Cochrane Deutschland

German GRADE Center Freiburg

Vermeidbare Wissenslücken – wieso, weshalb, warum ?

Joerg J Meerpohl

Co-Direktor, Cochrane Deutschland

UNIVERSITÄTS KLINIKUM FREIBURG

Interessenskonflikte

- Mitglied von Cochrane und GRADE
- Nicht offizielle Meinung von Cochrane / GRADE

- Editor u.a.
  - ZEFQ
  - Journal Negative Results in Biomedicine
  - Peer Review and Research Integrity

- Dank an Doug Altman / Iveta Simera (EQUATOR)
- Dank an Cochrane Deutschland und die DISCO Study Group

Cochrane Deutschland

German GRADE Center Freiburg

Gliederung

- Eine „gute“ Studie
- Probleme, u.a.
  - Nicht-Publikation
  - Berichtsqualität
  - Studienabbruch
- Nicht-durchgeführte Studien
- Zusammenfassung

Eine „gute“ Studie

- adressiert eine relevante Frage
  - Klinisch
  - Public Health
  - Versorgung
  - .....

Berliner Kurier, 24.02.2009

Männer mit Pelz vertragen mehr Pils

Sie haben mehr männliche Geschlechtshormone. Das macht trinkfest

Berlin - Sollten Sie in der Kneipe einen Mann sehen, der seine Brusthaare zählt, so rechnet der wahrscheinlich gerade durch, wie viel er noch verträgt. Was wie ein Scherz klingt, ist wissenschaftlicher Ernst. Eine Studie ergab: Je mehr Pelz, desto mehr Pils geht rein.

Männer, zeigt her eure Brusthaare! Wo nichts sprießt (außer Hoffnung), da ist Vorsicht bei Alkohol angesagt. Auf den haarigen Zusammenhang zwischen Trinkfestigkeit und Haarwuchs stieß Professor Dr. Siegfried E. Miederer, Ex-Chefarzt am Johannes-Krankenhaus Bielefeld.

Schütteres Brusthaar hat aber auch andere Gründe

Der Mediziner stellte in einer Untersuchung fest, dass Männer mit reichlich sprießendem Brustpelz mehr Alkohol vertragen können. Grund: Sie haben in der Regel einen höheren Spiegel an männlichen Geschlechtshormonen, den Androgenen. Dadurch sind ihre Leberzellen besser geschützt vor den Attacken promillehaltiger Getränke.

Aber auch das, warnt Professor Hademar Bankhofer, der die Studie entdeckte, ist kein Freibrief für mehr Alkohol. Dafür ist der Effekt eher gering. Außerdem sind an schütterem Brusthaar oft nicht zu wenig männliche Hormone, sondern deren mangelhafte Verwertung in den Zellen der Haut schuld.

Von Natur aus richtig massiv im Nachteil ist das weibliche Geschlecht, weiß Professor Bankhofer. Denn: Frauen haben geringere Konzentrationen des

Massiv im Nachteil – das weibliche Geschlecht

Alkohol abbauenden Enzyms Dehydrogenase im Körper, zusätzlich bremsen Östrogene den Alkohol-Abbau in der Leber. Folge: Frauen vertragen nur halb so viel wie Männer.

Eine „gute“ Studie

- adressiert eine relevante Frage,
- die noch nicht beantwortet ist.

Studien der Studien wegen

BMJ

BMJ 2012;344:e3054 doi: 10.1136/bmj.e3054 (Published 21 May 2012)

RESEARCH

Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis

OPEN ACCESS

Katharine Ker *research fellow*, Phil Edwards *senior lecturer*, Pablo Perel *clinical senior lecturer*, Haleema Shakur *senior lecturer*, Ian Roberts *professor of epidemiology*

Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

Abstract

Objective To assess the effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality in surgical patients.

Design Systematic review and meta-analysis.

Data sources Cochrane central register of controlled trials, Medline, and Embase, from inception to September 2011, the World Health Organization International Clinical Trials Registry Platform, and the reference lists of relevant articles.

Study selection Randomised controlled trials comparing tranexamic

useful new information. However, the effect of tranexamic acid on thromboembolic events and mortality remains uncertain. Surgical patients should be made aware of this evidence so that they can make an informed choice.

Introduction

In October 2011 the *BMJ* published a randomised controlled trial on the effect of tranexamic acid on blood transfusion in patients undergoing radical retropubic prostatectomy.[1] The

Ker, K., P. Edwards, P. Perel, H. Shakur, and I. Roberts, *Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis.* BMJ, 2012. **344**: p. e3054.

Studien der Studien wegen

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Introduction

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patients undergoing radical retropubic prostate

Trial	No with outcome/ No in group: Tranexamic acid	Control	Risk ratio (95% CI)	Risk ratio (95% CI)
Horrow 1990[52]	Not reported	Not reported		Not reported
Horrow 1991[53]	12/37	16/44		0.89 (0.49 to 1.64)
Coffey 1995[28]	9/16	8/14		0.93 (0.59 to 1.45)
Horrow 1995[54]	37/121	7/24		0.97 (0.67 to 1.41)
Karski 1995[63]	Not reported	Not reported		Not reported
Benoni 1996[10]	8/43	24/43		0.71 (0.51 to 0.98)
Boylan 1996[14]	Not reported	Not reported		Not reported
Hardy 1998[49]	28/42	27/44		0.83 (0.65 to 1.04)
Benoni 2000[12]	9/20	4/19		0.89 (0.71 to 1.11)
Tanaka 2001[114]	47/73	26/26		0.82 (0.69 to 0.97)
Casati 2001[18]	2/20	4/20		0.81 (0.68 to 0.96)
Benoni 2001[11]	4/18	8/20		0.79 (0.67 to 0.94)
Casati 2002[20]	11/29	19/29		0.77 (0.65 to 0.90)
Husted 2003[55]	2/20	7/20		0.75 (0.63 to 0.88)
Casati 2004[19]	9/52	13/50		0.74 (0.63 to 0.87)
Diprose 2005[33]	20/60	27/60		0.74 (0.64 to 0.86)
Johansson 2005[60]	8/47	23/53		0.71 (0.61 to 0.82)
Karski 2005[62]	24/147	41/165		0.70 (0.61 to 0.81)
Kultunen 2005[70]	5/20	12/20		0.69 (0.60 to 0.79)
Vaněk 2006[117]	3/32	6/30		0.68 (0.59 to 0.79)
Orpen 2006[94]	1/15	3/14		0.68 (0.59 to 0.78)
Murphy 2006[89]	13/50	14/50		0.69 (0.60 to 0.79)
Maddali 2007[78]	Not reported	Not reported		Not reported
Jimenez 2007[59]	9/24	19/26		0.68 (0.60 to 0.78)
Sadeghi 2007[105]	12/32	20/35		0.68 (0.60 to 0.77)
Chen 2008[25]	0/26	0/29		Not estimable
Elwatidy 2008[37]	4/32	12/32		0.67 (0.59 to 0.76)
Wong 2008[121]	23/73	30/74		0.68 (0.60 to 0.76)
Later 2009[73]	57/99	73/103		0.70 (0.63 to 0.78)
Taghaddomi 2009[113]	8/50	27/50		0.67 (0.61 to 0.75)
Zufferey 2010[131]	24/57	32/53		0.68 (0.61 to 0.75)
Gungorduk 2010[48]	2/330	7/330		0.67 (0.61 to 0.74)
Dadure 2011[30]	7/19	14/20		0.67 (0.60 to 0.74)
McConnell 2011[81]	0/22	0/22		Not estimable
Greiff 2011[46]	27/30	31/33		0.68 (0.62 to 0.75)
Crescenti 2011[1]	34/100	55/100		0.68 (0.62 to 0.74)

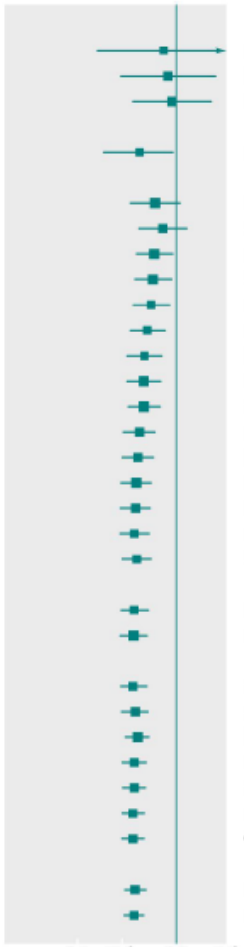


Fig 2 Cumulative meta-analysis of the effect of tranexamic acid in surgery on risk of blood transfu
concealed trials

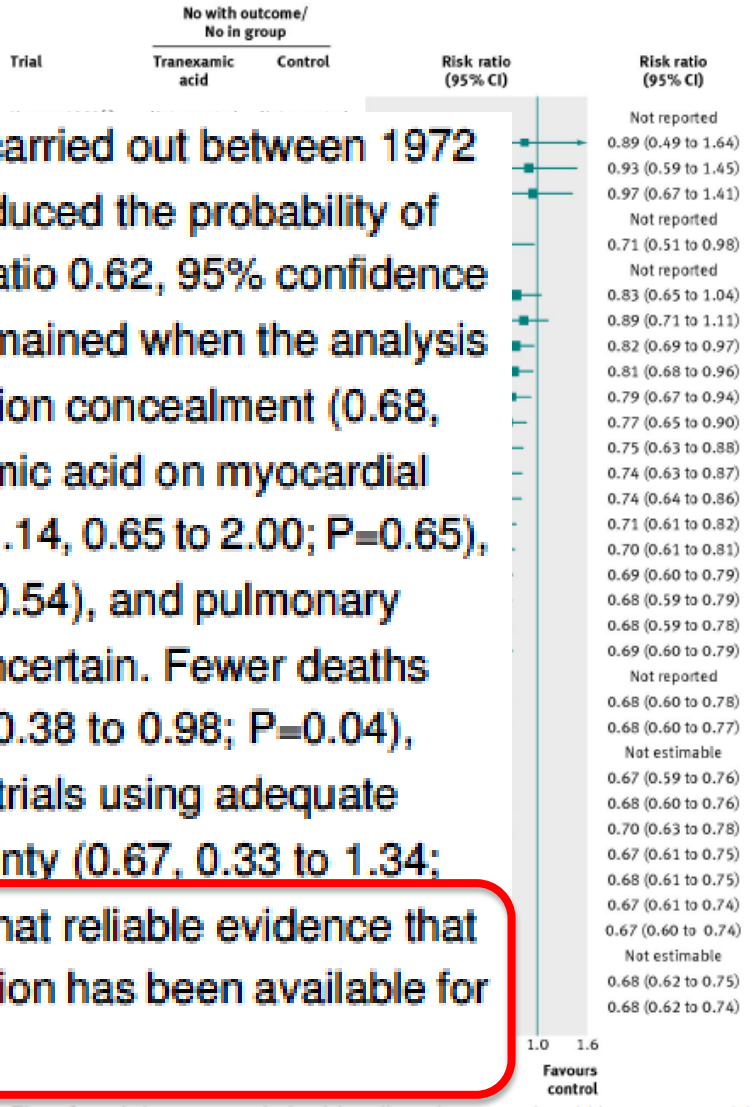
2012. **344**: p. e3054.

Studien der Studien wegen

BMI

BMJ 2012;344

Results 129 trials, totalling 10 488 patients, carried out between 1972 and 2011 were included. Tranexamic acid reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P<0.001). This effect remained when the analysis was restricted to trials using adequate allocation concealment (0.68, 0.62 to 0.74; P<0.001). The effect of tranexamic acid on myocardial infarction (0.68, 0.43 to 1.09; P=0.11), stroke (1.14, 0.65 to 2.00; P=0.65), deep vein thrombosis (0.86, 0.53 to 1.39; P=0.54), and pulmonary embolism (0.61, 0.25 to 1.47; P=0.27) was uncertain. Fewer deaths occurred in the tranexamic acid group (0.61, 0.38 to 0.98; P=0.04), although when the analysis was restricted to trials using adequate concealment there was considerable uncertainty (0.67, 0.33 to 1.34; P=0.25). Cumulative meta-analysis showed that reliable evidence that tranexamic acid reduces the need for transfusion has been available for over 10 years.



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Kollektives Vergessen

RESEARCH AND REPORTING METHODS | Annals of Internal Medicine

A Systematic Examination of the Citation of Prior Research in Reports of Randomized, Controlled Trials

Karen A. Robinson, PhD, and Steven N. Goodman, MD, MHS, PhD

Background: A randomized, controlled trial (RCT) should not be started or interpreted without accounting for evidence from preceding RCTs addressing the same question. Research has suggested that evidence from prior trials is often not accounted for in reports of subsequent RCTs.

Objective: To assess the extent to which reports of RCTs cite prior trials studying the same interventions.

Design: Meta-analyses published in 2004 that combined 4 or more trials were identified; within each meta-analysis, the extent to which each trial report cited the trials that preceded it by more than 1 year was assessed.

Measurements: The proportion of prior trials that were cited (prior research citation index), the proportion of the total participants from prior trials that were in the cited trials (sample size citation index), and the absolute number of trials cited were calculated.

Results: 227 meta-analyses were identified, comprising 1523 trials published from 1963 to 2004. The median prior research citation index was 0.21 (95% CI, 0.18 to 0.24), meaning that less than one quarter of relevant reports were cited. The median sample size citation index (0.24 [CI, 0.21 to 0.27]) was similar, suggesting that larger trials were not selectively cited. Of the 1101 RCTs that had 5 or more prior trials to cite, 254 (23%) cited no prior RCTs and 257 (23%) cited only 1. The median number of prior cited trials was 2, which did not change as the number of citable trials increased. The mean number of preceding trials cited by trials published after 2000 was 2.4, compared with 1.5 for those published before 2000 ($P < 0.001$).

Limitation: The investigators could not ascertain why prior trials were not cited, and noncited trials may have been taken into account in the trial design and proposal stages.

Conclusion: In reports of RCTs published over 4 decades, fewer than 25% of preceding trials were cited, comprising fewer than 25% of the participants enrolled in all relevant prior trials. A median of 2 trials was cited, regardless of the number of prior trials that had been conducted. Research is needed to explore the explanations for and consequences of this phenomenon. Potential implications include ethically unjustifiable trials, wasted resources, incorrect conclusions, and unnecessary risks for trial participants.

Primary Funding Source: None.

Ann Intern Med. 2011;154:50-55. www.annals.org
For author affiliations, see end of text.

Robinson, K.A. and S.N. Goodman, *A systematic examination of the citation of prior research in reports of randomized, controlled trials.* Ann Intern Med, 2011. **154**(1): p. 50-5.

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Number of Citable Trials	Reports, *n*	Reports That Cited 0 Trials, *n*	Reports That Cited 1 Trial, *n*	Reports That Cited 0 or 1 Trial, *n* (%)
≥3	1523	363	378	741 (49)
≥5	1101	254	257	511 (46)
≥10	508	138	123	261 (51)
≥15	282	79	69	148 (52)

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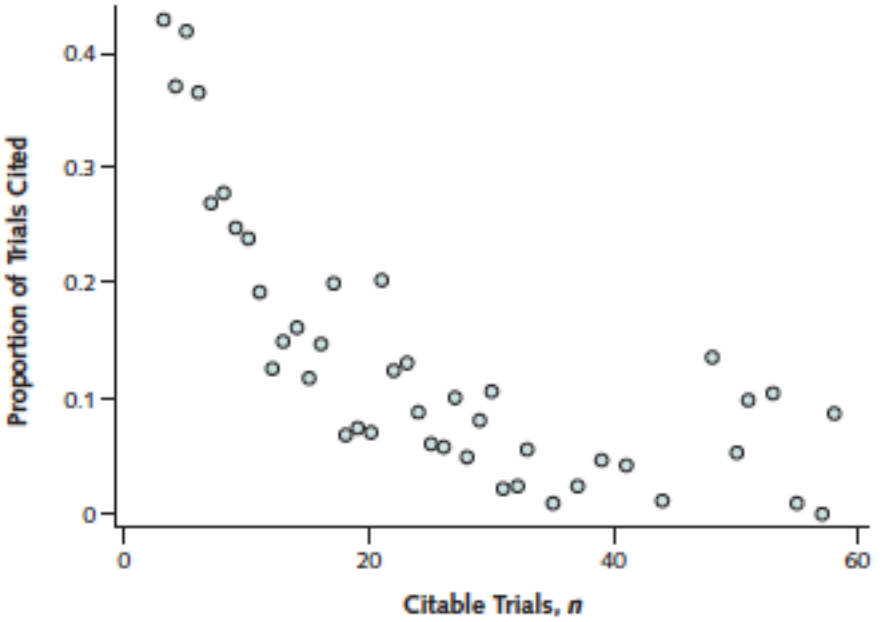
Figure 2. **Proportion of trials cited, by number of citable trials.**



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SR am Beginn jeder Studie?

RESEARCH

Many reports of randomised trials still don't begin or end with a systematic review of the relevant evidence

Mike Clarke, DPhil* Sally Hopewell, DPhil**
*All-Ireland Hub for Trials Methodology Research
**Centre for Statistics in Medicine and French Cochrane Centre

Correspondence to: m.clarke@qub.ac.uk

ABSTRACT

Background: Existing evidence should provide ethical, scientific and environmental justification for new randomised trials and users of the findings of these trials need to see them in the context of similar trials. Since 1997, audits have been done of reports of randomised trials in *Annals of Internal Medicine*, *BMJ*, *JAMA*, *Lancet*, and *New England Journal of Medicine* to see if results are placed in context in the Discussion section of the report and, since 2005, to see if systematic reviews are used in the Introduction section.
Methods: We handsearched each May 2012 issue of these five journals to identify reports of randomised trials. Introduction and Discussion sections were categorised on the basis of their use of systematic reviews.
Results: Thirty-five reports of randomised trials were included. Considering the Introduction sections: 5 were said to be the first trial, 1 used an updated systematic review in the design, 13 discussed previous systematic reviews, 10 mentioned other trials, and 6 didn't mention other trials or claim to be the first. Considering the Discussion sections: 2 were said to be the first trial, 2 contained a systematic review integrating the new trial, 11 mentioned a systematic review, and 20 made no apparent systematic attempt to place findings in full context. There was variability across the journals, with reports in the *Lancet* making notably more use of systematic reviews.
Conclusions: Many trials still do not use systematic reviews in their design and reporting.

BACKGROUND

The scientific, ethical and environmental justification for any new study should be a systematic review of the relevant research that already exists. This avoids waste that would come from seeking to answer a question with the new study that had been answered reliably by earlier studies, and should help to ensure that the new study is designed in a way that learns from successes and failures of the past.[1] When the study's findings are reported, these should be presented to readers within an updated systematic review of similar studies, to avoid undue emphasis solely on the results of the new study, to maximise the value of past studies (including the one being reported for the first time), and to provide the reader with a summary of all the relevant evidence.[2] In the Explanation and Elaboration document for the most recent CONSORT statement in 2010, the authors "recommend that, at a minimum, the discussion should be as systematic as possible and be based on a comprehensive search, rather than being limited to studies that support the results of the current trial."[3] Unfortunately, despite some progress towards achieving these goals, the healthcare literature still includes many reports of randomised trials that do not meet these standards. This study, which updates earlier audits, was conducted in 2012 to provide up-to-date data for a series of papers highlighting problems in, and suggesting solutions for, waste in research.

The earlier audits were conducted in May 1997[4], 2001[5], 2005[6], and 2009.[7] Those audits assessed a total of 106 reports of randomised trials from *Annals of Internal Medicine*, *BMJ*, *JAMA*, *Lancet* and the *New England Journal of Medicine*. The findings of the new trial were integrated into a systematic review in three (3%) of these (all published in the *Lancet*), and 22 (21%) cited a previous systematic review but did not integrate the findings of the trial. Considering the other 81 reports, 12 (11%) appeared to be the first trial and, hence, the totality of the evidence for the purpose of this audit. However, even though the reports of the other 69 (65%) trials included citations to trials, they did not provide information to suggest that these citations arose from a systematic attempt to set the results of the new trial in context.[7] Therefore, across a dozen years of these high profile journals, most reports of randomised trials had failed to provide the reader with sufficient information to assess the contribution of the new trial to the totality of the evidence base, and, as a consequence, failed to provide the reliable and robust evidence needed to help people make well-informed decisions and choices about the healthcare interventions that had been evaluated. However, alongside the publication of our 2009 audit in the *Lancet*,[7] an editorial by Clark and Horton outlined a new policy for that journal in which authors of all research studies, not just randomised trials, would be asked to include an updated systematic review in their Discussion section.[8] This led to the inclusion of a box in research reports in the *Lancet* that allows authors to describe a systematic review which integrates their findings.

	2009 N=29	2012 N=35
First trial addressing the question	5	5
Contained an updated systematic review which was used to design the new trial	1	1
Discussed a previous systematic review in the topic area for the trial	10	13
Contains references to other randomised trials	4	10
Does not contain references to other randomised trials, and does not claim to be the first trial	9	6

Table 1. Classification of Introduction sections in reports of randomised published in May 2009 and May 2012 in *Annals of Internal Medicine*, *BMJ*, *JAMA*, *Lancet*, and *New England Journal of Medicine*

Clarke, M. and S. Hopewell, *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): p. 145-148.

SR am Beginn jeder Studie?

RESEARCH

Many reports of randomised trials still don't begin or end with a systematic review of the relevant evidence

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	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

	2009 N=29	2012 N=35
First trial addressing the question	5	5
Contained an updated systematic	1	1
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Table 2. Classification of Discussion sections in reports of randomised published in May 1997, May 2001, May 2005, May 2009 and May 2012 in *Annals of Internal Medicine*, *BMJ*, *JAMA*, *Lancet*, and *New England Journal of Medicine*

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Clarke, M. and S. Hopewell, *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): p. 145-148.

SR bei der Studienplanung

RESEARCH ARTICLE Open Access

The use of systematic reviews in the planning, design and conduct of randomised trials: a retrospective cohort of NIHR HTA funded trials

Ashley P Jones[1*], Elizabeth Conroy[1], Paula R Williamson[1], Mike Clarke[2] and Carrol Gamble[1]

Abstract

Background: A systematic review, with or without a meta-analysis, should be undertaken to determine if the research question of interest has already been answered before a new trial begins. There has been limited research on how systematic reviews are used within the design of new trials, the aims of this study were to investigate how systematic reviews of earlier trials are used in the planning and design of new randomised trials.

Methods: Documentation from the application process for all randomised trials funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) between 2006 and 2008 were obtained. This included the: commissioning brief (if appropriate), outline application, minutes of the Board meeting in which the outline application was discussed, full application, detailed project description, referee comments, investigator response to referee comments, Board minutes on the full application and the trial protocol. Data were extracted on references to systematic reviews and how any such reviews had been used in the planning and design of the trial.

Results: 50 randomised trials were funded by NIHR HTA during this period and documentation was available for 48 of these. The cohort was predominately individually randomised parallel trials aiming to detect superiority between two treatments for a single primary outcome. 37 trials (77.1%) referenced a systematic review within the application and 20 of these (i.e. 41.7% of the total) used information contained in the systematic review in the design or planning of the new trial. The main areas in which systematic reviews were used were in the selection or definition of an outcome to be measured in the trial (7 of 37, 18.9%), the sample size calculation (7, 18.9%), the duration of follow up (8, 21.6%) and the approach to describing adverse events (9, 24.3%). Boards did not comment on the presence/absence or use of systematic reviews in any application.

Conclusions: Systematic reviews were referenced in most funded applications but just over half of these used the review to inform the design. There is an expectation from funders that applicants will use a systematic review to justify the need for a new trial but no expectation regarding further use of a systematic review to aid planning and design of the trial. Guidelines for applicants and funders should be developed to promote the use of systematic reviews in the design and planning of randomised trials, to optimise delivery of new studies informed by the most up-to-date evidence base and to minimise waste in research.

Keywords: Systematic review, Meta-analysis, Randomised controlled trial, Planning, Design

Table 3 The use of systematic reviews in trial design

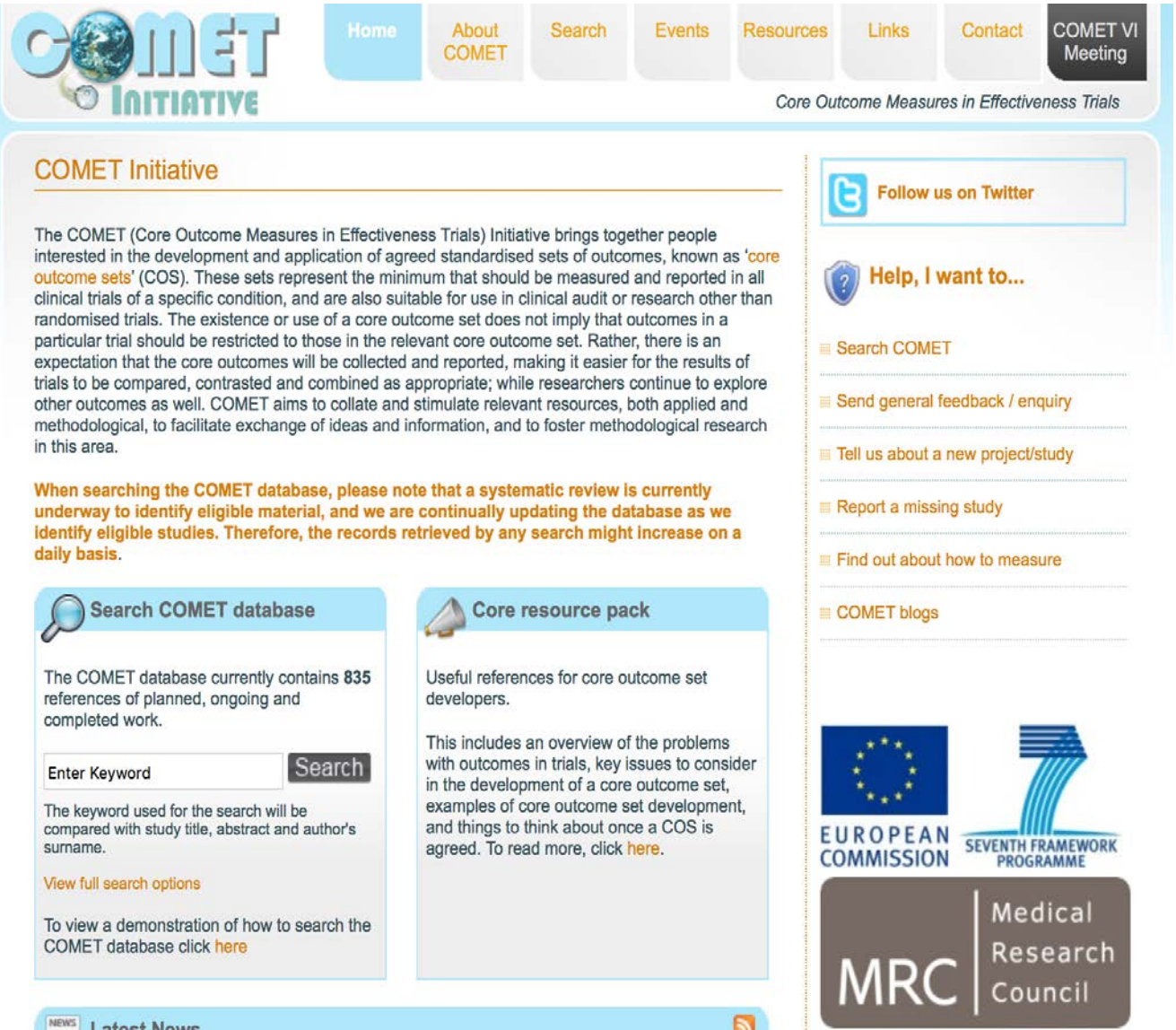
Area of use	Number of applications (%) (n=37)
Justification of treatment comparisons	6 (16.2)
Choice of frequency/dose	2 (5.4)
Selection or definition of outcome	7 (18.9)
Recruitment and consent	2 (5.4)
Estimating the difference to detect or margin of equivalence	6 (16.2)
Estimating the control group event rate	3 (8.1)
Inform standard deviation	1 (2.7)
Duration of follow up	8 (21.6)
Withdrawal rate	1 (2.7)
Adverse events	9 (24.3)

Jones, A.P., E. Conroy, P.R. Williamson, M. Clarke, and C. Gamble, *The use of systematic reviews in the planning, design and conduct of randomised trials: a retrospective cohort of NIHR HTA funded trials.* BMC Med Res Methodol, 2013. **13**: p. 50.

Eine „gute“ Studie

- adressiert eine wichtige Frage,
- die noch nicht beantwortet ist,
- misst (alle) relevante(n) Endpunkte,

COMET Initiative



"An agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care"

http://www.comet-initiative.org

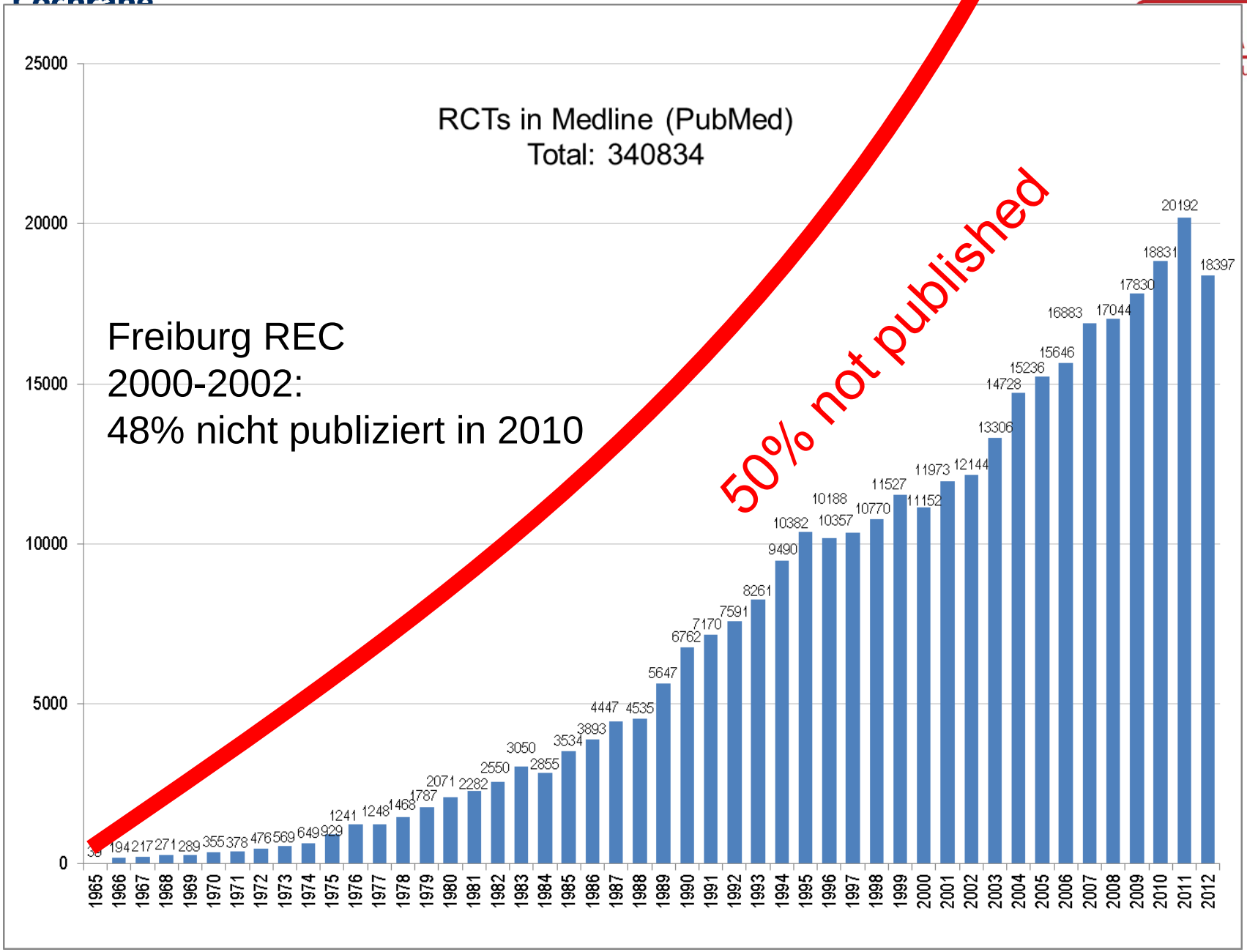
Angaben in verschiedenen Formaten

Endpunkt	Berichtet als	RCTs
Transfundiertes Volumen (mls)	Mittelwert und Standardfehler	4
	Mittelwert und Standardabweichung	2
	Mittelwert und etwas in Klammer	1
	Median und etwas in Klammer	1
	Zwei nicht benannte Zahlen e.g. x(y)	1
	Balkendiagramm mit Mittelwert pro Person pro Tag	1
Transfusionseinheiten	Mittelwert und Standardfehler	1
	Mittelwert alleine	1
	Gesamt in jeder Gruppe	1
Volumen angepasst an Patientengewicht (mls/kg)	Mittelwert und Standardabweichung	1
Patienten, die eine Transfusion hatten	Anzahl an Patienten	3
Nicht berichtet	Nicht berichtet	1

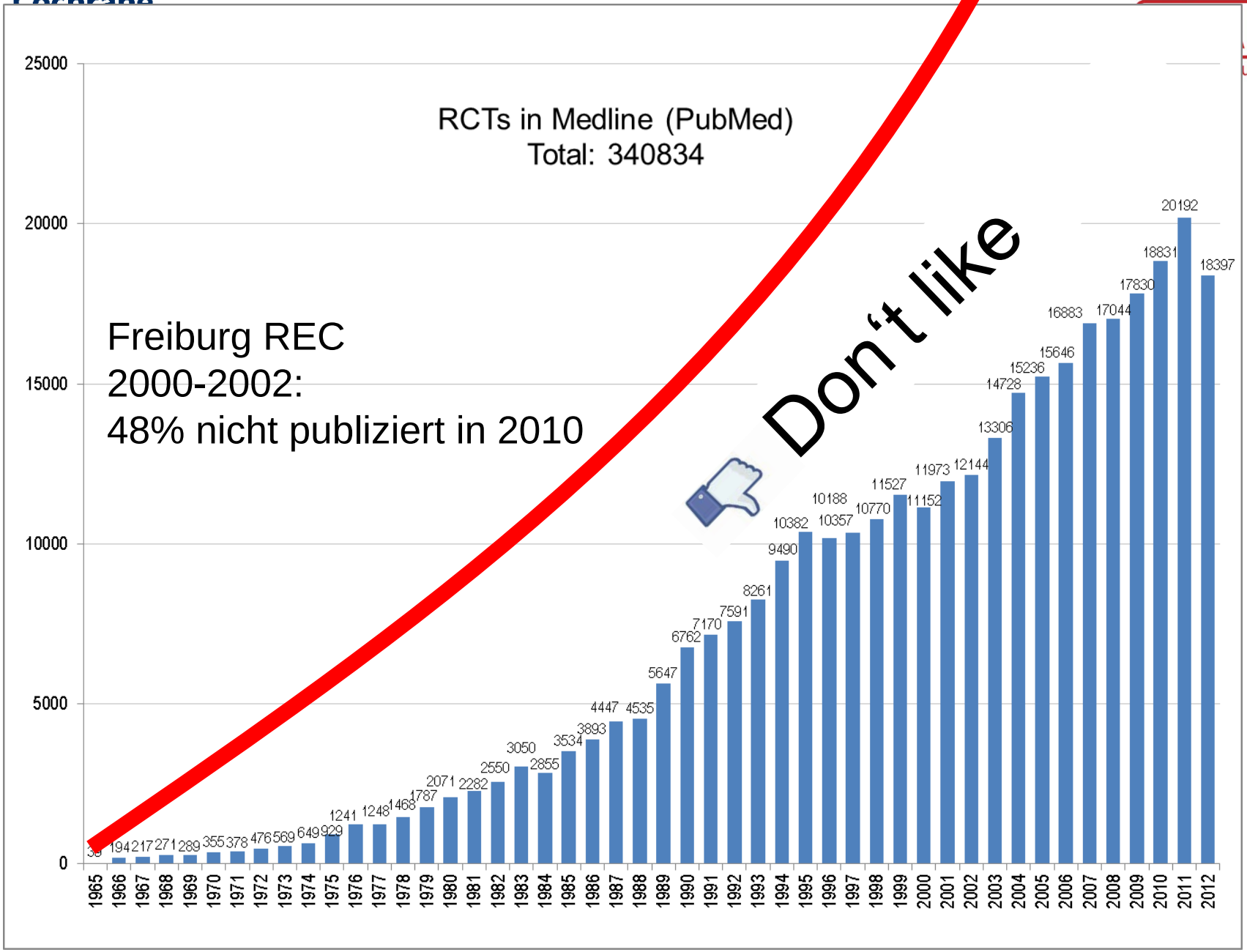
Source: Phil Wiffen

Die „ideale“ Studie

- adressiert eine wichtige Frage,
- die noch nicht beantwortet ist,
- misst (alle) relevante(n) Endpunkte,
- ist veröffentlicht,



Blumle, A., J.J. Meerpohl, M. Schumacher, and E. von Elm, *Fate of clinical research studies after ethical approval--follow-up of study protocols until publication.* PLoS One, 2014. **9**(2): p. e87184.



Blumle, A., J.J. Meerpohl, M. Schumacher, and E. von Elm, *Fate of clinical research studies after ethical approval--follow-up of study protocols until publication.* PLoS One, 2014. **9**(2): p. e87184.

Nicht nur ein Freiburger Problem

PLOS ONE

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. German Cochrane Centre, Medical Center – University of Freiburg, Berliner Allee 29, 79110 Freiburg, Germany, **2.** Institute of Medical Biometry and Statistics, Medical Center – University of Freiburg, Freiburg, Germany, **3.** Department of Neonatology, University Hospital Zurich, Zurich, Switzerland, **4.** Cochrane Switzerland, Institute of Social and Preventive Medicine (IUMSP), University Hospital Lausanne, Biopôle 2, Route de la Corniche 10, 1010 Lausanne, Switzerland, **5.** US Cochrane Center, John Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America

*meerpohl@cochrane.de

¶ The complete membership of the OPEN consortium is provided in the Acknowledgements.

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OPEN ACCESS

Citation: Schmucker C, Schell LK, Portalupi S, Oeller P, Cabrera L, et al. (2014) Extent of Non-Publication in Cohorts of Studies Approved by

Abstract

Schmucker, C., L.K. Schell, S. Portalupi, P. Oeller, L. Cabrera, D. Bassler, G. Schwarzer, R.W. Scherer, G. Antes, E. von Elm, J.J. Meerpohl, and OPEN. consortium. PLoS One, 2014. **9**(12): p. e114023.

Cochrane Deutschland

Anteil publizierter Studien aus EthK/StR

Study	Events	Total	Proportion	95%−CI	W(random
Bluemle (2014)	419	807	0.52	[0.48; 0.55]	6.3%
Chan (2004)	102	274	0.37	[0.31; 0.43]	6.1%
Cooper (1997)	41	159	0.26	[0.19; 0.33]	5.7%
De Jong (2010)	23	80	0.29	[0.19; 0.40]	5.2%
Decullier (2005)	190	501	0.38	[0.34; 0.42]	6.2%
Dickersin (1992)	390	514	0.76	[0.72; 0.80]	6.2%
Easterbrook (1991)	138	285	0.48	[0.42; 0.54]	6.1%
Hall (2007)	84	190	0.44	[0.37; 0.52]	5.9%
Menzel (2007)	71	99	0.72	[0.62; 0.80]	5.4%
Olofsson (2000)	58	133	0.44	[0.35; 0.52]	5.7%
Pich (2003)	38	123	0.31	[0.23; 0.40]	5.6%
Rodriguez (2009)	40	125	0.32	[0.24; 0.41]	5.6%
Stern (1997)	189	321	0.59	[0.53; 0.64]	6.1%
Sune (2013)	380	785	0.48	[0.45; 0.52]	6.3%
Turer (2007)	101	197	0.51	[0.44; 0.58]	6.0%
Von Elm (2008)	233	451	0.52	[0.47; 0.56]	6.2%
Wise (1996)	30	68	0.44	[0.32; 0.57]	5.2%
Random effects model		**5112**	**0.46**	**[0.40; 0.52]**	**100%**
Prediction interval				**[0.22; 0.72]**	

Heterogeneity: I−squared=94.4%, tau−squared=0.2471

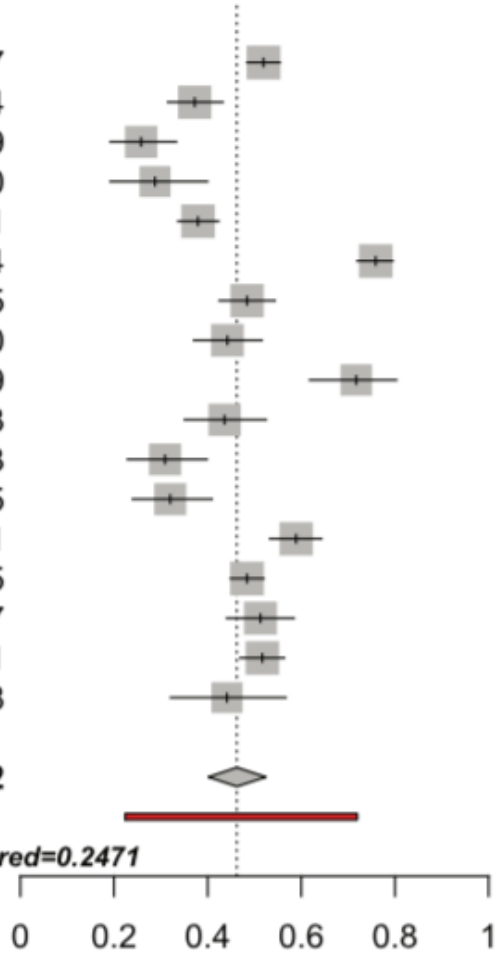


Fig. 2. Weighted proportion of published studies for 17 MRPs following studies after REC approval.

Cochrane Deutschland

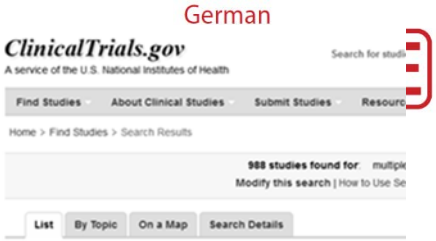
Anteil publizierter Studien aus EthK/StR

	Anzahl Forschungs-berichte	% als Volltext publizierter Studien (95%-KI)	I^2	Prädiktionsinterval
EthK	17	**46,2% (40,2-52,4)**	94%	22-72%
StR	22	**54,2% (42,0-65,9)**	99%	13-90%

Ergebnisse basieren **auf 39 Forschungsberichten**, die über 20.000 Studien evaluierten!

Cochrane Deutschland

German



Studiencharakteristika - Assoziation mit einer späteren Publikation

	Studiencharakteristika	Anzahl Forschungs-berichte	Assoziation mit Vollpublikation (OR [95%-KI])	I^2
EthK	**Signifikante vs. nicht signifikante Ergebnisse**	4	**2,9 (2,2 - 3,5)**	**0%**
	RCT vs. Beobachtungsstudie	2	**2,0 (1,3 - 3,3)**	**0%**
	Grundlagen- vs. klinische Forschung	2	1,1 (0,6 - 2,1)	49%
StR	**Phase III vs. Phase II Studien**	10	**2,0 (1,6 - 2,5)**	**22%**
	RCT vs. Beobachtungsstudie	3	**1,2 (1,0 – 1,5)**	**0%**
	Öffentliche Förderung vs. Industrieförderung	8	**2,2 (1,7 - 2,9)**	**44%**

UNIVERSITÄTS KLINIKUM FREIBURG

„Benefit“

Trial	Reboxetine (n/N)	Placebo (n/N)	Odds ratio (95% CI)	Weight (%)	Odds ratio (95% CI)
Remission					
014	60/126	34/128		13.2	2.51 (1.49 to 4.25)
015	47/110	40/111		12.7	1.32 (0.77 to 2.27)
046	132/252	124/247		19.1	1.09 (0.77 to 1.55)
047	109/238	101/239		18.7	1.15 (0.80 to 1.66)
050	48/144	54/143		14.4	0.82 (0.51 to 1.34)
045	30/88	33/86		10.8	0.83 (0.45 to 1.54)
049	29/106	27/104		11.0	1.07 (0.58 to 1.98)
Total	455/1064	413/1058		100.00	1.17 (0.91 to 1.51)
Total heterogeneity: I^2=49.0%, P=0.068; total effect: P=0.216					
Response					
014	70/126	43/128		13.1	2.47 (1.49 to 4.11)
015	65/110	58/111		12.3	1.32 (0.78 to 2.25)
046	144/252	136/247		19.3	1.09 (0.76 to 1.55)
047	120/238	108/239		19.0	1.23 (0.86 to 1.77)
050	60/144	63/143		14.4	0.91 (0.57 to 1.45)
045	38/88	39/86		10.5	0.92 (0.50 to 1.67)
049	42/106	35/104		11.4	1.29 (0.74 to 2.27)
Total	539/1064	482/1058		100.00	1.24 (0.98 to 1.56)
Total heterogeneity: I^2=42.1%, P=0.110; total effect: P=0.071					
091	20/27	5/25			11.43 (3.10 to 42.12)

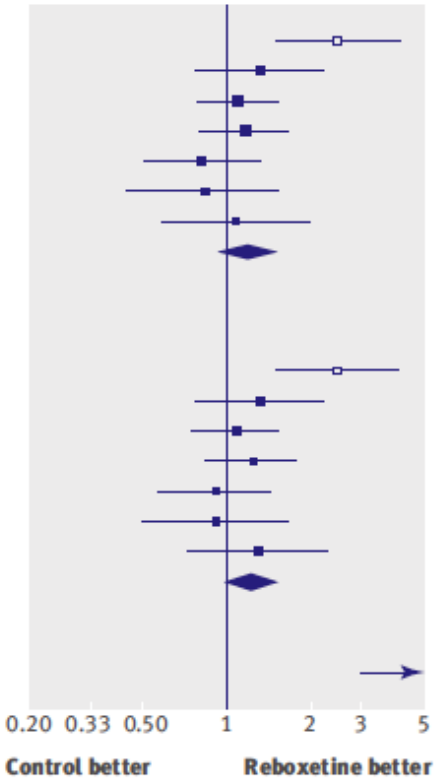


Fig 2 | Forest plot showing meta-analyses of remission and response rates for trials that compared reboxetine with placebo. Empty boxes show published studies and filled boxes show unpublished studies. Study 091 is not included in the pooled analysis of response of reboxetine versus placebo because of high heterogeneity (see text for details). CI, confidence interval; n, number of patients with event; N, number of patients in treatment group

Eyding, D., M. Lelgemann, U. Grouven, M. Harter, M. Kromp, T. Kaiser, M.F. Kerekes, M. Gerken, and B. Wieseler, *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. **341**: p. c4737.

Die „ideale“ Studie

- adressiert eine wichtige Frage,
- die noch nicht beantwortet ist,
- misst (alle) relevante(n) Endpunkte,
- ist veröffentlicht,
- berichtet vollständig und transparent
  - Methoden
  - Ergebnisse

Selektives Berichten von Endpunkten ist häufig

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PLOS ONE

Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias — An Updated Review

Kerry Dwan*, Carrol Gamble, Paula R. Williamson, Jamie J. Kirkham, for the Reporting Bias Group[¶]

Department of Biostatistics, University of Liverpool, Liverpool, England

Abstract

Background: The increased use of meta-analysis in systematic reviews of healthcare interventions has highlighted several types of bias that can arise during the completion of a randomised controlled trial. Study publication bias and outcome reporting bias have been recognised as a potential threat to the validity of meta-analysis and can make the readily available evidence unreliable for decision making.

Methodology/Principal Findings: In this update, we review and summarise the evidence from cohort studies that have assessed study publication bias or outcome reporting bias in randomised controlled trials. Twenty studies were eligible of which four were newly identified in this update. Only two followed the cohort all the way through from protocol approval to information regarding publication of outcomes. Fifteen of the studies investigated study publication bias and five investigated outcome reporting bias. Three studies have found that statistically significant outcomes had a higher odds of being fully reported compared to non-significant outcomes (range of odds ratios: 2.2 to 4.7). In comparing trial publications to protocols, we found that 40–62% of studies had at least one primary outcome that was changed, introduced, or omitted. We decided not to undertake meta-analysis due to the differences between studies.

Conclusions: This update does not change the conclusions of the review in which 16 studies were included. Direct empirical evidence for the existence of study publication bias and outcome reporting bias is shown. There is strong evidence of an association between significant results and publication; studies that report positive or significant results are more likely to be published and outcomes that are statistically significant have higher odds of being fully reported. Publications have been found to be inconsistent with their protocols. Researchers need to be aware of the problems of both types of bias and efforts should be concentrated on improving the reporting of trials.

Citation: Dwan K, Gamble C, Williamson PR, Kirkham JJ, for the Reporting Bias Group (2013) Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias — An Updated Review. PLoS ONE 8(7): e66844. doi:10.1371/journal.pone.0066844

Editor: Isabelle Boutron, University Paris Descartes, France

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Funding: This updated review was funded by the Medical Research Council (MRC) hub for trial methodology. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: kerry.dwan@liverpool.ac.uk

¶ Membership of the Reporting Bias Group is provided in the Acknowledgments.

- SR zu “Outcome reporting bias”
  - Stat. signifikante Endpunkte werden häufiger berichtet als nicht-signifikante (Range OR: 2.2-4.7)
  - In 40-62% der Studien wurde mindestens ein primärer Endpunkt geändert

Dwan, K., C. Gamble, P.R. Williamson, J.J. Kirkham, and G. Reporting Bias, *Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review.* PLoS One, 2013. **8**(7): p. e66844.

Welche Resourcen nutzen?

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PLOS | MEDICINE

Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data

Beate Wieseler[1]*, Natalia Wolfram[1], Natalie McGauran[1], Michaela F. Kerekes[1], Volker Vervölgyi[1], Petra Kohlepp[1], Marloes Kamphuis[1], Ulrich Grouven[1,2]

1 Institute for Quality and Efficiency in Health Care, Cologne, Germany, 2 Hanover Medical School, Hanover, Germany

Abstract

Background: Access to unpublished clinical study reports (CSRs) is currently being discussed as a means to allow unbiased evaluation of clinical research. The Institute for Quality and Efficiency in Health Care (IQWiG) routinely requests CSRs from manufacturers for its drug assessments. Our objective was to determine the information gain from CSRs compared to publicly available sources (journal publications and registry reports) for patient-relevant outcomes included in IQWiG health technology assessments (HTAs) of drugs.

Methods and Findings: We used a sample of 101 trials with full CSRs received for 16 HTAs of drugs completed by IQWiG between 15 January 2006 and 14 February 2011, and analyzed the CSRs and the publicly available sources of these trials. For each document type we assessed the completeness of information on all patient-relevant outcomes included in the HTAs (benefit outcomes, e.g., mortality, symptoms, and health-related quality of life; harm outcomes, e.g., adverse events). We dichotomized the outcomes as "completely reported" or "incompletely reported." For each document type, we calculated the proportion of outcomes with complete information per outcome category and overall. We analyzed 101 trials with CSRs; 86 had at least one publicly available source, 65 at least one journal publication, and 50 a registry report. The trials included 1,080 patient-relevant outcomes. The CSRs provided complete information on a considerably higher proportion of outcomes (86%) than the combined publicly available sources (39%). With the exception of health-related quality of life (57%), CSRs provided complete information on 78% to 100% of the various benefit outcomes (combined publicly available sources: 20% to 53%). CSRs also provided considerably more information on harms. The differences in completeness of information for patient-relevant outcomes between CSRs and journal publications or registry reports (or a combination of both) were statistically significant for all types of outcomes. The main limitation of our study is that our sample is not representative because only CSRs provided voluntarily by pharmaceutical companies upon request could be assessed. In addition, the sample covered only a limited number of therapeutic areas and was restricted to randomized controlled trials investigating drugs.

Conclusions: In contrast to CSRs, publicly available sources provide insufficient information on patient-relevant outcomes of clinical trials. CSRs should therefore be made publicly available.

Please see later in the article for the Editors' Summary.

Citation: Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, et al. (2013) Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes:

Wieseler, B., N. Wolfram, N. McGauran, M.F. Kerekes, V. Vervölgyi, P. Kohlepp, M. Kamphuis, and U. Grouven, *Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data.* PLoS Med, 2013. **10**(10): p. e1001526.

Welche Resourcen nutzen?

Table 3. Completeness of information for trial outcomes in CSRs, registry reports, and journal publications.

Type of Outcome	Number of Outcomes	Outcomes with Complete Information, *n* (Percent[a])			
		Not Publicly Available	Publicly Available		
		CSR[b] (*n*=101)	Journal Publication and/or Registry Report[c] (*n*=86)	Journal Publication Only (*n*=65)	Registry Report[c] Only (*n*=50)
All outcomes[d]	1,080	930 (86)	425 (39)	250 (23)	242 (22)
Benefit outcomes	456	385 (84)	158 (35)	88 (19)	88 (19)
Mortality	92	92 (100)	49 (53)	28 (30)	30 (33)
Clinical events	119	108 (91)	38 (32)	32 (27)	8 (7)
Symptoms	215	168 (78)	65 (30)	26 (12)	46 (21)
HRQoL	30	17 (57)	6 (20)	2 (7)	4 (13)
Harm outcomes	624	545 (87)	267 (43)	162 (26)	154 (25)
AEs	101	93 (92)	55 (54)	21 (21)	41 (41)
SAEs	101	89 (88)	52 (51)	24 (24)	37 (37)
Withdrawal due to AEs	101	92 (91)	73 (72)	51 (51)	42 (42)
Special AEs[e]	321	271 (84)	87 (27)	66 (21)	34 (11)

Trial sample: all studies with a CSR.
[a]Total number of outcomes with complete information/total number of corresponding outcomes in sample.
[b]CSRs submitted to regulatory authorities.
[c]Reports posted in trial results registries.
[d]All outcomes are mutually exclusive.
[e]AEs of special interest in the given indication.
doi:10.1371/journal.pmed.1001526.t003

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Compl
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Beate Wies
Petra Kohle
1 Institute for Qua

Abstract

Backgrou
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Conclusio
clinical trials. CSRs should therefore be made publicly available.

Please see later in the article for the Editors' Summary.

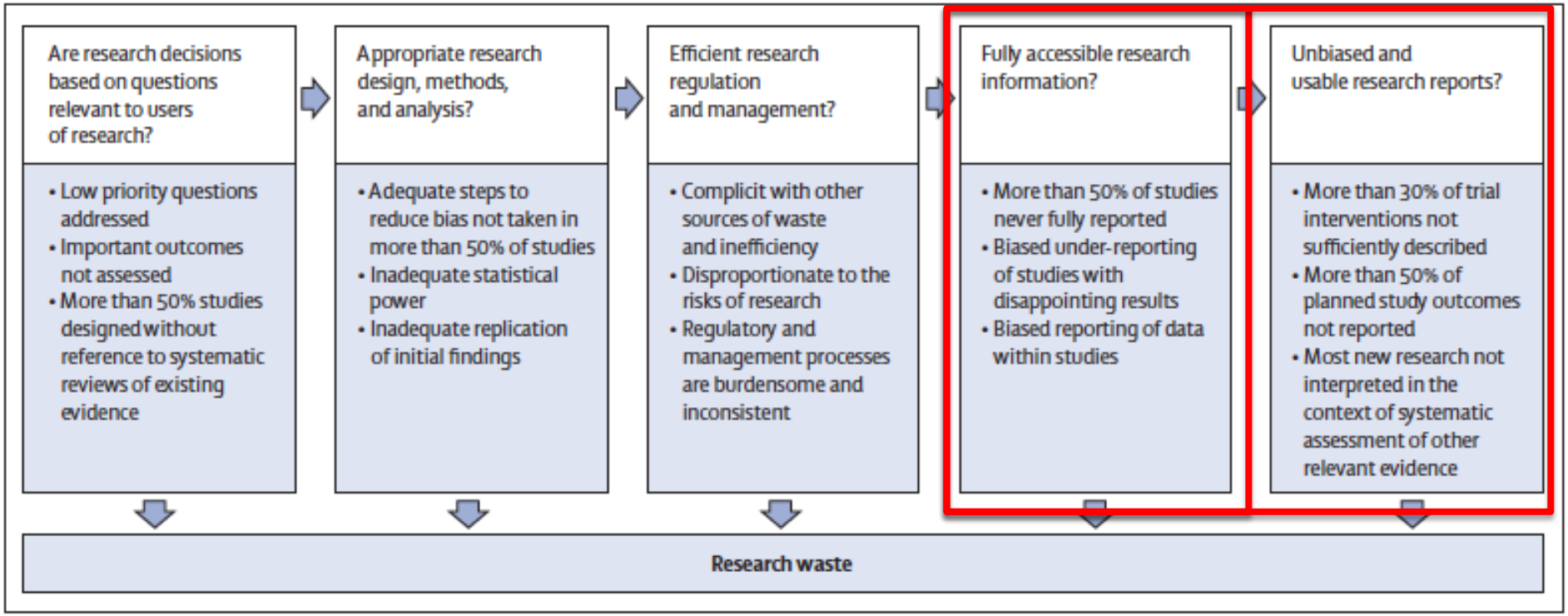
Citation: Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, et al. (2013) Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes:

Wieseler, B., N. Wolfram, N. McGauran, M.F. Kerekes, V. Vervölgyi, P. Kohlepp, M. Kamphuis, and U. Grouven, *Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data.* PLoS Med, 2013. **10**(10): p. e1001526.

Selektives Berichten

- Selektives Berichten von Endpunkten
  - Nicht alle erhobenen Endpunkte werden berichtet
- Selektives Berichten eines spezifischen Endpunkts
  - Selektion aus multiplen Zeitpunkten
  - Werte bei Studienende vs Veränderung gegenüber Studienbeginn
  - Kontinuierlich vs dichotom (Wahl der “cut-offs”)
  - Verschiedene Messinstrumente für gleichen Endpunkt, z.B. Schmerzen
  - Subskalen (z.B. Lebensqualität)

„Waste“ in der Forschung



Macleod, M.R., S. Michie, I. Roberts, U. Dirnagl, I. Chalmers, J.P. Ioannidis, R. Al-Shahi Salman, A.W. Chan, and P. Glasziou, *Biomedical research: increasing value, reducing waste.* Lancet, 2014. **383**(9912): p. 101-4.

Qualität der Berichterstattung von methodischen Studieninformationen

Chan A.-W., Altman D.G. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet* 2005;365:1159–62

Untersucht: 519 RCTs, publiziert & indexiert in PubMed in 12/2000

Folgende Hauptaspekte der Studiendurchführung fehlten:

- 73% Fallzahlberechnung
- 55% Definition primärer Endpunkt
- 60% Verblindung: ja/nein?
- 79% Methode der Generierung der Randomisierungssequenz
- 82% Methode der Geheimhaltung der Behandlungsfolge

Chan, A.W. and D.G. Altman, *Epidemiology and reporting of randomised trials published in PubMed journals.* Lancet, 2005. **365**(9465): p. 1159-62.

Reproduzierbarkeit -von Interventionen-

DOI: 10.1093/jnci/djq117
Advance Access publication on April 21, 2010.

ARTICLE

Adequacy of Published Oncology Randomized Controlled Trials to Provide Therapeutic Details Needed for Clinical Application

Jennifer M. Duff, Helen Leather, Edmund O. Walden, Kourtney D. LaPlant, Thomas J. George Jr

Manuscript received July 9, 2009; revised March 15, 2010; accepted March 16, 2010.

Correspondence to: Thomas J. George Jr, MD, FACP, Division of Hematology Oncology, Department of Medicine, Health Science Center, University of Florida, PO Box 100278, Gainesville, FL 32610-0278 (e-mail: thom.george@medicine.ufl.edu).

Background Randomized controlled trials (RCTs) improve clinical care through evidence-based results. Guidelines exist for RCT result reporting, but specific details of therapeutic administration promote clinical application and reproduction of the trial design. We assess the reporting methodology in RCTs published in major oncology journals.

Methods Ten essential elements of RCT reporting were identified and included drug name, dose, route, cycle length, maximum number of cycles, premedication, growth factor support, patient monitoring parameters, and dosing adjustments for hematologic and organ-specific toxicity. All therapy-based oncology RCTs published between 2005 and 2008 in the *New England Journal of Medicine* (*NEJM*), *Journal of Clinical Oncology* (*JCO*), *Journal of the National Cancer Institute* (*JNCI*), *Blood*, and *Cancer* were analyzed for inclusion of these 10 elements.

Results Of 339 identified articles, 262 were included in the final analysis (165 from *JCO*, 31 from *NEJM*, 27 from *Cancer*, 20 from *JNCI*, and 19 from *Blood*). Premedication, growth factor support, and dose adjustments for toxicities were each reported less than half of the time. Only 30 articles (11%) met the main objective of complete data reporting (ie, all 10 essential elements) and was highest in *JNCI* (5/20; 25%), followed by *Cancer* (5/27; 18%), *JCO* (18/165; 11%), *Blood* (1/19; 5%), and *NEJM* (1/31; 3%). The presence of an online appendix did not substantially improve complete reporting.

Conclusions RCTs published in major oncology journals do not consistently report essential therapeutic details necessary for translation of the trial findings to clinical practice. Potential solutions to improve reporting include modification of submission guidelines, use of online appendices, and providing open access to trial protocols.

J Natl Cancer Inst 2010;102:702–705

- 262 RCTs aus hochrangigen onkolog. Zeitschriften
- Nur 11% der Artikel berichten alle 10 “essentiellen” Details der Intervention
  - z.B. Medikamentenname, Dosis, Applikationsmodus…

Duff, J.M., H. Leather, E.O. Walden, K.D. LaPlant, and T.J. George, Jr., *Adequacy of published oncology randomized controlled trials to provide therapeutic details needed for clinical application.* J Natl Cancer Inst, 2010. **102**(10): p. 702-5.

Disseminationsbias Taxonomie

1. Ergebnisabhängige „Nicht-Publikation“ ganzer Studien (klassischer Publikationsbias)
2. Selektives Berichten von Information aus Studien in Publikationen
   - Ergebnissen (e.g. Endpunkten, Subgruppen)
   - Statistischen Analysen (e.g. ITT vs PP)
3. Unvollständiges Berichten, so dass Ergebnisse nicht in Metaanalysen eingeschlossen werden können

4. Systematische Fehlinterpretation der quantitativen Ergebnisse (Spin)

Abgebrochene Studien

Research

Original Investigation

Prevalence, Characteristics, and Publication of Discontinued Randomized Trials

Benjamin Kasenda, MD; Erik von Elm, MD, MSc; John You, MD, MSc; Anette Blümle, PhD; Yuki Tomonaga, MSc; Ramon Saccilotto, MD, MSc; Alain Amstutz, BSc; Theresa Bengough, BSc; Joerg J. Meerpohl, MD; Mihaela Stegert, MD; Kari A. O. Tikkinen, MD, PhD; Ignacio Neumann, MD, MSc; Alonso Carrasco-Labra, MD, MSc; Markus Faulhaber, MD, MSc; Sohail M. Mulla, BSc; Dominik Mertz, MD, MSc; Elie A. Akl, MD, PhD, MPH; Dirk Bassler, MD, MSc; Jason W. Busse, DC, PhD; Ignacio Ferreira-González, MD, PhD; Francois Lamontagne, MD, MSc; Alain Nordmann, MD, MSc; Viktoria Gloy, PhD; Heike Raatz, MD, MSc; Lorenzo Moja, MD, MSc; Rachel Rosenthal, MD, MSc; Shanil Ebrahim, PhD; Stefan Schandelmaier, MD; Sun Xin, PhD; Per O. Vandvik, MD, PhD; Bradley C. Johnston, PhD; Martin A. Walter, MD; Bernard Burnand, MD, MSc; Matthias Schwenkglenks, PhD; Lars G. Hemkens, MD; Heiner C. Bucher, MD, MPH; Gordon H. Guyatt, MD, MSc; Matthias Briel, MD, MSc

IMPORTANCE The discontinuation of randomized clinical trials (RCTs) raises ethical concerns and often wastes scarce research resources. The epidemiology of discontinued RCTs, however, remains unclear.

OBJECTIVES To determine the prevalence, characteristics, and publication history of discontinued RCTs and to investigate factors associated with RCT discontinuation due to poor recruitment and with nonpublication.

DESIGN AND SETTING Retrospective cohort of RCTs based on archived protocols approved by

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Research

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Table 2. Prevalence of Randomized Clinical Trial (RCT) Discontinuatio

	RCTs Involving Patients			
	Sponsorship			
	Industry (n = 551)	Investigator (n = 343)	All (n = 894)	Full Journal Publication (n = 530)
Completion status				
Completed	394 (71.5) [68.1-75.2]	181 (52.8) [47.3-58.1]	575 (64.3) [61.1-67.4]	417 (78.7) [75.0-82.0]
Discontinued	119 (21.6) [18.3-25.3]	130 (37.9) [32.8-43.3]	249 (27.9) [25.0-30.9]	113 (21.3) [18.1-25.0]
Unclear	38 (6.9) [5.0-9.4]	32 (9.3) [6.6-13.0]	70 (7.8) [6.2-9.8]	0 [0.0-0.9]
Reason for discontinuation				
Poor recruitment[a]	40 (7.3) [5.3-9.8]	60 (17.5) [13.7-22.0]	100 (11.2) [9.2-13.5]	40 (7.5) [5.5-10.2]
Futility[b]	25 (4.5) [3.0-6.7]	12 (3.5) [1.9-6.2]	37 (4.1) [3.0-5.7]	18 (3.4) [2.1-5.4]
Administrative reasons[c]	20 (3.6) [2.3-5.7]	16 (4.7) [2.8-7.6]	36 (4.0) [2.9-5.6]	8 (1.5) [0.7-3.1]
Harm	17 (3.1) [1.9-5.0]	7 (2.0) [0.9-4.3]	24 (2.7) [1.8-4.0]	12 (2.3) [1.2-4.0]
Unknown reason[d]	6 (1.1) [0.4-2.5]	18 (5.3) [3.2-8.3]	24 (2.7) [1.8-4.0]	21 (4.0) [2.6-6.0]
Benefit	2 (0.4) [0.06-1.5]	7 (2.0) [0.9-4.2]	9 (1.0) [0.5-2.0]	9 (1.7) [0.8-3.3]
External evidence	6 (1.1) [0.4-2.5]	2 (0.6) [0.1-2.3]	8 (0.9) [0.4-1.8]	2 (0.4) [0.0-1.5]
Lack of funding	1 (0.2) [0.01-1.2]	4 (1.2) [0.4-3.2]	5 (0.6) [0.2-1.4]	0 [0.0-0.9]
Other	2 (0.4) [0.06-1.5]	4 (1.2) [0.4-3.2]	6 (0.7) [0.3-1.5]	3 (0.6) [0.2-1.7]

72,5%

45,4%

40,2%

14,9%

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Strategische Forschungspriorisierung

Health Policy

Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?

John-Arne Røttingen, Sadie Regmi, Mari Eide, Alison J Young, Roderik F Viergever, Christine Årdal, Javier Guzman, Danny Edwards, Stephen A Matlin, Robert F Terry

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Department of Health Management and Health Economics, Institute for Health and Society, University of Oslo, Norway (Prof J-A Røttingen MD, C Årdal MBA); Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA (J-A Røttingen); Harvard Global Health Institute, Harvard University, Cambridge, MA, USA (J-A Røttingen); Institute for Science, Ethics and Innovation and School of Medicine,

The need to align investments in health research and development (R&D) with public health demands is one of the most pressing global public health challenges. We aim to provide a comprehensive description of available data sources, propose a set of indicators for monitoring the global landscape of health R&D, and present a sample of country indicators on research inputs (investments), processes (clinical trials), and outputs (publications), based on data from international databases. Total global investments in health R&D (both public and private sector) in 2009 reached US$240 billion. Of the US$214 billion invested in high-income countries, 60% of health R&D investments came from the business sector, 30% from the public sector, and about 10% from other sources (including private non-profit organisations). Only about 1% of all health R&D investments were allocated to neglected diseases in 2010. Diseases of relevance to high-income countries were investigated in clinical trials seven-to-eight-times more often than were diseases whose burden lies mainly in low-income and middle-income countries. This report confirms that substantial gaps in the global landscape of health R&D remain, especially for and in low-income and middle-income countries. Too few investments are targeted towards the health needs of these countries. Better data are needed to improve priority setting and coordination for health R&D, ultimately to ensure that resources are allocated to diseases and regions where they are needed the most. The establishment of a global observatory on health R&D, which is being discussed at WHO, could address the absence of a comprehensive and sustainable mechanism for regular global monitoring of health R&D.

Introduction

R&D that involves the implementation of three elements

Røttingen, J.-A., S. Regmi, M. Eide, A.J. Young, R.F. Viergever, C. Årdal, J. Guzman, D. Edwards, S.A. Matlin, and R.F. Terry, *Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?* The Lancet. 2013 **382**(9900): p. 1286-1307.

Strategische Forschungspriorisierung

Health Policy

Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?

John-Arne Røttingen, Sadie Regmi, Mari Eide, Alison J Young, Roderik F Viergever, Christine Årdal, Javier Guzman, Danny Edwards, Stephen A Matlin, Robert F Terry

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Zusammenfassung

Wissenslücken reduzieren durch

- Strategische, internationale Forschungsplanung
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- Verringerung von Disseminationsbias
- Verbesserung der Berichtsqualität von Studien
- Sicherung des Zugangs zu anderen Datenquellen


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