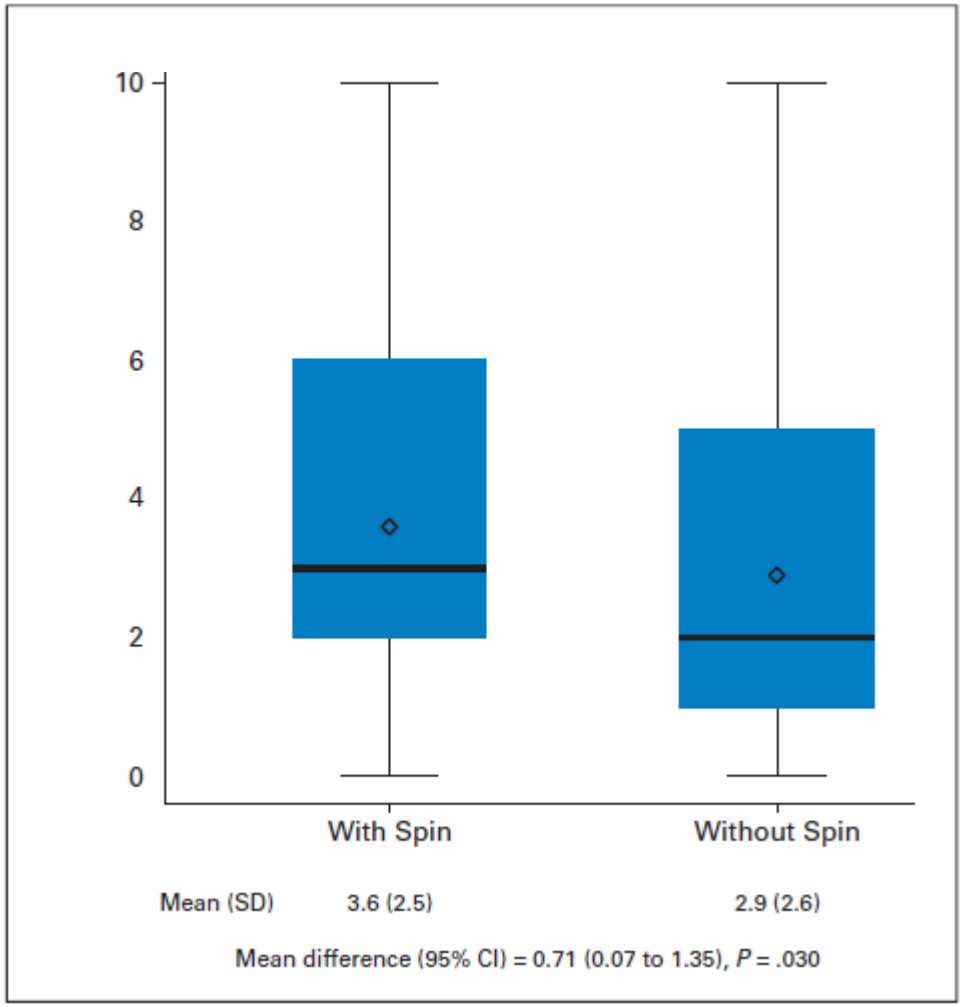
End Point	Placebo (N=110)	Isosorbide Mononitrate (N=110)	Treatment Difference*	P Value
		mean (95% CI)		
Efficacy				
Activity as assessed on accelerometry				
Daily arbitrary accelerometer units during 120-mg phase: primary end point	9303 (8884–9723)	8922 (8500–9345)	−381 (−780 to 17)	0.06
No. of hours of activity per day	9.31 (9.05–9.56)	9.01 (8.75–9.27)	−0.30 (−0.55 to −0.05)	0.02
Daily arbitrary accelerometer units for all treatment doses	9623 (9271–9976)	9185 (8822–9547)	−439 (−792 to −86)	0.02
Blood pressure — mm Hg				
Systolic	129 (125–132)	125 (122–128)	−3.7 (−7.2 to −0.3)	0.04
Diastolic	70 (69–72)	69 (67–71)	−1.6 (−3.5 to 0.3)	0.10
Mean arterial blood pressure — mm Hg	90 (88–92)	88 (86–90)	−2.3 (−4.4 to −0.2)	0.03

Ref: https://www.nejm.org/doi/full/10.1056/NEJMoa1510774



Based on this abstract, do you think treatment A would be beneficial to patients?
Scale, 0 [very unlikely] to 10 [very likely]

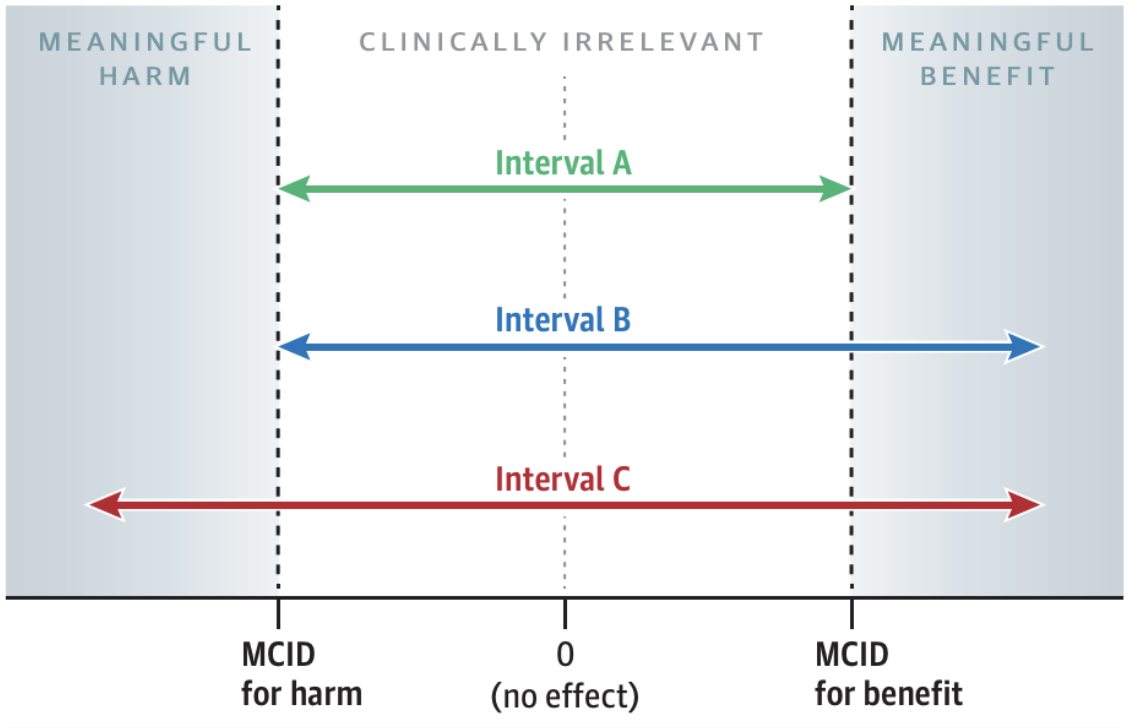
Based on this abstract, do you think treatment A would be beneficial to patients?
(Scale, 0 [ver



Mean difference = 0.71 (95% CI, 0.07-1.35); P .03

P-value

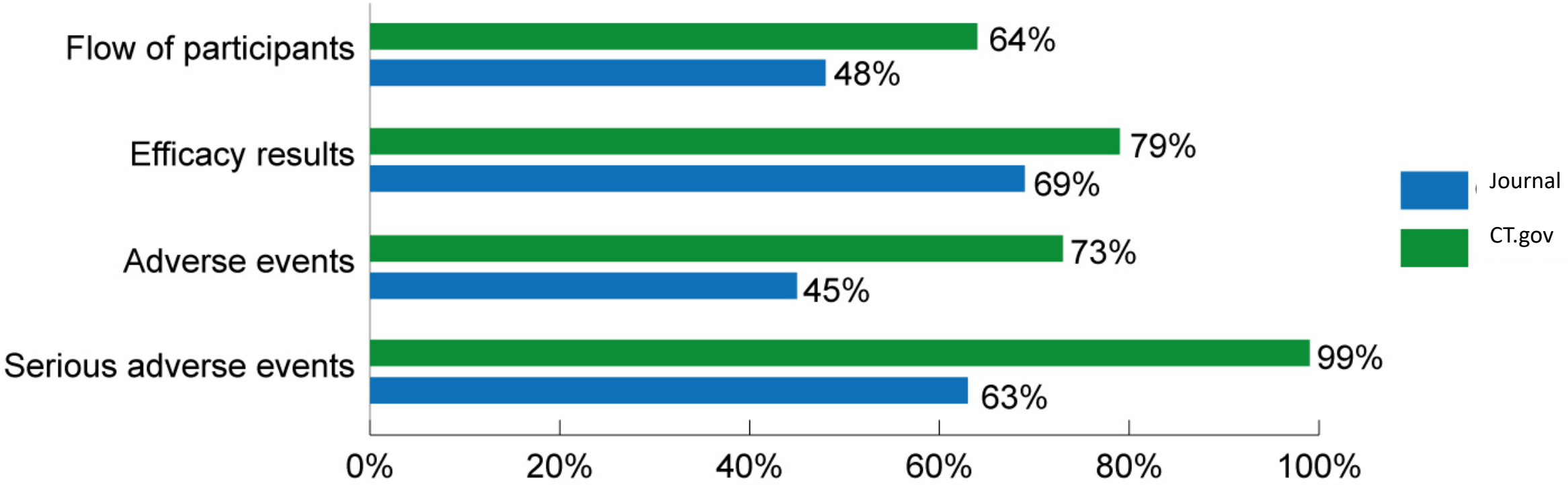
Figure. Three Possible Confidence Intervals From a Study With Statistically Nonsignificant Results



MCID indicates minimal clinically important difference.

Rôle des registres d'essais

202 essais cliniques publiés avec des résultats postés sur les registres



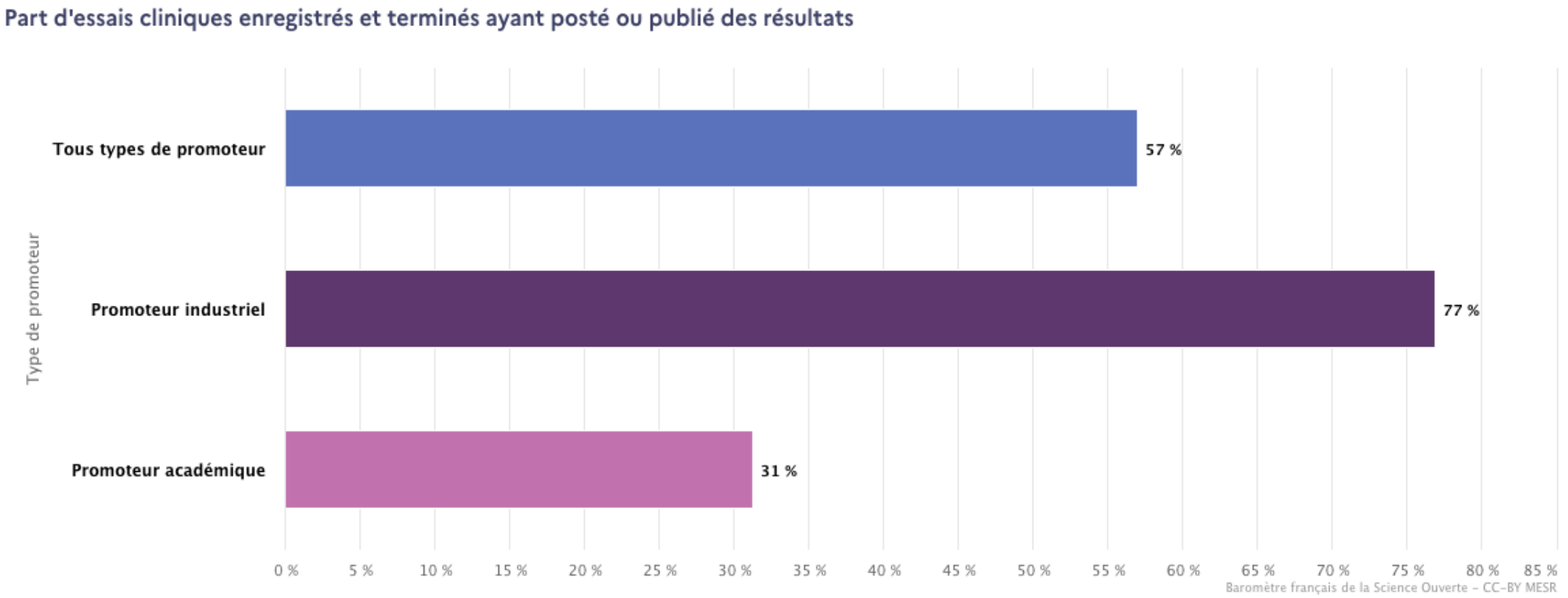
Riveros C, Dechartres A, Perrodeau E, Haneef R, Boutron I, Ravaud P, Plos Med, 2013

Respect de la législation

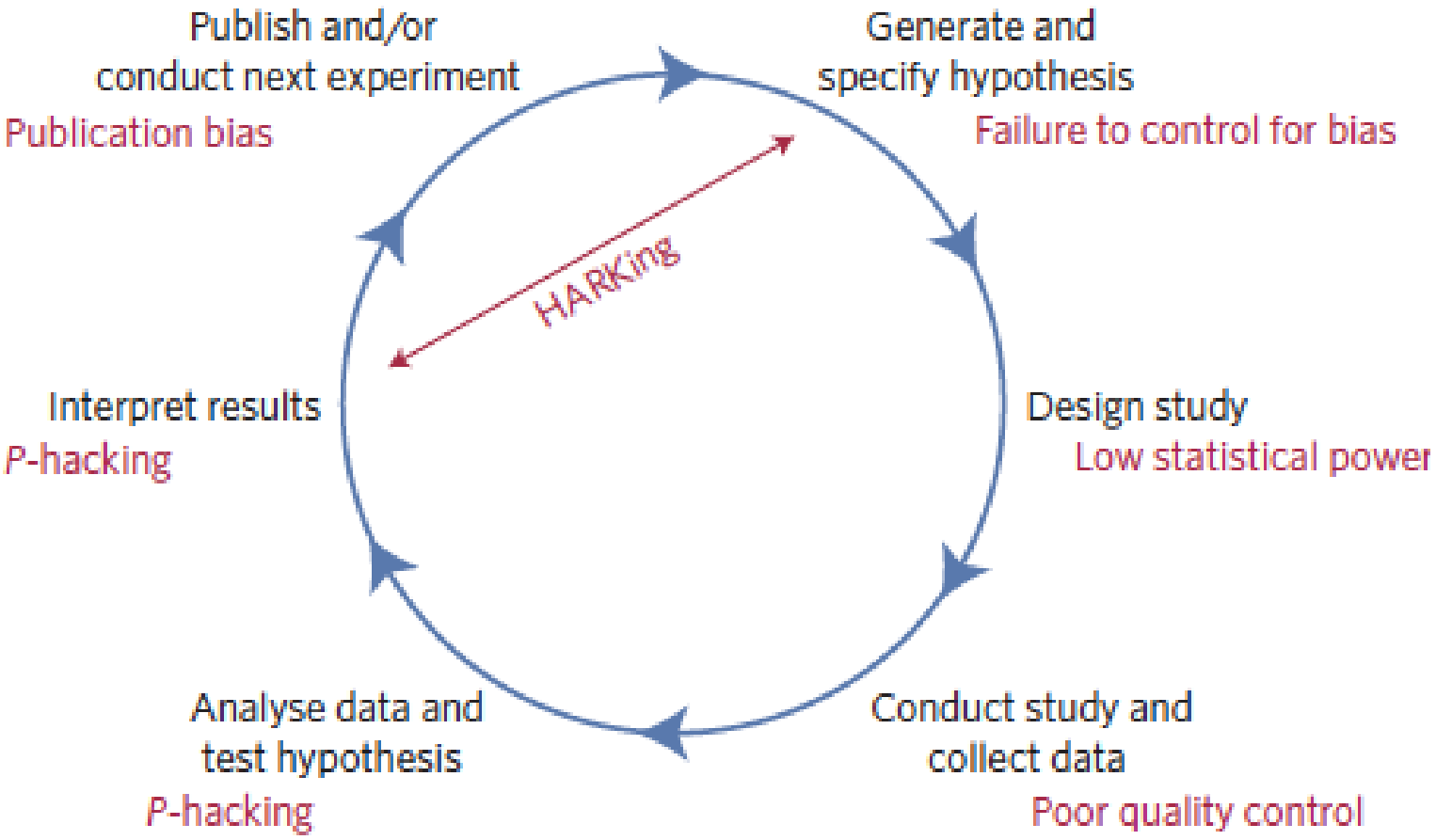
Accès aux résultats des essais cliniques via les registres
Baromètre de la science ouverte

MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR, DE LA RECHERCHE ET DE L'INNOVATION
Liberté Égalité Fraternité

French Open Science Monitor

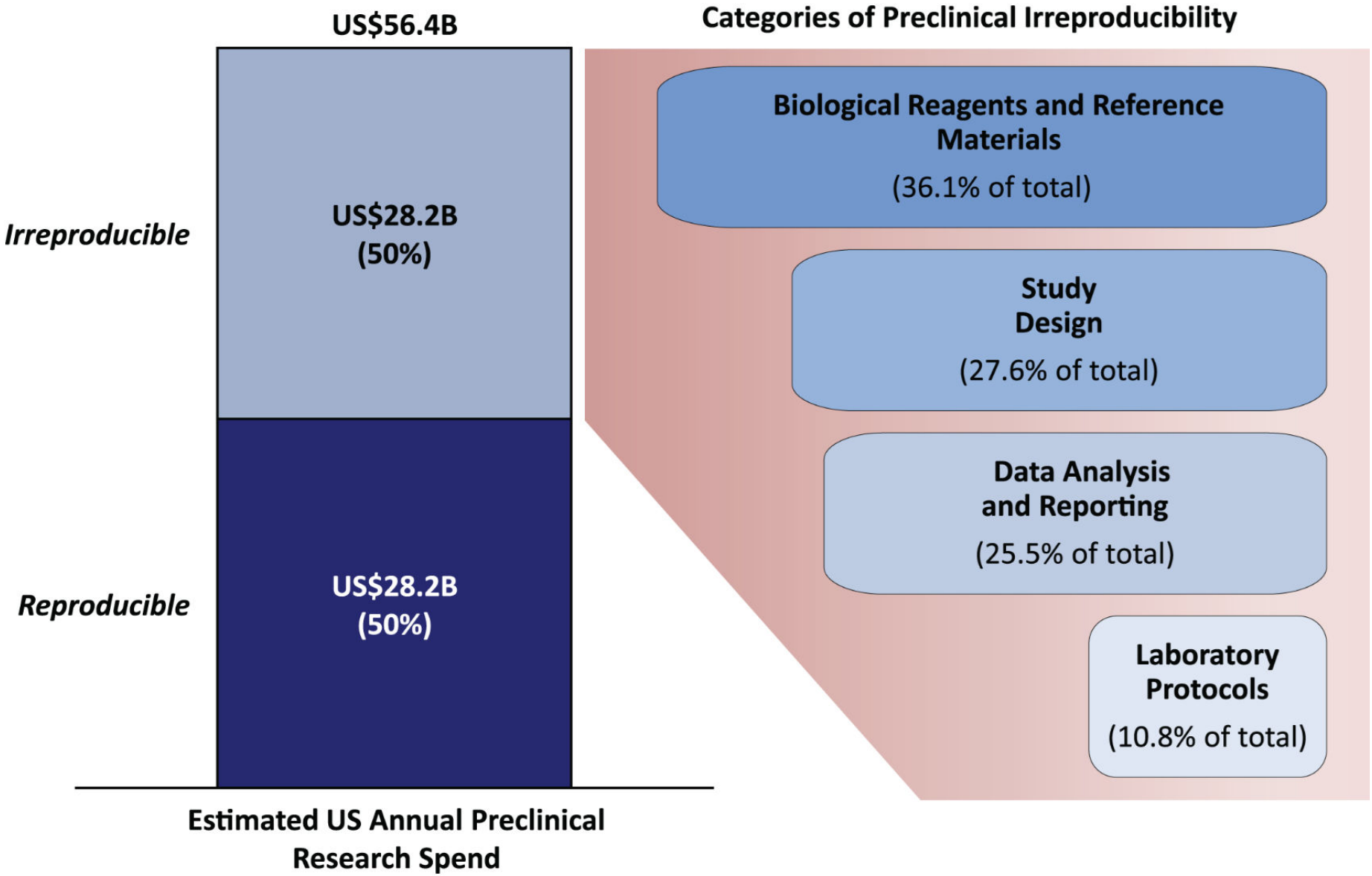


What are the threats to reproducible science



Munafò, M., Nosek, B., Bishop, D. *et al.* A manifesto for reproducible science. *Nat Hum Behav* **1**, 0021 (2017)

Research quality and reproducibility is being questioned



Freedman Plos Biol 2015

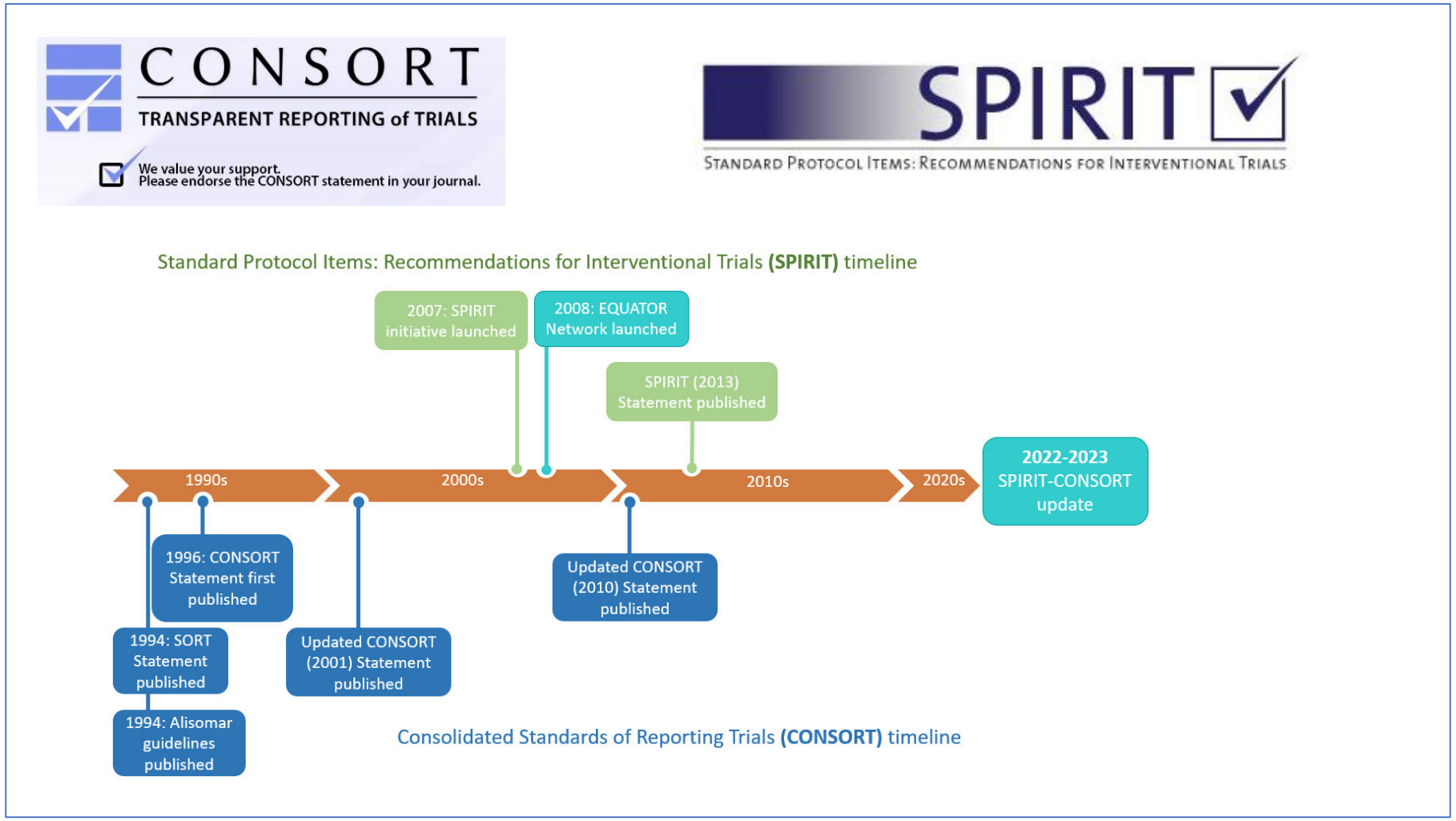
Les informations essentielles ne sont pas dans les articles

- Absence de transparence
  - > 30% des essais: pas de description de l'intervention
  - > 50% : pas de description de la randomisation
  - 50% pas de description du critère de jugement principal

- Cochrane Systematic Reviews
  - 75% des essais ont au moins un domaine de l'échelle permettant d'évaluer le risque de biais non décrit

Glasziou, Meats, Heneghan, Shepperd, BMJ. 2008
Glasziou, Altman, Bossuyt, Boutron, Clarke, Julious, Michie, Moher, Wager. Lancet. 2014
Yordanov, Dechartres, Porcher, Boutron, Altman, Ravaud, BMJ, 2015
Kapp P, Esmail L, Ghosn L, Ravaud P, Boutron I BMC Med 2022

Plan



Hopewell S, Boutron I, Chan AW, Collins GS, de Beyer JA, Hróbjartsson A, Hansen Nejstgaard C, Østengaard L, Schulz KF, Tunn R, Moher D Nature Med 2022

Pre-registration

PNAS

The preregistration revolution

Brian A. Nosek[a,b,1], Charles R. Ebersole[b], Alexander C. DeHaven[a], and David T. Mellor[a]

[a]Center for Open Science, Charlottesville, VA 22903; and [b]Department of Psychology, University of Virginia, Charlottesville, VA 22904

Edited by Richard M. Shiffrin, Indiana University, Bloomington, IN, and approved August 28, 2017 (received for review June 15, 2017)

Progress in science relies in part on generating hypotheses with existing observations and testing hypotheses with new observations. This distinction between postdiction and prediction is appreciated conceptually but is not respected in practice. Mistaking generation of postdictions with testing of predictions reduces the credibility of research findings. However, ordinary biases in human reasoning, overconfidence in post hoc explanations (postdic the likelihood of believing that there is evidence f there is not. Presenting postdictions as predicti the attractiveness and publishability of findings b uncertainty. Ultimately, this decreases reproduci

OSF HOME ▾ Search Support Donate Sign Up Sign In

Sharing of Individual Participa... Metadata Files Analytics Registrations

for COVID-19

555.5KB Public 0 ···

Contributors: Laura Esmail, Isabelle Boutron

Date created: 2023-01-03 06:08 PM | Last Updated: 2023-03-30 04:51 PM

Identifier: DOI 10.17605/OSF.IO/D46KJ

Category: Project

Files

Filter

Name	Modified
Sharing of Individual Participant-leve...	
OSF Storage (United States)	
IPD Project Implementation.pdf	2023-01-05 01:4...
IPD Project Implementationv2....	2023-03-30 04:5...
IPD Sharing Covid-19 FINAL.xlsx	2023-03-30 04:5...

Citation

Recent Activity

Laura Esmail added file IPD Project Implementationv2.pdf to OSF Storage in Sharing of Individual Participant-level Data by Trialists of Randomized Clinical Trials of Pharmacologic Treatments for COVID-19

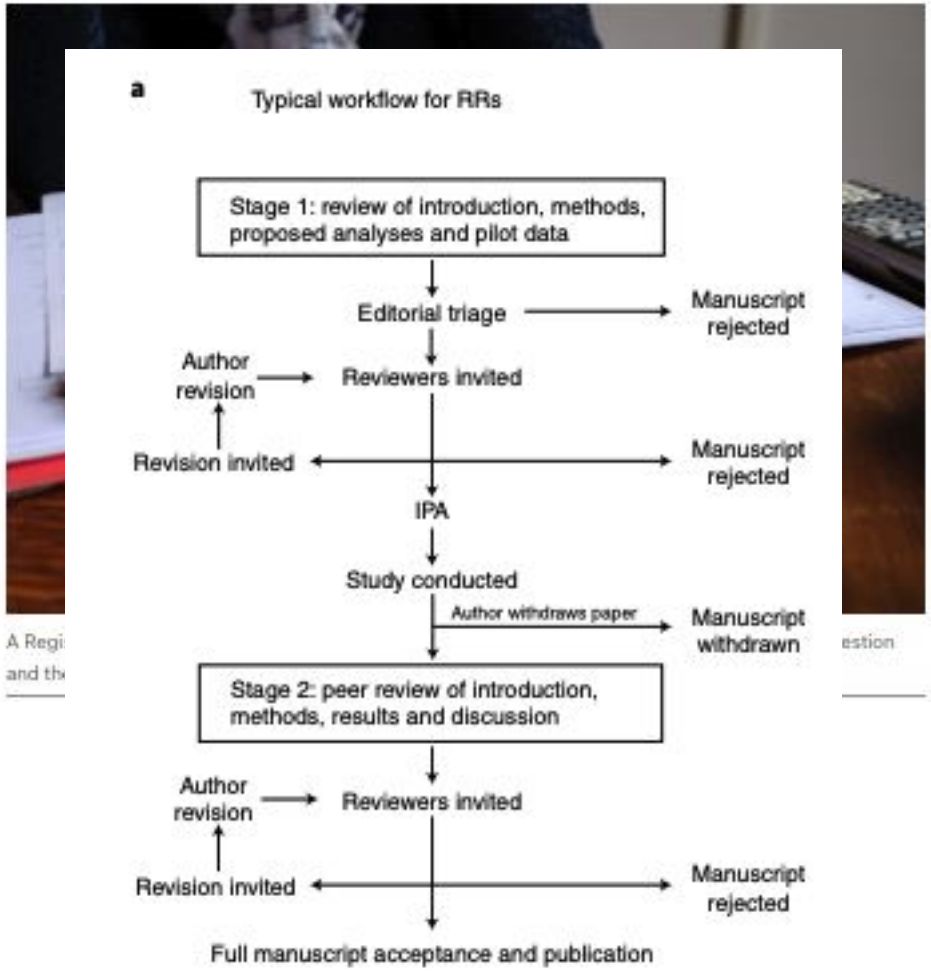
2023-03-30 04:51 PM

Laura Esmail added file IPD Sharing Covid-19 FINAL.xlsx to OSF Storage in Sharing of Individual Participant-level Data by Trialists of Randomized Clinical Trials of Pharmacologic Treatments for COVID-19

2023-03-30 04:51 PM

Nature welcomes Registered Reports

From this week, *Nature* will be publishing an additional type of research paper – designed to encourage rigour and replication.



Nature Human Behaviour 2022

Transparency and open research practices

Open science in Horizon Europe

Did you know that open science is a legal obligation under Horizon Europe? Its purpose is to foster greater transparency and trust for the benefit of scientific research and for the benefit of EU citizens.

What are the open science practices under Horizon Europe? There are two mandatory practices: Open access to publications and open access to research data based on the principle of 'as open as possible, as closed as necessary'. Additionally, there are several recommended practices to consider when appropriate. Examples include involving all relevant knowledge actors (including citizens), early open sharing of research and research outputs beyond publications, sharing research data and open peer-reviews. These practices are outlined in the Horizon Europe Standard Application Form and the Programme Guide.

Excellence #@REL-EVA-RE@#

Excellence – aspects to be taken into account.

- Clarity and pertinence of the project's objectives, and the extent to which the proposed work is ambitious, and goes beyond the state of the art.
- Soundness of the proposed methodology, including the underlying concepts, models, assumptions, interdisciplinary approaches, appropriate consideration of the gender dimension in research and innovation content, and the quality of open science practices, including sharing and management of research outputs and engagement of citizens, civil

L'ANR met en place un plan de gestion des données pour les projets financés dès 2019

Data Management Plan – General Definition

Data Management Plans (DMPs) are a **key element** of good data management. A DMP describes the data management life cycle for the data to be collected, processed and/or generated by a Horizon 2020 project. As part of making research data findable, accessible, interoperable and re-usable (FAIR), a **DMP should include information** on:

- the handling of research data during & after the end of the project
- what data will be collected, processed and/or generated
- which methodology & standards will be applied
- whether data will be shared/made open access and
- how data will be curated & preserved (including after the end of the project).

A DMP is required for all projects participating in the extended ORD pilot, unless they opt out of the ORD pilot. However, projects that opt out are still encouraged to submit a DMP on a voluntary basis.

Transparency and open research practices

equator network

Enhancing the QUAlity and Transparency Of health Research

Home | About us | Library | Toolkits | Courses & events | News | Blog

Home > Library > Reporting guideline > The ARRIVE Guidelines 2.0: updated guidelines for reporting a

Search for reporting guidelines

Use your browser's Back button to return to your search results

The ARRIVE Guidelines 2.0: updated guidelines for reporting animal research

Reporting guideline provided for? (i.e. exactly what the authors state in the paper)	Reporting any area of bioscience research using laboratory animals

Nature

Reporting standards and availability of data, materials, code and protocols

An inherent principle of publication is that others should be able to replicate and build upon the authors' published claims. A condition of publication in a Nature Portfolio journal is that **authors are required to make materials, data, code, and associated protocols promptly available to readers without undue qualifications.** Any restrictions on the availability of materials or information must be disclosed to the editors at the time of submission. Any restrictions must also be disclosed in the submitted manuscript.

After publication, readers who encounter refusal by the authors to comply with these policies should contact the chief editor of the journal. In cases where editors are unable to resolve a complaint, the journal may refer the matter to the authors' funding institution and/or publish a formal statement of correction, attached online to the publication, stating that readers have been unable to obtain necessary materials to replicate the findings.

Annals of Internal Medicine

EDITORIAL

Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors

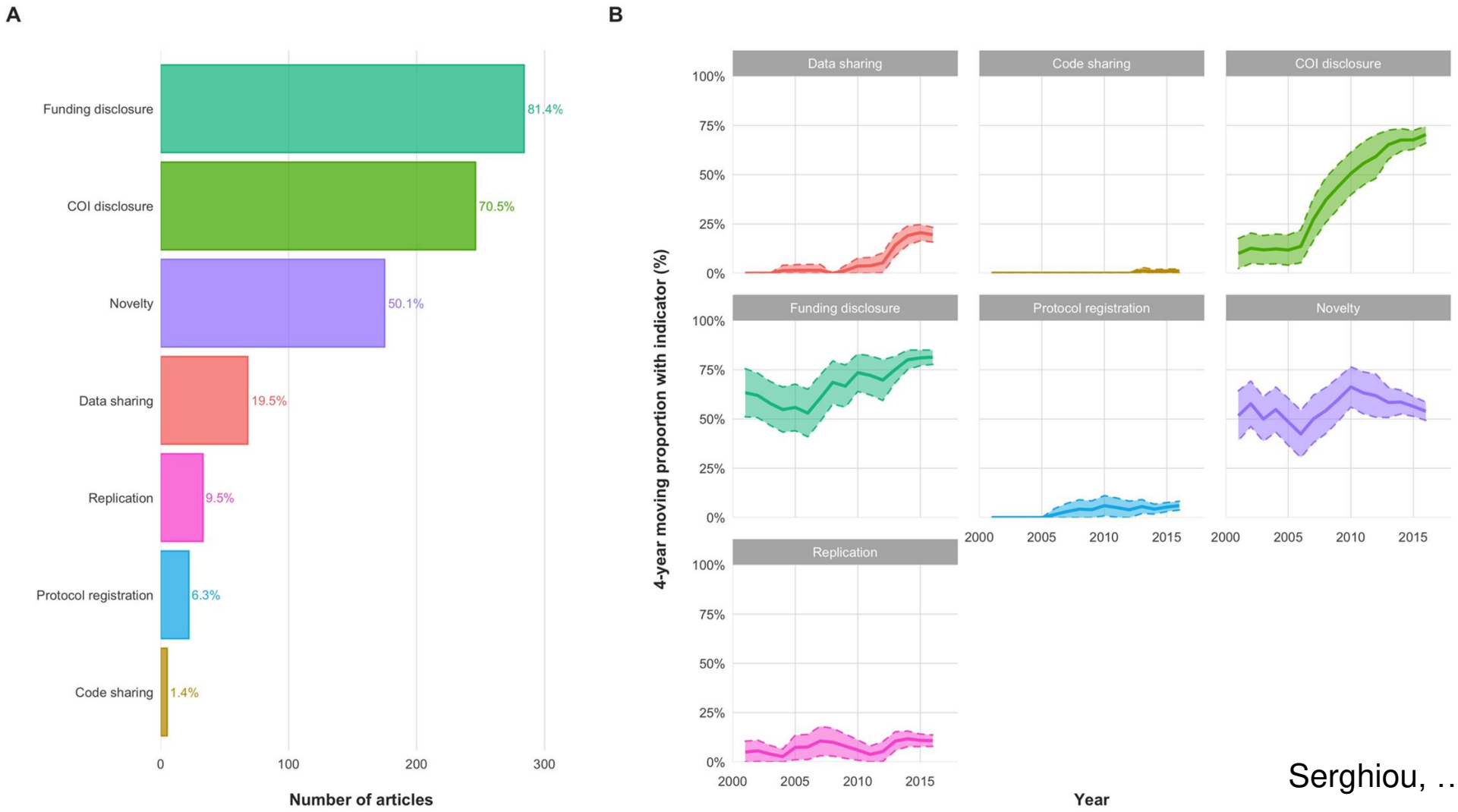
The International Committee of Medical Journal Editors (ICMJE) believes there is an ethical obligation to responsibly share data generated by interventional clinical trials because trial participants have put themselves at risk. In January 2016 we published a proposal aimed at helping to create an environment in which the

ples of data sharing statements that would meet these requirements are in the Table.

These initial requirements do not yet mandate data sharing, but investigators should be aware that editors may take into consideration data sharing statements when making editorial decisions. These minimum re-

Assessment of transparency indicators across the biomedical literature

2.75 million articles on PubMed Central



Serghiou, … Ioannidis Plos Biol

Plan

Cochrane France

Université Paris Cité

Université Sorbonne Paris Nord

Inserm
La science pour la santé
From science to health

INRAE