

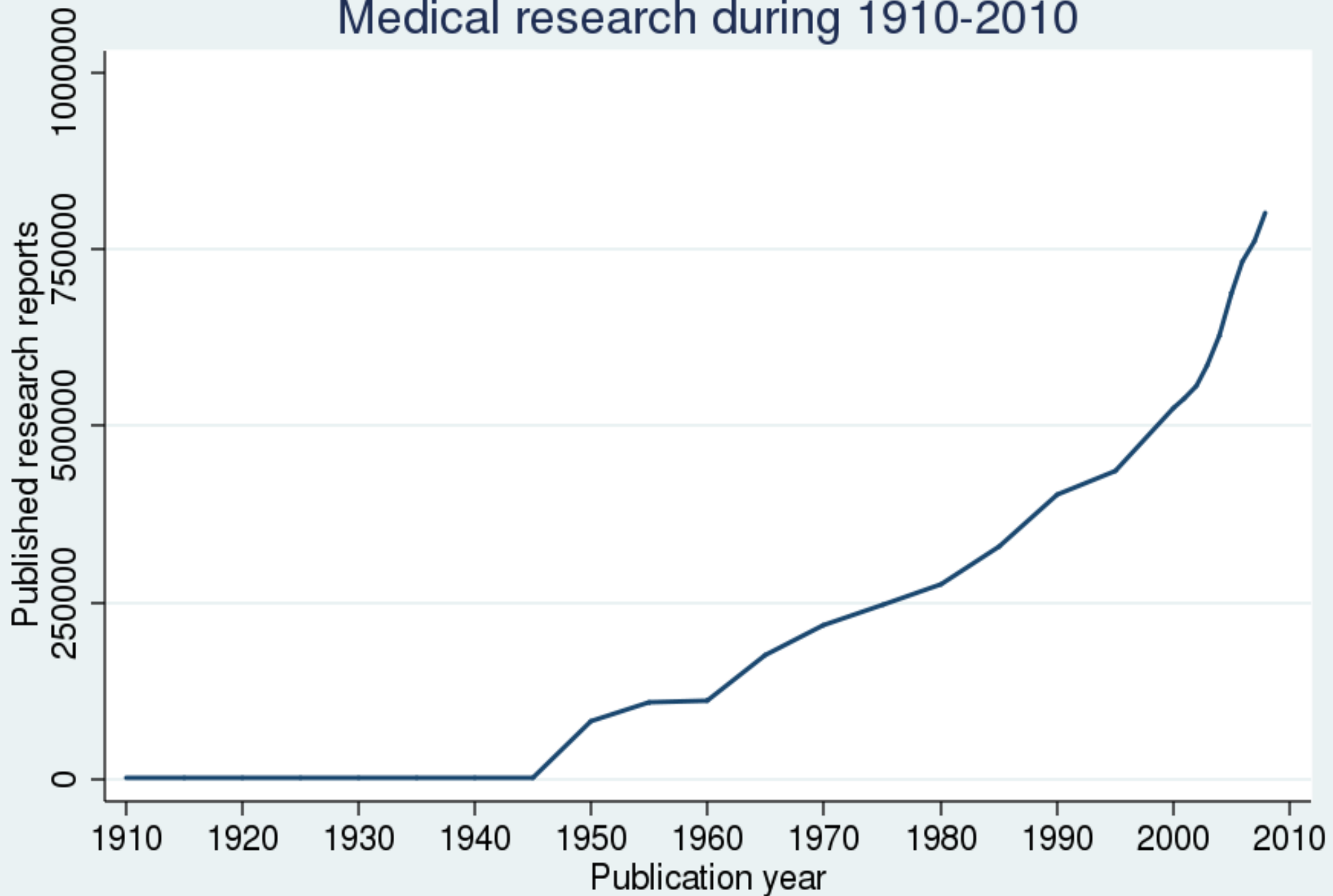
Guidelines

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Guidelines

A guideline is any document that aims to streamline particular processes according to a set routine.

Medical research during 1910-2010



Source: US National Library of Medicine

Medical research as a modern science

Randomised controlled trial

Medical Research Council (1948) Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *British Medical Journal*, 2: 769-83.

Observational cohort study

Doll R, Hill AB. (1950) Smoking and carcinoma of the lung. Preliminary report, *British Medical Journal*, 2: 739-748.

Case-control study

Doll R, Hill AB. (1954) The mortality of doctors in relation to their smoking habits. *British Medical Journal*, 228:1451-5

Table 1. Methodological Input in Relation to Study Design

Design	Methodologist, No./Total (%)		
	Biostatistician	Epidemiologist	Other
Randomized controlled trial	43/65 (66)	15/65 (23)	7/65 (11)
Systematic review	18/34 (53)	14/34 (41)	2/34 (6)
Observational	197/385 (51)	127/385 (33)	61/385 (16)
Economic	8/14 (57)	3/14 (21)	3/14 (21)
Other	7/16 (44)	3/16 (19)	6/16 (38)
Total	273/514 (53)	162/514 (32)	79/514 (15)

Altman et al. JAMA 2002;287:2817-2820

Essay

Why Most Published Research Findings Are False

John P.A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the

factors that influence this problem and some corollaries thereof.

Modelling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p -value less than 0.05. Research is not most appropriately represented and summarized by p -values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

should be interpreted based only on p -values. Research findings are defined here as any relationship reaching

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R+1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α . Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV.

Table 1. Summary of Empirical Evidence of Prevalence of Methodological Problems in Published Reports of Randomized Trials*

Deficiency	Evidence
Failing to specify eligibility criteria	25% of 364 reports in surgery journals
Not reporting an adequate method for generating random numbers	68% of 206 reports in obstetrics and gynecology journals; 52% of 80 reports in general medical journals
Not reporting the mechanism used to allocate interventions	89% of 196 reports in rheumatoid arthritis journals; 48% of 206 reports in obstetrics and gynecology journals; 44% of 80 reports in general medical journals
Failing to state whether blinding was used	51% of 506 reports in cystic fibrosis journals; 33% of 196 reports in rheumatoid arthritis journals; 38% of 68 reports in dermatology journals
Incorrect analysis of multiple observations	63% of 196 reports in rheumatoid arthritis journals
Inadequate information on harmful consequences of interventions	61% of 192 reports in 7 medical areas
Incorrect method of comparison of subgroups	58% of 50 reports in general journals

*Data from Altman et al.²

Douglas G Altman. JAMA 2002;287:2765

Recent developments

A. ICH harmonized tripartite guideline (1998)

- E9 Statistical principles for clinical trials, 1998
- Note for guidance, Points to consider, etc.

B. Public registration of study protocols (2005)

- ClinicalTrials.gov, etc.
- WHO ICTRP

C. Reporting guidelines (1996-2010)

- CONSORT (RCTs)
- PRISMA (Systematiska reviews)
- STROBE (Observationella studier)
- STARD (Diagnostiska studier)
- ARRIVE (Djurförsök)



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	_____
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	_____
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	_____
	2b	Specific objectives or hypotheses	_____
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	_____
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	_____
Participants	4a	Eligibility criteria for participants	_____
	4b	Settings and locations where the data were collected	_____
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	_____
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	_____
	6b	Any changes to trial outcomes after the trial commenced, with reasons	_____
Sample size	7a	How sample size was determined	_____
	7b	When applicable, explanation of any interim analyses and stopping guidelines	_____
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	_____
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	_____
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	_____
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	_____
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	_____

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,

Table 2. Animal Research: Reporting *In Vivo* experiments: The ARRIVE guidelines.

	ITEM	RECOMMENDATION
TITLE	1	Provide as accurate and concise a description of the content of the article as possible.
ABSTRACT	2	Provide an accurate summary of the background, research objectives (including details of the species or strain of animal used), key methods, principal findings, and conclusions of the study.
INTRODUCTION		
Background	3	<ol style="list-style-type: none">Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale.Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.
METHODS		
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.
Study design	6	For each experiment, give brief details of the study design, including: <ol style="list-style-type: none">The number of experimental and control groups.Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g., randomisation procedure) and when assessing results (e.g., if done, describe who was blinded and when).The experimental unit (e.g. a single animal, group, or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: <ol style="list-style-type: none">How (e.g., drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s).When (e.g., time of day).Where (e.g., home cage, laboratory, water maze).Why (e.g., rationale for choice of specific anaesthetic, route of administration, drug dose used).
Experimental animals	8	<ol style="list-style-type: none">Provide details of the animals used, including species, strain, sex, developmental stage (e.g., mean or median age plus age range), and weight (e.g., mean or median weight plus weight range).Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug- or test-naïve, previous procedures, etc.
Housing and husbandry	9	Provide details of: <ol style="list-style-type: none">Housing (e.g., type of facility, e.g., specific pathogen free (SPF); type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish).Husbandry conditions (e.g., breeding programme, light/dark cycle, temperature, quality of water etc. for fish, type of food, access to food and water, environmental enrichment).Welfare-related assessments and interventions that were carried out before, during, or after the experiment.

Impact of E9 (ICH-GCP)

- Equivalence or non-inferiority replaced 'ns'
- Problem with interim analyses recognized
- Sample size calculations performed
- Pre-specification of analysis recognized
- ITT and PP analysis sets used
- Missing value problem recognized
- Subgroup analysis problem recognized

Brown D, Day S, Hemmings R, Wright D. Assessing the impact of ICH E9. Pharm Stat. 2008;7:77-87.

Systematic reviews of orthopedic literature

The ITT principle was recognized in 96 of 274 (35%) published randomized trials.

Herman A, Botser IB, Tenenbaum S, and Chechick A. Intention-to-treat analysis and accounting for missing data in orthopaedic randomized clinical trials. J Bone Joint Surg Am. 2009;91:2137-2143.

Systematic reviews of orthopedic literature

A high proportion (42%) of clinical studies in high-impact-factor orthopedic journals involve the inappropriate use of multiple observations from single individuals

Bryant et al. How Many Patients? How Many Limbs?
Analysis of Patients or Limbs in the Orthopaedic Literature.
JBJS Am 2006;88:41-45.

Guideline documents generate citations

More citations => higher impact factor

Editors want to publish guidelines

Guidelines submitted or in press

Mithoefer K, Saris D, Farr J, Kon E, Zaslav K, Ranstam, J, Yao J, Shove M, Levine D, Dalemans W, Brittberg M. **Guidelines** for the Design and Conduct of Clinical Studies in Knee Articular Cartilage Repair.

Roos EM, Engelhart E, Ranstam J, Anderson AF, Irrgang J, Marx R, Tegner Y, Davis AM. ICRS **Recommendation** Document: Patient-reported outcome instruments for use in patients with articular cartilage defects.

Ranstam J, Kärrholm J, Pulkkinen P, Mäkelä K, Espehaug B, Pedersen AB, Mehnert F, Furnes O. **Recommendation** for statistical analysis of arthroplasty data.

Problem med kvalitetsregister

- Ofta okänt bortfall (“täckningsgrad”)
- Ofta okänd datavaliditet
- Ofta oklar statistisk analys
- Ingen peer review av rapporter
- Utgör underlag för kliniskt förbättringsarbete
- Används för klinisk forskning
- Drar mycket resurser

Guidelines för kvalitetsregister?

- Systemutveckling
- Registerinnehåll
- Registrering av data
- Validering av data
- Analys av data
- Rapportering