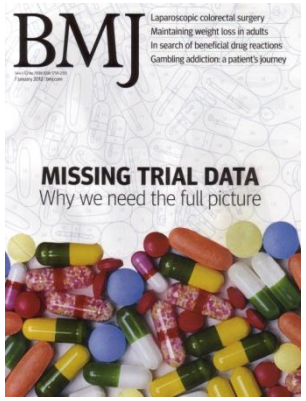
BMJ Group



Sharing Clinical Research Data
An Institute of Medicine Workshop
October 4 & 5, 2012
Washington, DC

Fundamentals and Benefits of Sharing Participant-Level Clinical Trial Data

Elizabeth Loder, MD, MPH
Clinical Epidemiology Editor, *BMJ*
Associate Professor of Neurology
Harvard Medical School

What I aim to cover

What is it we are thinking of sharing?

Why should we share?

What are the benefits?

What is it we are thinking of sharing?

“Participant level data”

“Raw data”

Screening No.	Patient Initials	Date	SCREENING DAYS -28 TO -8
012345	SYD	08/10/2001	

DATE INFORMED CONSENT WAS SIGNED: 07/22/2001

DEMOGRAPHICS

Date of Birth:	SEX: (Check One)	RACE: (Check One)
11/06/1965	1 ☐ Male 2 ☑ Female	1 ☑ White 2 ☐ Black 3 ☐ Asian 4 ☐ American Indian or Alaskan Native 5 ☐ Pacific Islander 96 ☐ Other, Specify:

Patient thinks grandmother ... (?)

Patient is not a native english speaker so the birth control questions were confusing to her.

ALCOHOL / TOBACCO / CAFFEINE USAGE

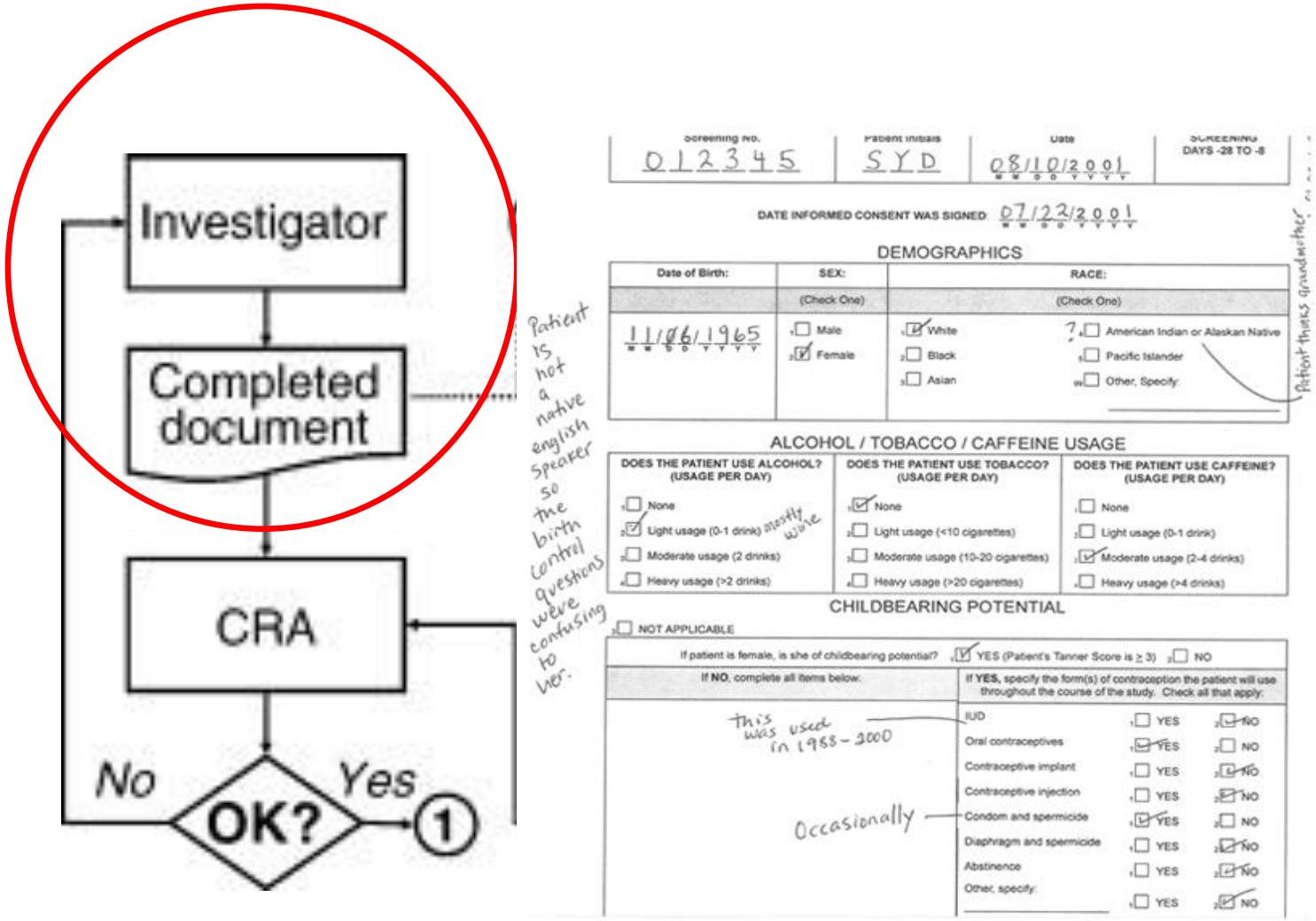
DOES THE PATIENT USE ALCOHOL? (USAGE PER DAY)	DOES THE PATIENT USE TOBACCO? (USAGE PER DAY)	DOES THE PATIENT USE CAFFEINE? (USAGE PER DAY)
1 ☐ None 2 ☑ Light usage (0-1 drink) mostly wine 3 ☐ Moderate usage (2 drinks) 4 ☐ Heavy usage (>2 drinks)	1 ☑ None 2 ☐ Light usage (<10 cigarettes) 3 ☐ Moderate usage (10-20 cigarettes) 4 ☐ Heavy usage (>20 cigarettes)	1 ☐ None 2 ☐ Light usage (0-1 drink) 3 ☑ Moderate usage (2-4 drinks) 4 ☐ Heavy usage (>4 drinks)

CHILDBEARING POTENTIAL

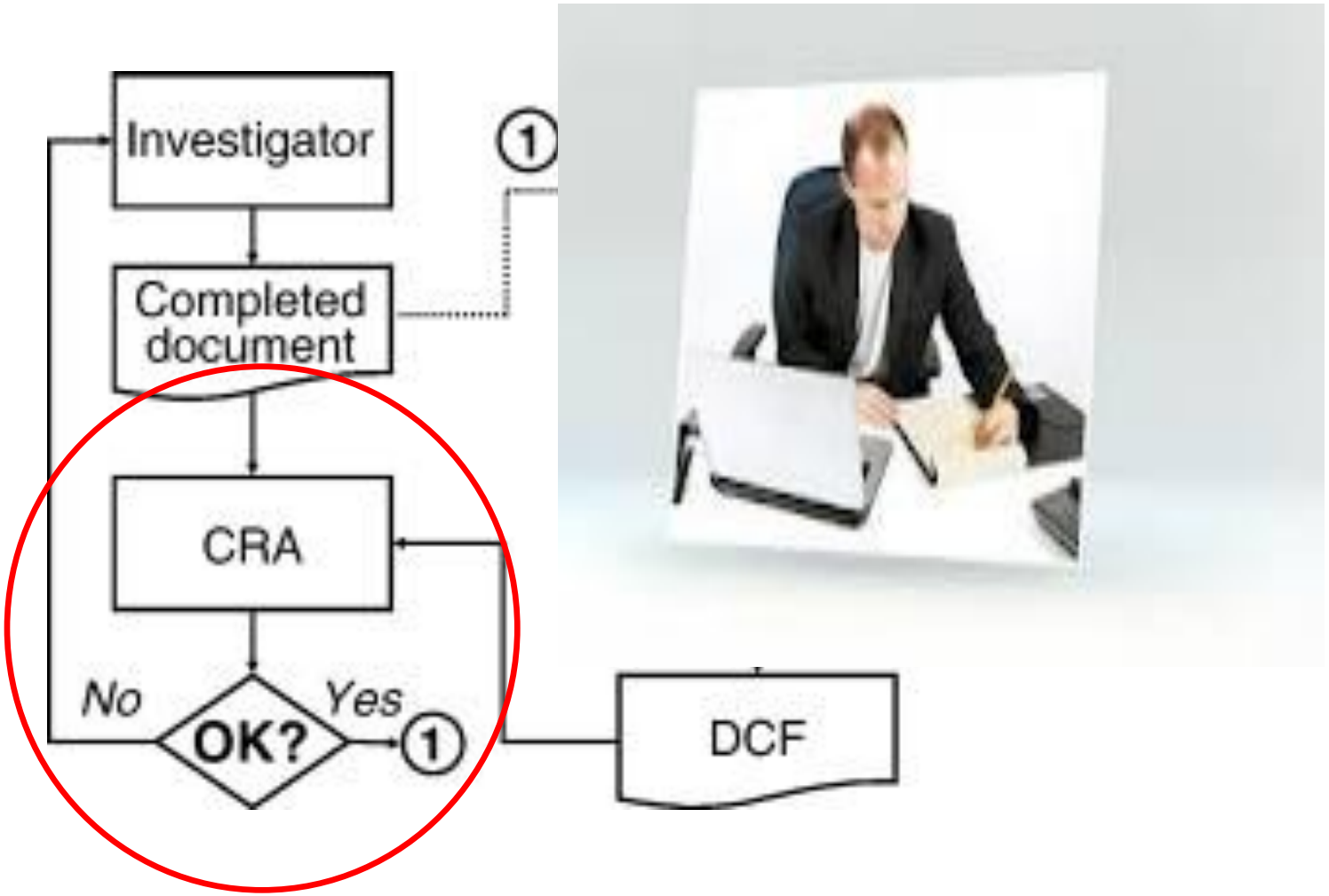
3 ☐ NOT APPLICABLE

If patient is female, is she of childbearing potential? 1 ☑ YES (Patient's Tanner Score is ≥ 3) 2 ☐ NO

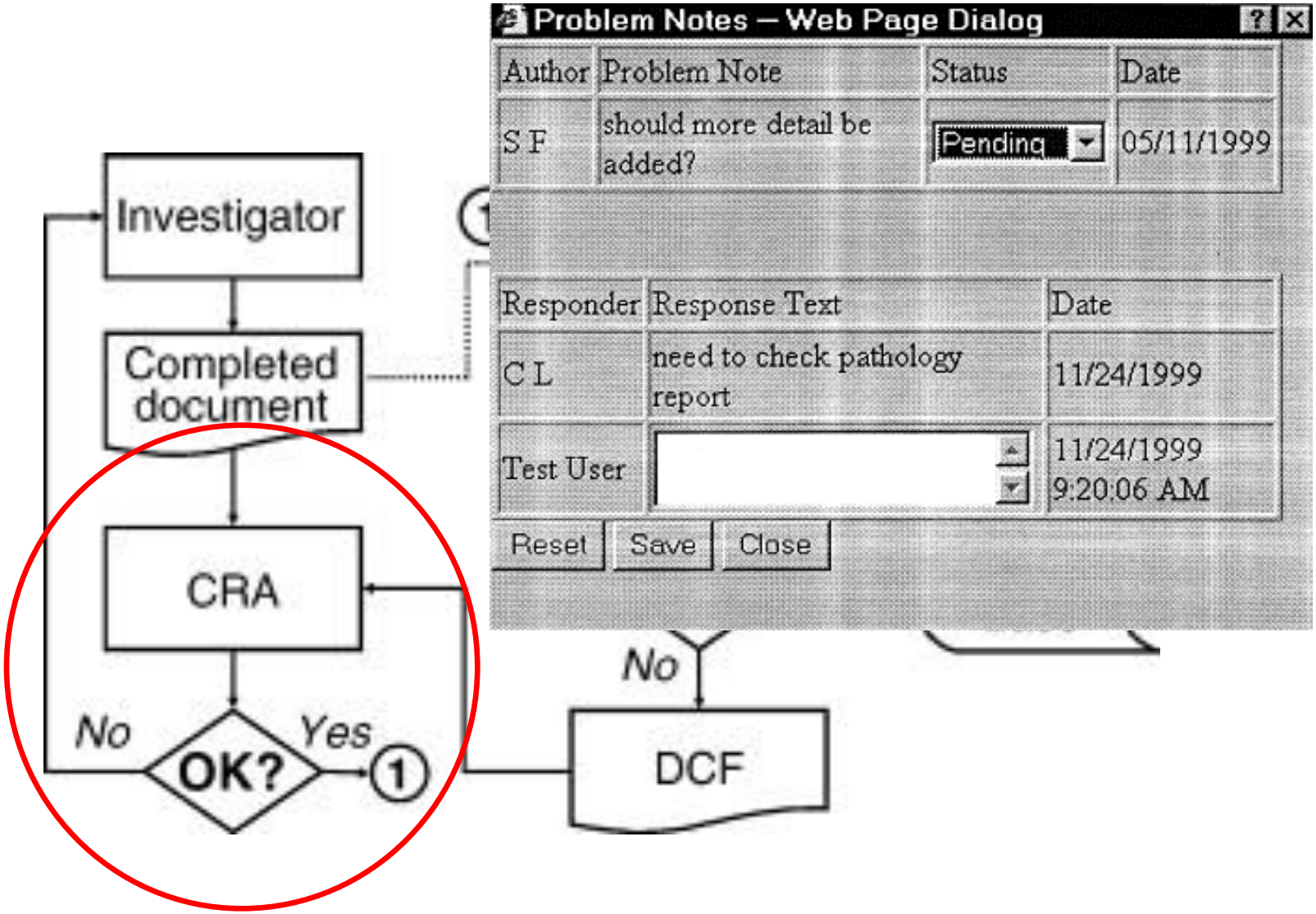
If NO, complete all items below.	If YES, specify the form(s) of contraception the patient will use throughout the course of the study. Check all that apply:		
this was used in 1988 - 2000	IUD	1 ☐ YES	2 ☑ NO
	Oral contraceptives	1 ☑ YES	2 ☐ NO
	Contraceptive implant	1 ☐ YES	2 ☑ NO
	Contraceptive injection	1 ☐ YES	2 ☑ NO
Occasionally	Condom and spermicide	1 ☑ YES	2 ☐ NO
	Diaphragm and spermicide	1 ☐ YES	2 ☑ NO
	Abstinence	1 ☐ YES	2 ☑ NO
	Other, specify:	1 ☐ YES	2 ☑ NO



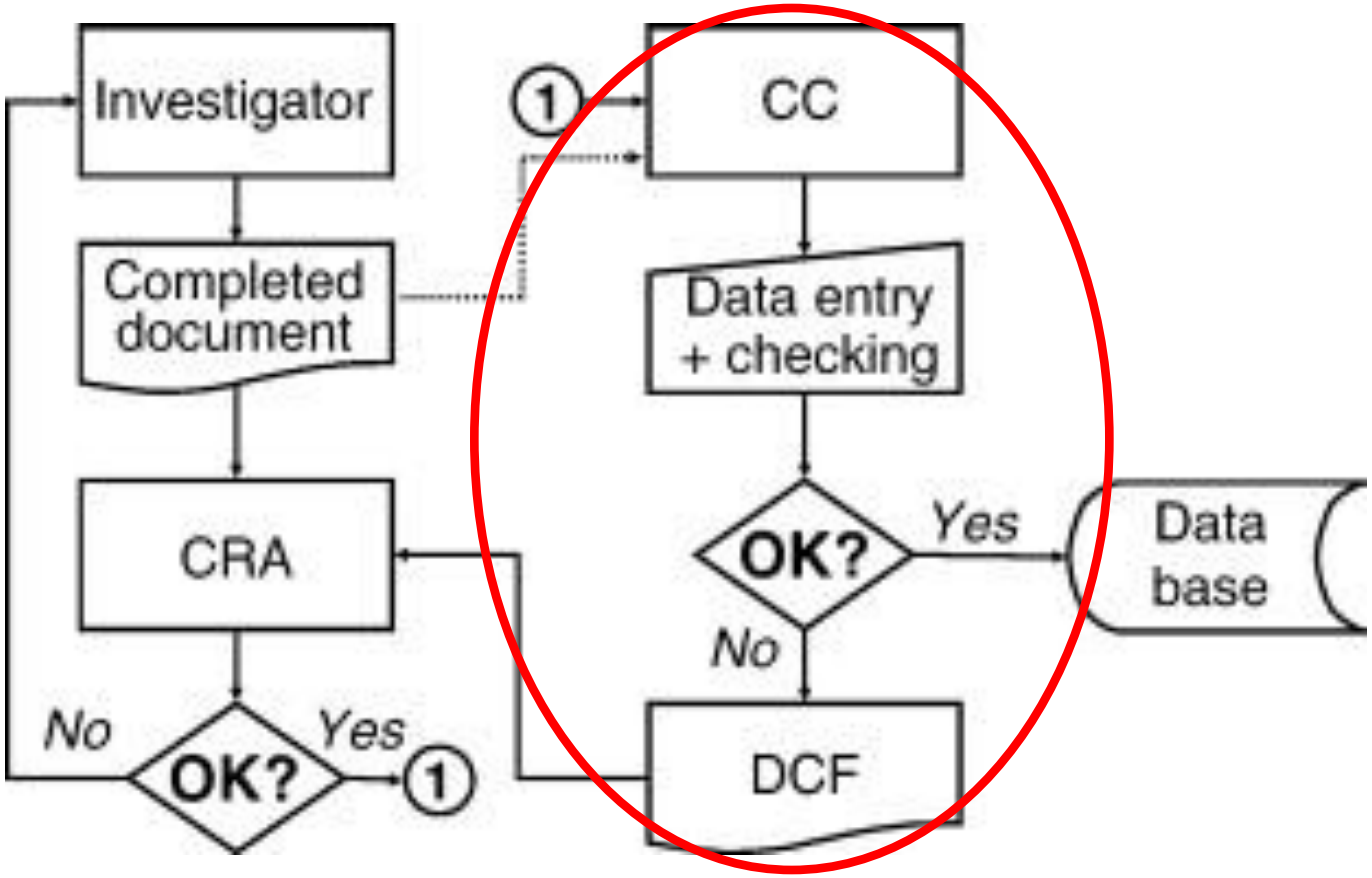
Kirwan B. Quality management of a large, double-blind, multicenter clinical trial: the ACTION experience. Contemporary Clinical Trials 2008/29(2):259-269.



Kirwan B. Quality management of a large, double-blind, multicenter clinical trial: the ACTION experience. Contemporary Clinical Trials 2008/29(2):259-269.



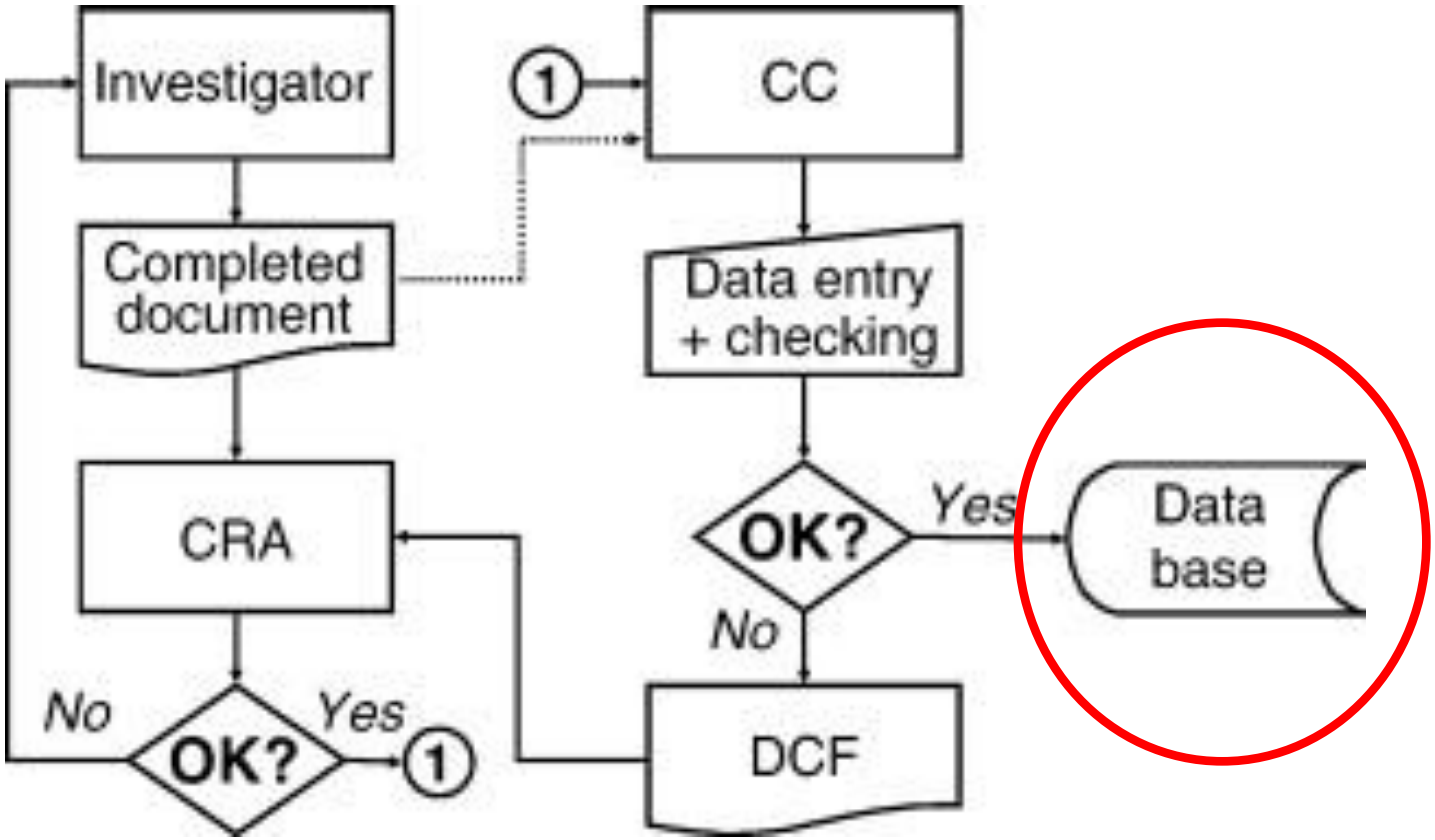
Kirwan B. Quality management of a large, double-blind, multicenter clinical trial: the ACTION experience. Contemporary Clinical Trials 2008/29(2):259-269.



Data flow in the ACTION trial. All investigator-completed documents except Serious Adverse Event (SAE) reports and notification forms were first verified on-site by Clinical Research Associate (CRA). Documents were sent to the Coordinating Centre (CC) for data processing. A Data Clarification Form (DCF) was generated if necessary. SAE reports and notification forms were sent by telefax directly to the CC (dotted arrow).

Kirwan B. Quality management of a large, double-blind, multicenter clinical trial: the ACTION experience.

Contemporary Clinical Trials 2008/29(2):259-269.



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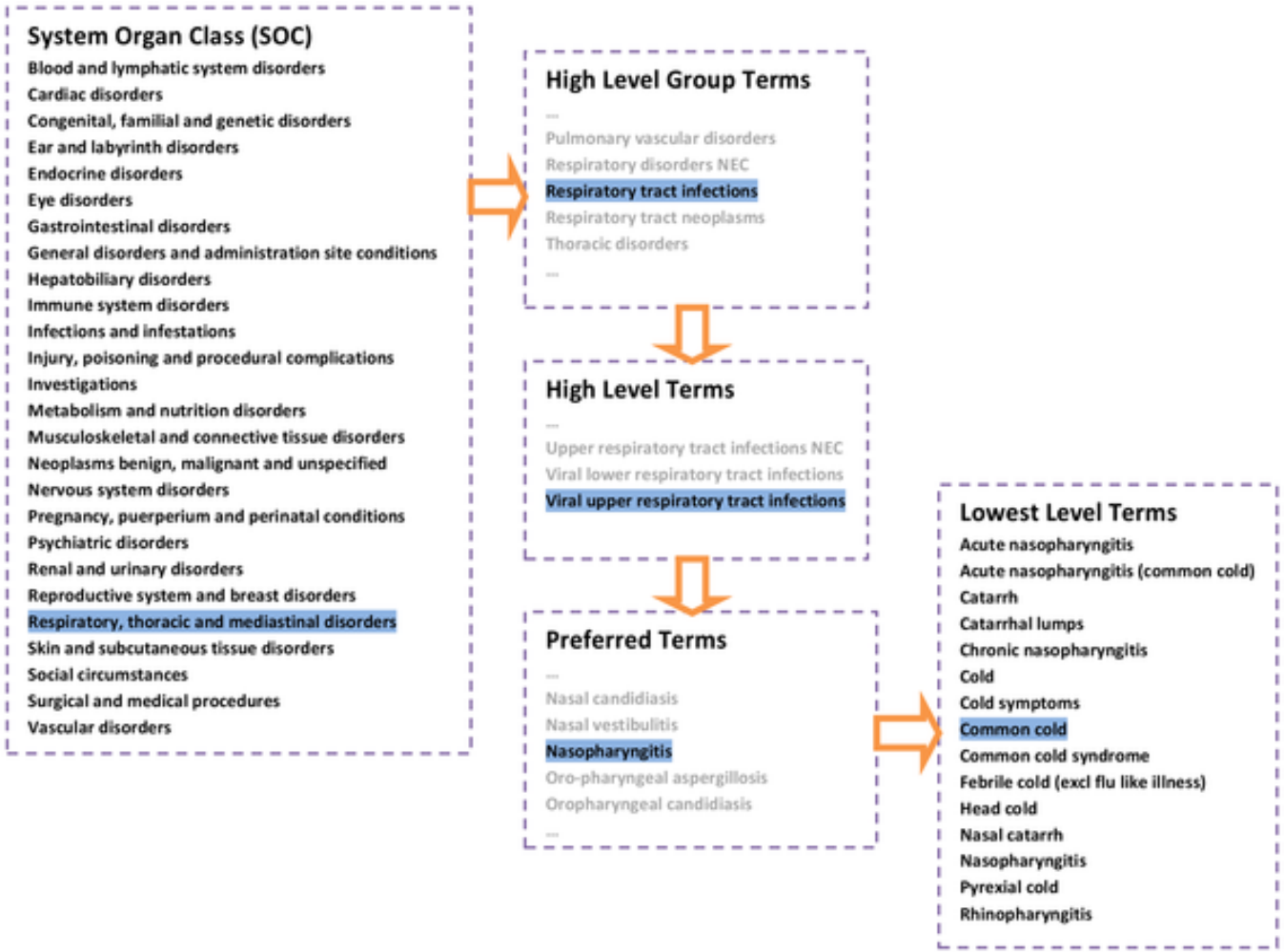
Contemporary Clinical Trials 2008/29(2):259-269.

Challenges in Coding Adverse Events



The MedDRA 5-level hierarchy demonstrated by using ‘common cold’ as an example

Schroll JB, Maund E, Gøtzsche PC (2012) Challenges in Coding Adverse Events in Clinical Trials: A Systematic Review. PLoS ONE 7(7): e41174. doi:10.1371

"Raw data about adverse events should mean the original descriptions, exactly as reported narratively by patients or researchers on the case report forms, before any coding or adjudication has taken place for categorization purposes."

Gotzsche P. Why we need easy access to all data from all clinical trials and how to accomplish it. Trials 2011, 12:249 doi:10.1186/1745-6215-12-249

What is it we are thinking of sharing?

"…all data from all randomized clinical trials, including raw anonymized individual participant data that do not allow identification of individual participants, and the corresponding trial protocols to become publicly available free of charge and in easily accessible electronic formats…"

THE COCHRANE COLLABORATION

Preparing, maintaining and disseminating systematic reviews of the effects of health care

The Cochrane Collaboration. 5 October 2011. Accessed at: http://www.cochrane.org/about-us/our-policies/support-free-access-to-all-data-from-all-clinical-trials

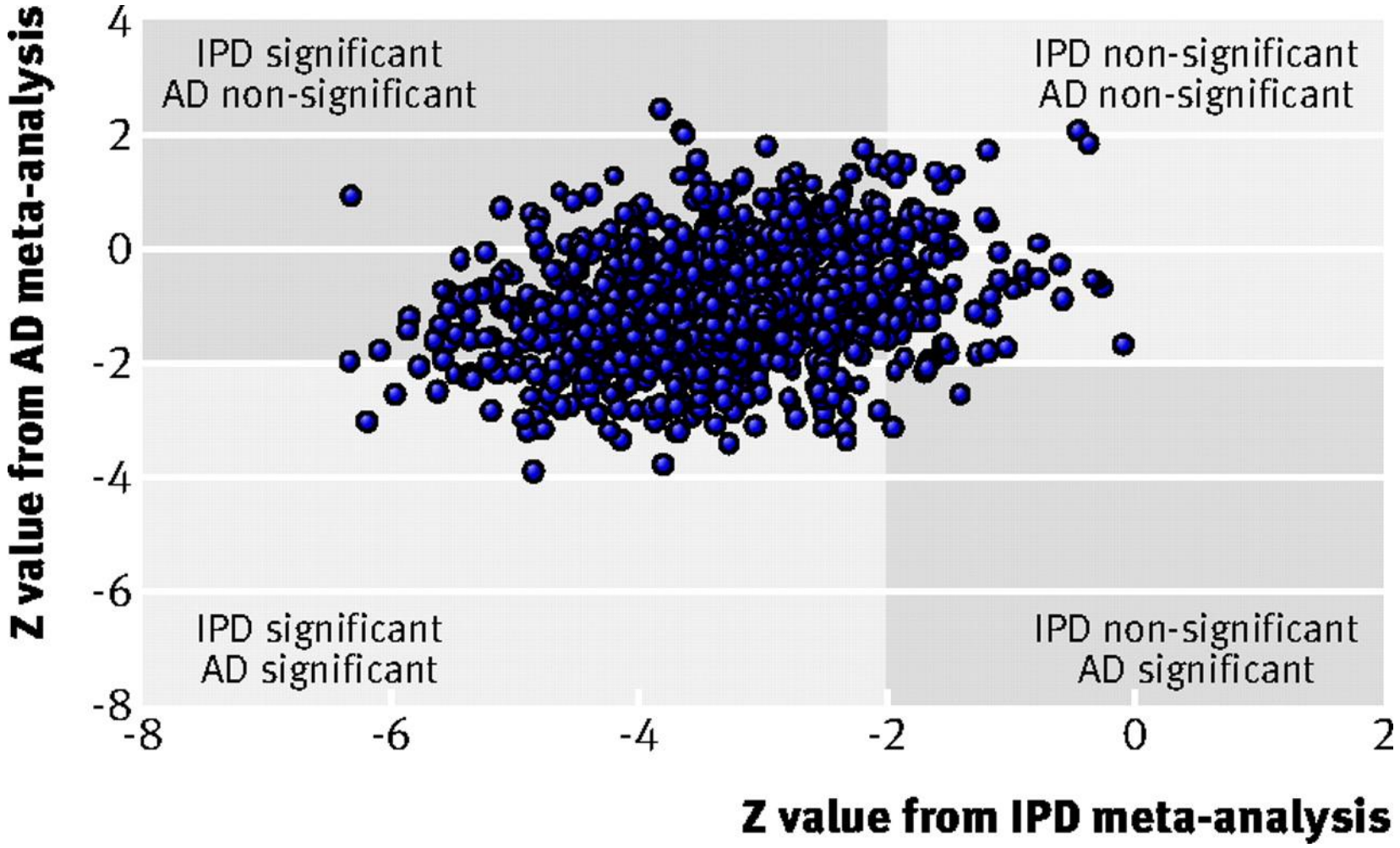
Example of individual participant data from 10 hypertension trials that assess effect of treatment versus placebo on systolic blood pressure

Study ID	Patient ID	Age (years)	Sex (1=male, 0=female)	Treatment group (1=treatment, 0=control)	Systolic blood pressure before treatment (mm Hg)	Systolic blood pressure after treatment (mm Hg)
1	1	46	1	1	137	111
1	2	35	1	0	143	133
…	…	…	…	…	…	…
1	1520	62	0	0	209	219
2	1	55	0	1	170	155
2	2	38	1	1	144	139
…	…	…	…	…	…	…
2	368	44	1	0	153	129
3	1	51	1	1	186	166
3	2	39	0	1	201	144
…	…	…	…	…	…	…
3	671	54	0	0	166	141
…	…	…	…	…	…	…
10	1	71	0	1	149	128
10	2	59	1	0	168	169
…	…	…	…	…	…	…
10	978	63	0	1	174	128

Dotted line indicates where non-displayed rows of data occur.
Hypothetical data based on Wang et al.[27]

Riley RD, et al. BMJ 2010;340:c221

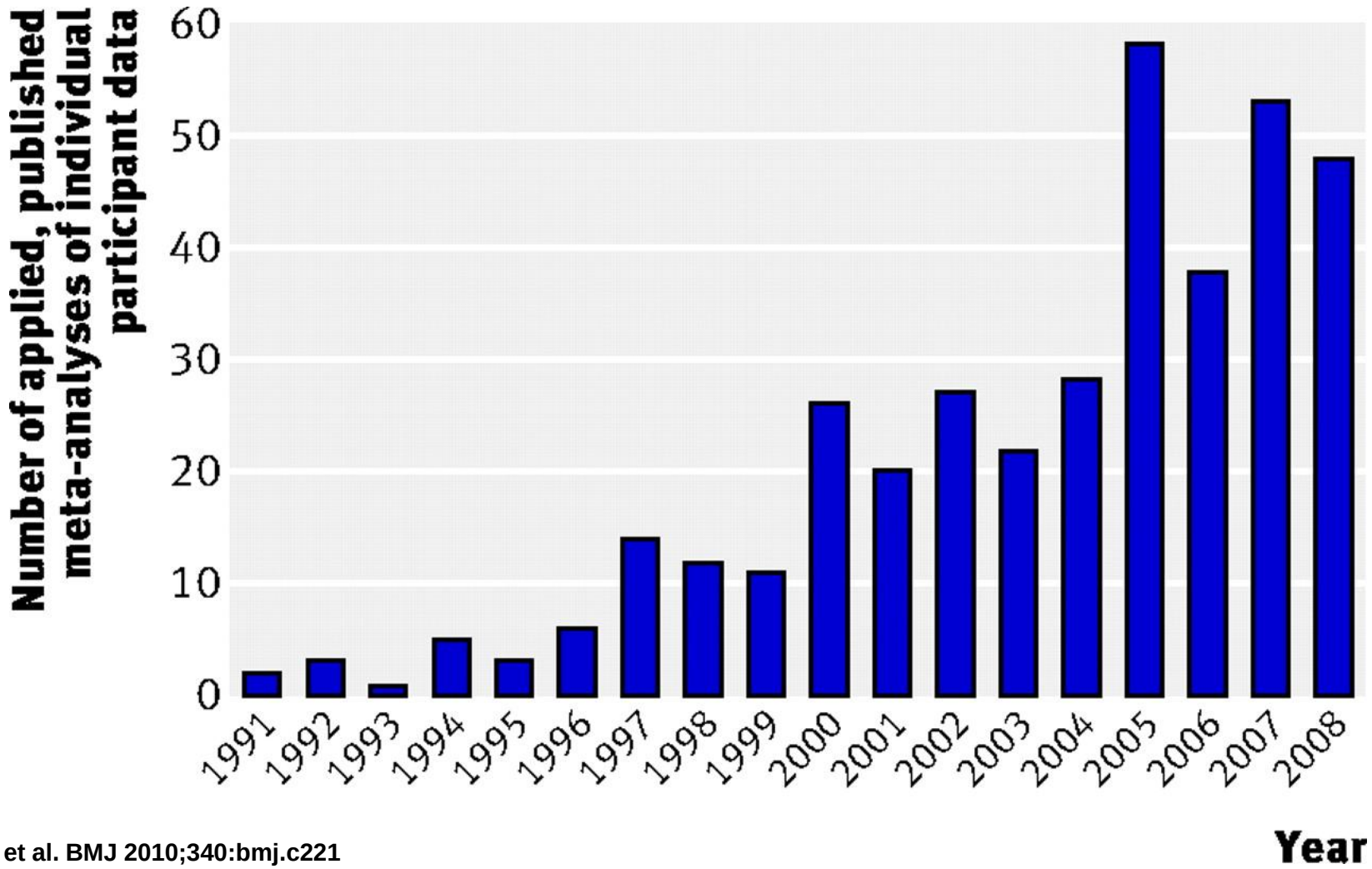
Fig 2 Comparison of the power of meta-analyses to detect a differential treatment effect across two groups of patients when individual participant data (IPD) or aggregate data (AD) are used.



Riley R D et al. BMJ 2010;340:bmj.c221

cdbjflsrhejg

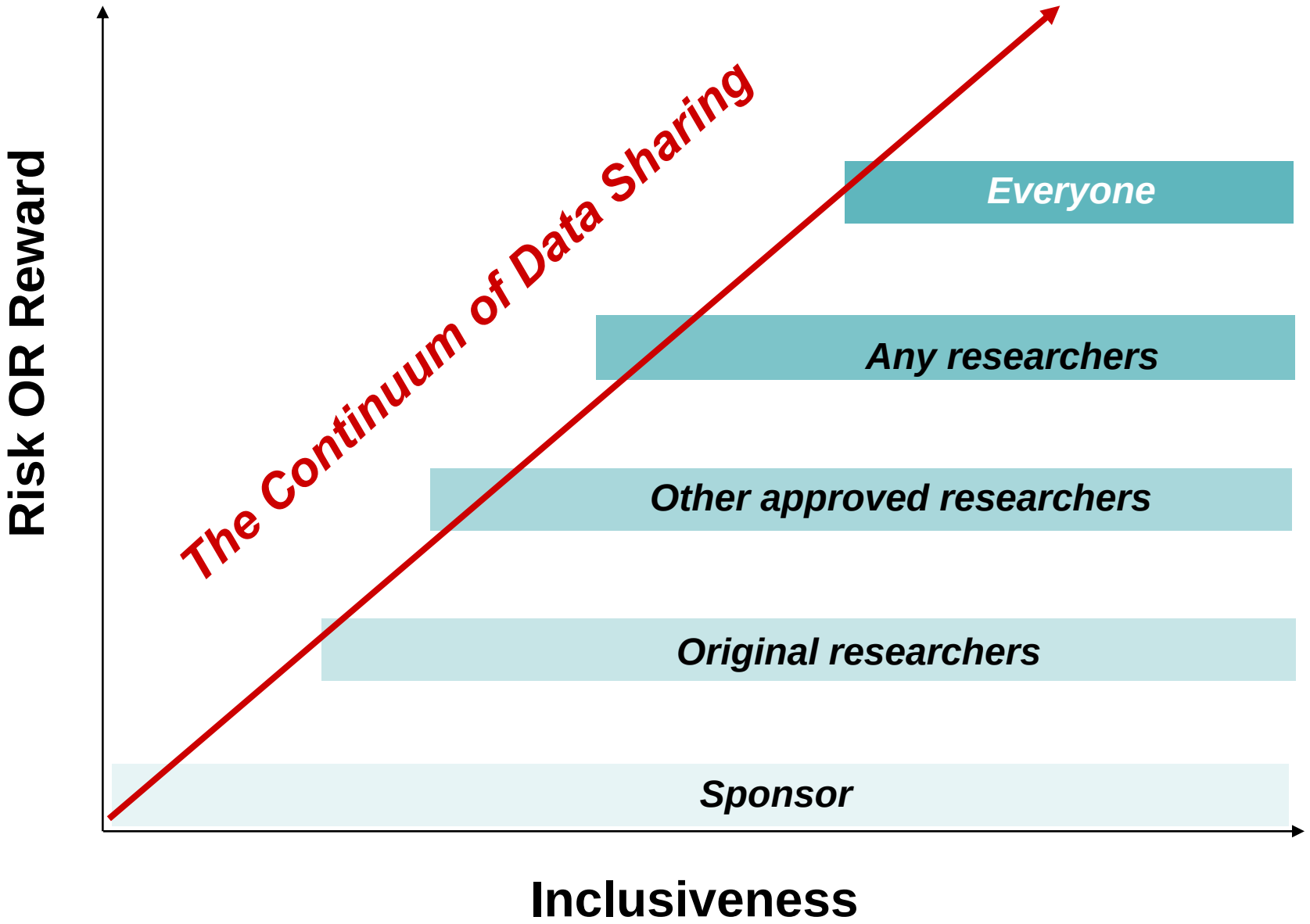
Fig 1 Number of distinct, applied meta-analyses of individual participant data published up to March 2009, as identified by a systematic review of Medline, Embase, and the Cochrane Library.



Riley R D et al. BMJ 2010;340:bmj.c221

cdbjflsrhejg

What does “sharing” mean?



Phrases that resonate throughout their statements

- Research is a public good
- Restoration of trust
- Respect for research participants
- Higher quality science
- Faster progress
- Avoid duplication
- Better value for money

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD

THE COCHRANE COLLABORATION

BILL & MELINDA GATES foundation

wellcome trust

MRC Medical Research Council

Larry Page, the founder of Google, has called on scientists to make more of their research available. **"We have to unlock the wealth of scientific knowledge and get it to everyone."**

Reasons and Benefits: Main Themes

Ethical and Moral

- To fulfill obligations to research participants
- Minimize known risks and potential harm from unnecessary exposure to previously tested interventions
- Medical research is a public good

Practical and Scientific

- Detect and deter selective or inaccurate reporting of research
- To ensure access to valid information about previously performed trials and avoid duplication
- Accelerate research and enhance collaboration by making knowledge available
- Restore trust in the clinical research enterprise

Very similar to the arguments for trial registration!

Krleza-Jeric K et al. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa Statement. BMJ 2005;330:956-958.

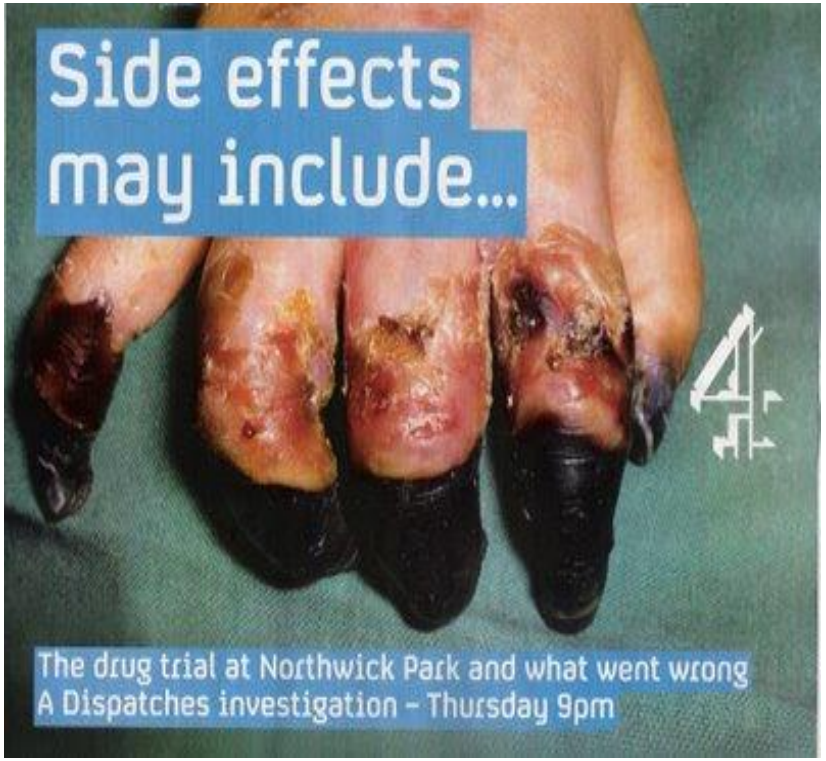
Obligations to Research Participants

People participate in clinical research at least in part in the expectation that it might benefit others in the future.

"Patients who put themselves at risk to provide these data earn our respect for their participation…"

-- Jeff Drazen

A Duty to Future Research Participants



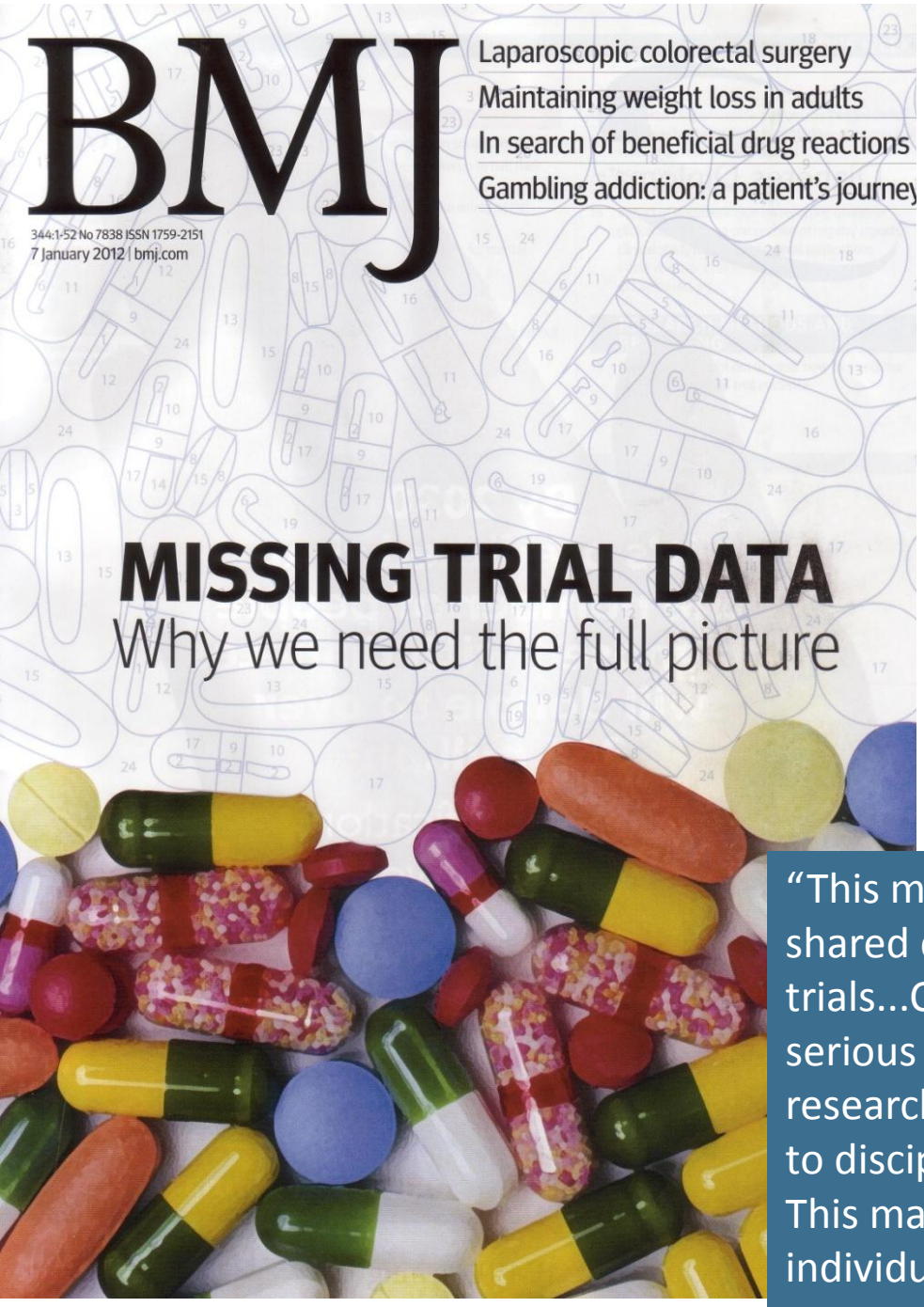
Might the adverse effects of TGN1412 have been predicted if unpublished information had been available?

Chalmers, I. The Lancet, Volume 368, Issue 9554,
Pages 2206 - 2207, 23 December 2006

Medical research is a public good

"The development of new therapies is, in the end, a group endeavor: taxpayers support basic research, companies fund trials, academic medical centers provide the space and equipment, and scientists conduct the research."

Kimmelman J, London A.
http://scienceprogress.org/2010/06/clinical-trials-and-the-common-good/



EDITORIALS

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Missing clinical trial data

A threat to the integrity of evidence based medicine

Richard Lehman senior research fellow, Department of Primary Care, University of Oxford, Oxford OX1 2ET, UK
Elizabeth Loder clinical epidemiology editor, *BMJ*, London WC1H 9JR, UK elizloder@bmj.com

Clinical medicine involves making decisions under uncertainty. Clinical research aims to reduce this uncertainty, usually by performing experiments on groups of people who consent to run the risks of such trials in the belief that the resulting knowledge will benefit others. Most clinicians assume that the complex regulatory systems that govern human research ensure that this knowledge is relevant, reliable, and properly disseminated. It generally comes as a shock to clinicians, and certainly to the public, to learn that this is far from the case.

The linked cluster of papers on unpublished evidence should reinforce this sense of shock. These articles confirm the fact that a large proportion of evidence from human trials is unreported, and much of what is reported is done so inadequately. We are not dealing here with trial design, hidden bias, or problems of data analysis—we are talking simply about the absence of the data. And this is no academic matter, because missing data about harm in trials can harm patients, and incomplete data about benefit can lead to futile costs to health systems. Moreover, researchers or others who deliberately conceal trial results have breached their ethical duty to trial participants.

The linked articles look closely at the extent, causes, and consequences of unpublished evidence from clinical trials. Hart and colleagues incorporated unpublished evidence into existing meta-analyses of nine drugs approved by the US Food and Drug Administration in 2001 and 2002.[1] These reanalyses produced identical estimates of drug efficacy in just three of 41 cases (7%); in the remaining cases, estimates of drug efficacy were evenly split between more (19/41) and less (19/41). It is sometimes assumed that incorporation of missing data will reduce estimates of drug benefits, but this study shows that "publication bias" can cut both ways.

Missing data about harm in trials can harm patients, and incomplete data about benefit can lead to futile costs to health systems

describes in the Research Methods and Reporting section, prior registration of all trials became a condition for later publication.[2] Chan details the ways in which authors of systematic reviews can search for unpublished evidence, and he strikes an optimistic note when he states that "Key stakeholders—including medical journal editors, legislators, and funding agencies—provide enforcement mechanisms that have greatly improved adherence to registration practices."

However, two studies we publish give little cause for optimism that this adherence extends to timely sharing of trial results. A survey of publicly funded research in the United States

US Food and Drug Administration Amendments Act of 2007 made publication of a results summary on ClinicalTrials.gov within 12 months mandatory for all eligible trials in the US "initiated or ongoing as of September 2007"—Prayle and colleagues examine the extent to which this has happened.[4] The tally stands at 22%. When the word "mandatory" turns out to mandate so little, the need for stronger mechanisms of enforcement becomes very clear.

Most clinical interventions in current use, however, are based on trials carried out before the era of mandatory registration, and here the task of data retrieval by systematic reviewers and national advisory bodies becomes impossible. Wieseler and colleagues show that the different documents available to researchers and regulators—internally produced study reports, study findings published in peer reviewed journals, and results posted in results registries—supplement each other, but that reporting quality is highest in study reports. However, the effort required to find and collate these sources can be prodigious and seldom guarantees completeness.[5] In their just published Cochrane review update on antiviral treatments for influenza, Jefferson and colleagues describe a painstaking search for information from undisclosed trials stretching over several years.[6]

There is an "Alice in Wonderland" feel to these investigators' efforts—acting on the public's behalf, searching over hill and dale and among the paperwork of regulatory bodies and drug companies to put together pieces of data that should have been freely available in the first place. Even when data on individual participants are made available, they form only part of the jigsaw, and Ahmed and colleagues describe the problems of fitting in such data when the whole picture is not known.[7]

Finally, to find the randomised clinical trials that have been published in the medical literature, nearly every student, clinician, or researcher turns first to Medline among the biomedical databases. But Wieland and colleagues find that

"This may require the global organisation of a suitable shared database for all raw data from human trials...Concealment of data should be regarded as the serious ethical breach that it is, and clinical researchers who fail to disclose data should be subject to disciplinary action by professional organisations. This may achieve quicker results than legislation in individual countries, although this is also desirable."

Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses

Beth Hart,[1] Andreas Lundh,[2] Lisa Bero[1]

EDITORIAL by Lehman and Loder

[1]Department of Clinical Pharmacy, Institute for Health Policy Studies, University of California, San Francisco, 3333 California St, Suite 420, San Francisco, CA 94118, USA
[2]Nordic Cochrane Centre, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark
Correspondence to: L Bero
berol@pharmacy.ucsf.edu

Cite this as: *BMJ* 2012;344:d7202
doi: 10.1136/bmj.d7202

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;343:d7202

STUDY QUESTION

What effect does inclusion of unpublished trial outcome data obtained from the Food and Drug Administration (FDA) have on the results of meta-analyses of drug trials?

SUMMARY ANSWER

In general, the effect of including unpublished FDA trial outcome data varies by drug and outcome.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

When unfavourable results of drug trials are not published, meta-analyses and systematic reviews that are based on only published data may overestimate the efficacy of drugs. Addition of unpublished trial outcome data to published meta-analyses changed their results; the direction of the effect varied by drug and outcome.

Addition of unpublished FDA trial data caused 46% of the summary estimates from the meta-analyses to show lower efficacy of the drug, 7% to show identical efficacy, and 46% to show greater efficacy.

Selection criteria for systematic reviews

We identified eligible systematic reviews containing at [illegible]analysis by searching Medline, Embase, [illegible]ane Library in November 2010. We [illegible]natic reviews that were done after FDA [illegible]gs with unpublished FDA outcome data, [illegible]in English, had outcomes and compara- [illegible]e same as for the trials with unpublished [illegible]ad participants' characteristics consist- [illegible]A approved indications for the drug. We [illegible]natic reviews in which included trials [illegible]ced or that combined trials across mul- tiple drug classes. We also excluded systematic reviews that used non-standard meta-analytic techniques (such as Bayesian or network meta-analyses) or that used inappropriate or invalid methods for calculation of summary statistics (such as unweighted pooled analyses).

Primary outcome(s)

The main outcome was the effect of including unpublished FDA trial data on the summary estimates of meta-analyses of drug trials.

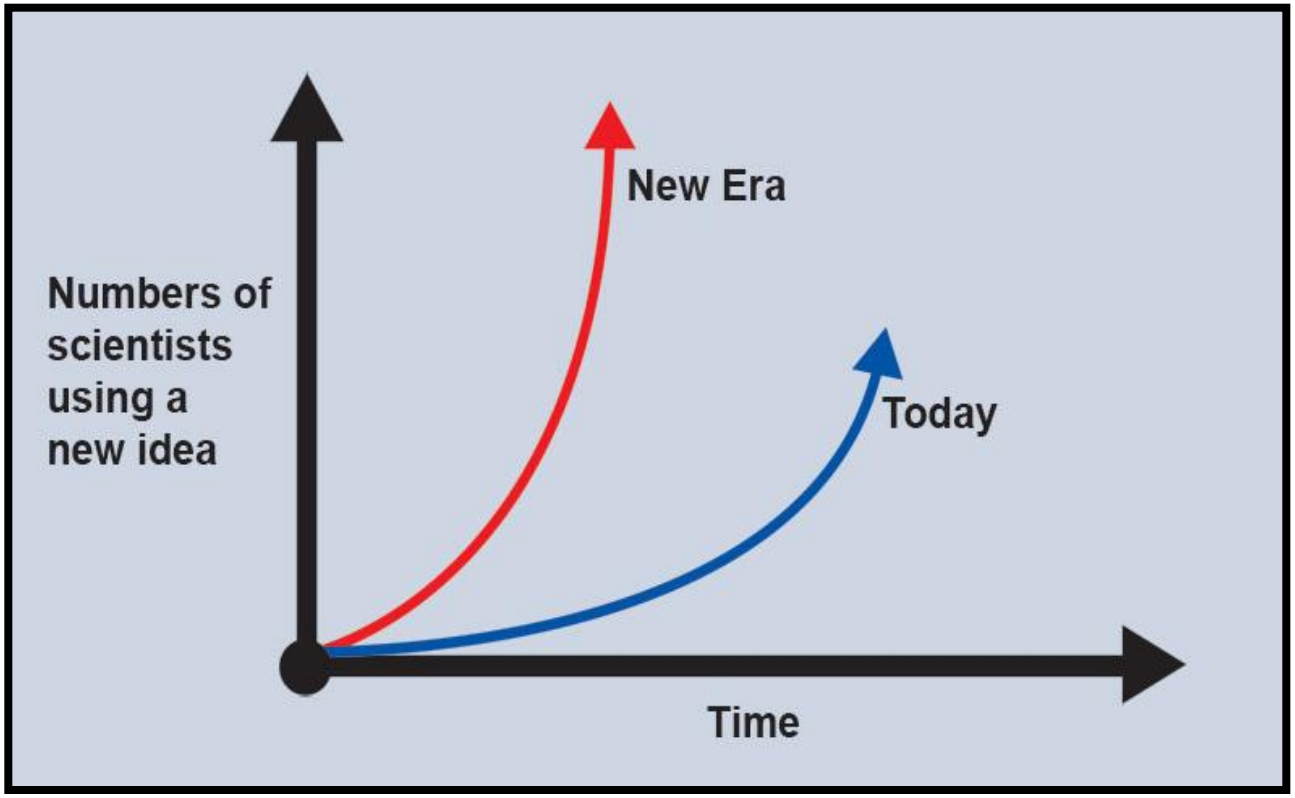
Main results and role of chance

We reanalysed 42 meta-analyses (41 efficacy outcomes, one harm outcome) for nine drugs across six drug classes. Overall, addition of unpublished FDA trial data caused 46% (19/41) of the summary estimates from the meta-analyses to show less efficacy of the drug (range 1-53% change in summary estimate), 7% (3/41) to show identical drug efficacy, and 46% (19/41) to show greater drug efficacy (2-166% change in summary estimate).

Bias, confounding, and other reasons for caution

We were able to identify systematic reviews for only nine of the 24 drugs for which unpublished FDA trial outcome data were available. One reason for the lack of relevant systematic reviews may be that reviewers are unaware of unpublished outcomes and so do not include these outcomes in their protocols. Therefore, selective reporting of FDA trial outcomes could affect systematic reviews by influencing the research questions that are asked, as well

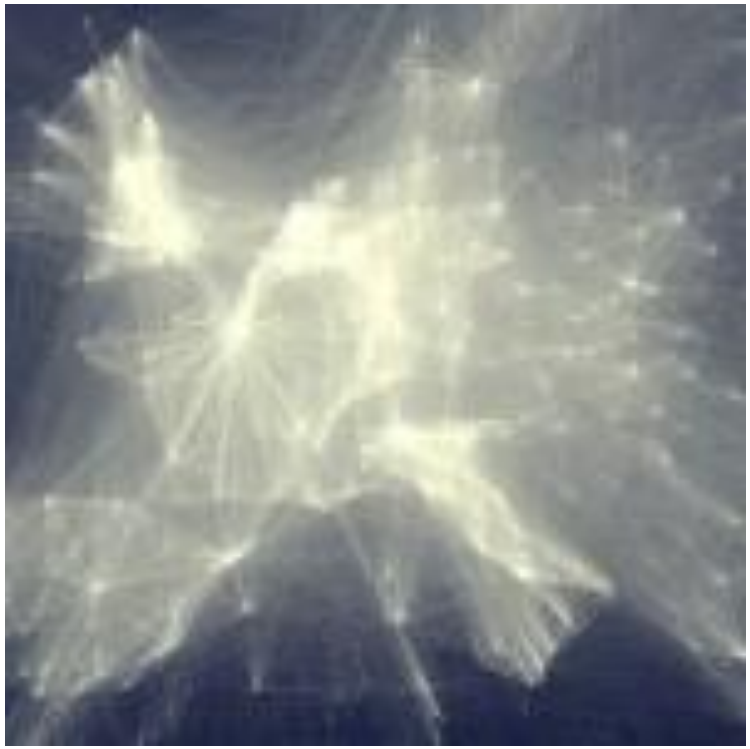
Accelerate research

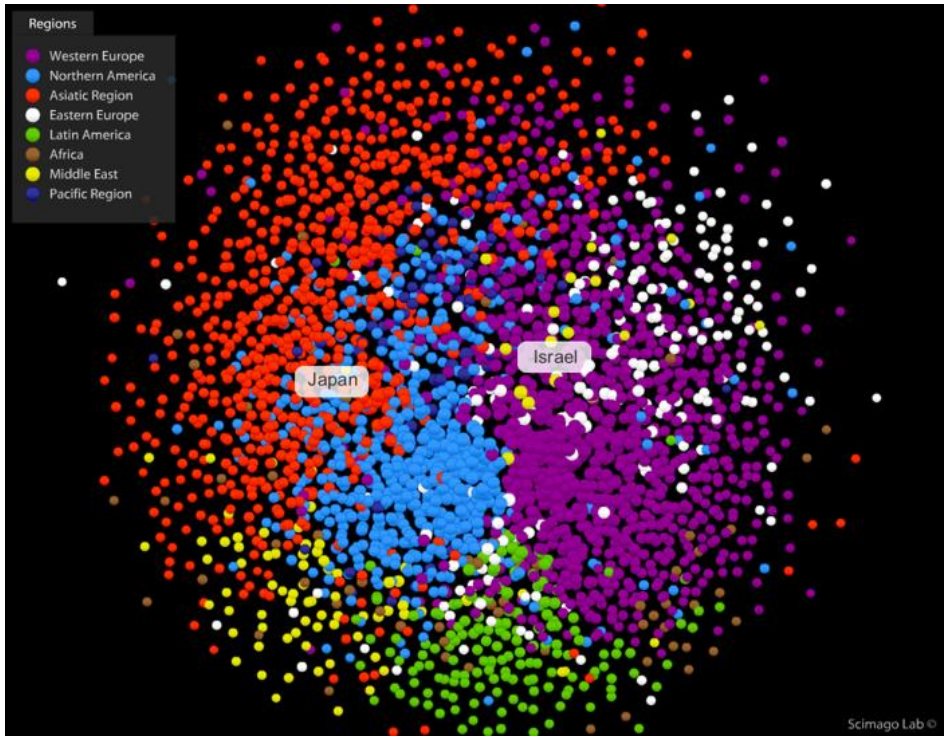


Compressing decades to years, years to months, and months to days

Spence K. USDOE OSTI. Presentation at Fesabid 2007, the 10th Spanish Conference on Documentation June 12–13, 2007

Collaboration and cooperation among scientists





http://olihb.com/2011/01/23/map-of-scientific-collaboration-between-researchers/ and http://www.scimagolab.com/blog/2011/institutional-collaboration-in-global-science/

Benefits: Citizen Science

"The next ~~Beethoven~~ Pasteur will from ~~Colorado~~ Maryland come…"

The Maryland native, who won $75,000 at the Intel International Science and Engineering Fair in May for his creation, cites **search engines and free online science papers as the tools that allowed him to create the test**…."

Benefits of Sharing:

Restore trust in the clinical research enterprise

"The clinical research enterprise faces its greatest crisis ever: widespread distrust. Without public and patient support, there can be no translation of innovations into medical therapies. In the absence of study volunteers, clinical trials cannot be conducted and, ultimately, public health advances cannot be realized. An alarmingly low 4 to 6% of ELIGIBLE patients participate in US-based clinical trials annually."

http://www.ciscrp.org/professional/medheroes_campaign.html


HERO
HOT LEGALITEAS
Medical heroes can be found in everyday places
CISCRP

Benefits of Sharing:

Restore trust in the clinical research enterprise

A Randomized Study of How Physicians Interpret Research Funding Disclosures

Aaron S. Kesselheim, M.D., J.D., M.P.H., Christopher T. Robertson, Ph.D., J.D., Jessica A. Myers, Ph.D., Susannah L. Rose, Ph.D., Victoria Gillet, B.A., Kathryn M. Ross, M.B.E., Robert J. Glynn, Ph.D., Steven Joffe, M.D., and Jerry Avorn, M.D.

CONCLUSIONS

Physicians discriminate among trials of varying degrees of rigor, but industry sponsorship negatively influences their perception of methodologic quality and reduces their willingness to believe and act on trial findings, independently of the trial's quality. These effects may influence the translation of clinical research into practice.

N ENGL J MED 367;12 NEJM.ORG SEPTEMBER 20, 2012

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Data from: Efficacy and safety of four weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial

When using this data, please cite the original article:

Lötvall J, Bakke PS, Bjermer L, Steinshamn S, Scott-Wilson C, Crim C, Sanford L, Haumann B (2012) Efficacy and safety of four weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. BMJ Open 2(1): e000370. doi:10.1136/bmjopen-2011-000370

Additionally, please cite the Dryad data package:

Lötvall J, Bakke PS, Bjermer L, Steinshamn S, Scott-Wilson C, Crim C, Sanford L, Haumann B (2012) Data from: Efficacy and safety of four weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. Dryad Digital Repository. doi:10.5061/dryad.7p1r30q5

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Dryad Package Identifier doi:10.5061/dryad.7p1r30q5 97 views

Abstract BACKGROUND: Fluticasone furoate/vilanterol (FF/VI) is a nov
corticosteroid/long-acting β2 agonist combination in developm
pulmonary disease (COPD) and asthma. TRIAL DESIGN: A m
double-blind, parallel-group, placebo-controlled study. METHO
patients with moderate-to-severe COPD treated with placebo c
weeks. Study objectives were to assess the safety and efficac
administered for 4 weeks via a novel dry powder inhaler. Co-pr
change from baseline in weighted mean (wm) heart rate 0–4 h
incidence of adverse events (AEs). Secondary end points inclu
trough forced expiratory volume in one second (FEV1) (23–24
FEV1 (0–4 h postdose; day 28). Patients were randomised to
placebo in a 2:1 ratio; all patients and investigators were blind
treatment. RESULTS: 60 patients (mean age 64 years) were r
placebo: n=20), and all contributed data to the analysis. Mean
bronchodilator FEV1 per cent predicted was comparable betw
placebo: 60.1%). The wm heart rate 0–4 h postdose was simil
(difference: 0.6 beats per minute; 95% CI −3.9 to 5.1). More o
reported in the FF/VI group (68%) compared with the placebo
common drug-related AEs in the FF/VI group were oral candid
(5%). There were no clinically relevant effects on laboratory va
potassium, or on vital signs or ECGs/Holters. The FF/VI group
improvements compared with placebo in trough FEV1 (mean c
postdose wm FEV1 (mean difference 236 ml). CONCLUSION:
tolerability profile and improves lung function compared with pl

Keywords Chronic airways disease, RESPIRATORY MEDICINE, THORA

Date Deposited 2012-01-26T16:43:37Z

Show Full Metadata

FF-VI_348_study_Dryad-DATA 19 downloads View File Details

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Open Access Research

BMJ open accessible medical research

Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial

J Lötvall,[1] P S Bakke,[2] L Bjermer,[3] S Steinshamn,[4,5] C Scott-Wilson,[6] C Crim,[6] L Sanford,[7] B Haumann[7]

To cite: Lötvall J, Bakke PS, Bjermer L, *et al*. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. *BMJ Open* 2012;**2**:e000370. doi:10.1136/bmjopen-2011-000370

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://bmjopen.bmj.com).

Received 31 August 2011
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ABSTRACT

Background: Fluticasone furoate/vilanterol (FF/VI) is a novel once-daily (OD) inhaled corticosteroid/long-acting β_2 agonist combination in development for chronic obstructive pulmonary disease (COPD) and asthma.

Trial design: A multicentre, randomised, double-blind, parallel-group, placebo-controlled study.

Methods: Participants were patients with moderate-to-severe COPD treated with placebo or FF/VI 400/25 μg OD for 4 weeks. Study objectives were to assess the safety and efficacy of FF/VI 400/25 μg OD administered for 4 weeks via a novel dry powder inhaler. Co-primary end points were change from baseline in weighted mean (wm) heart rate 0—4 h postdose at day 28 and the incidence of adverse events (AEs). Secondary end points included change from baseline in trough forced expiratory volume in one second (FEV_1) (23—24 h postdose; day 29) and wm FEV_1 (0—4 h postdose; day 28). Patients were randomised to receive FF/VI 400/25 μg or placebo in a 2:1 ratio; all patients and investigators were blinded to active or placebo treatment.

ARTICLE SUMMARY

Article focus

- Is the once-daily inhaled corticosteroid/long-acting β_2 agonist (ICS/LABA) combination FF/VI efficacious with a favourable safety and tolerability profile in COPD?

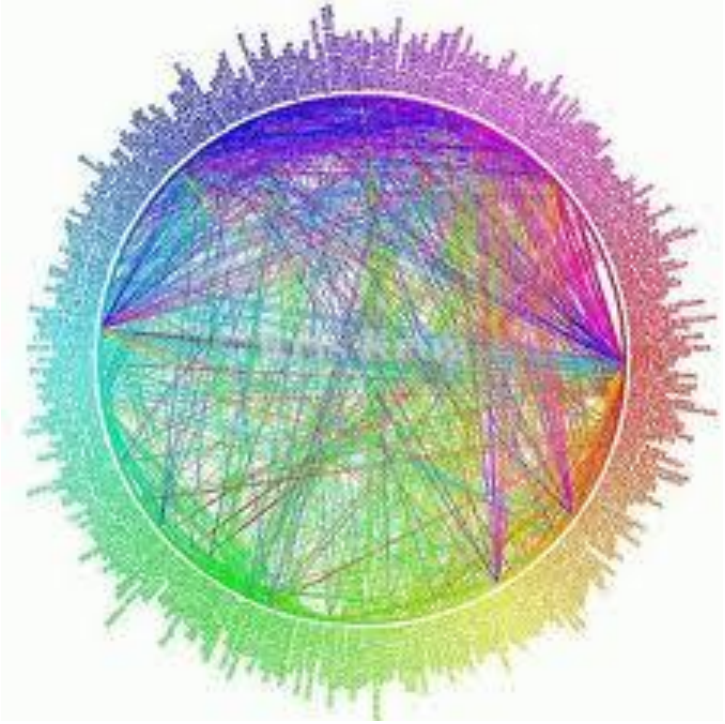
Key messages

- In patients with moderate-to-severe COPD, FF/VI 400/25 μg once daily improved lung function. AEs frequently experienced with other ICS/LABA combinations were generally reported at similar frequencies in the placebo and active treatment arms.

Strengths and limitations of this study

- This paper is the first to present clinical data on inhaled FF/VI combination therapy in patients with chronic obstructive lung disease. Given the 4-week duration of this study, there was no end point or surrogate marker to specifically address the relative clinical effects of FF in COPD (such as

We are engaged in one of the great struggles of human knowledge



Thanks !

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