ClinicalTrials.gov and Addressing Challenges in Finding Evidence

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Evidence Based Regulatory Decision Making

- **Requires access to all relevant evidence**
  - Not just those data submitted by a sponsor
  - Not just those analyses submitted by a sponsor
- **Barriers to complete access to evidence**:
  - Missing (invisible) trials or other studies
  - Unreported or changed outcome measures
  - Unreported (or obscured) AEs
  - Incomplete or changed analyses

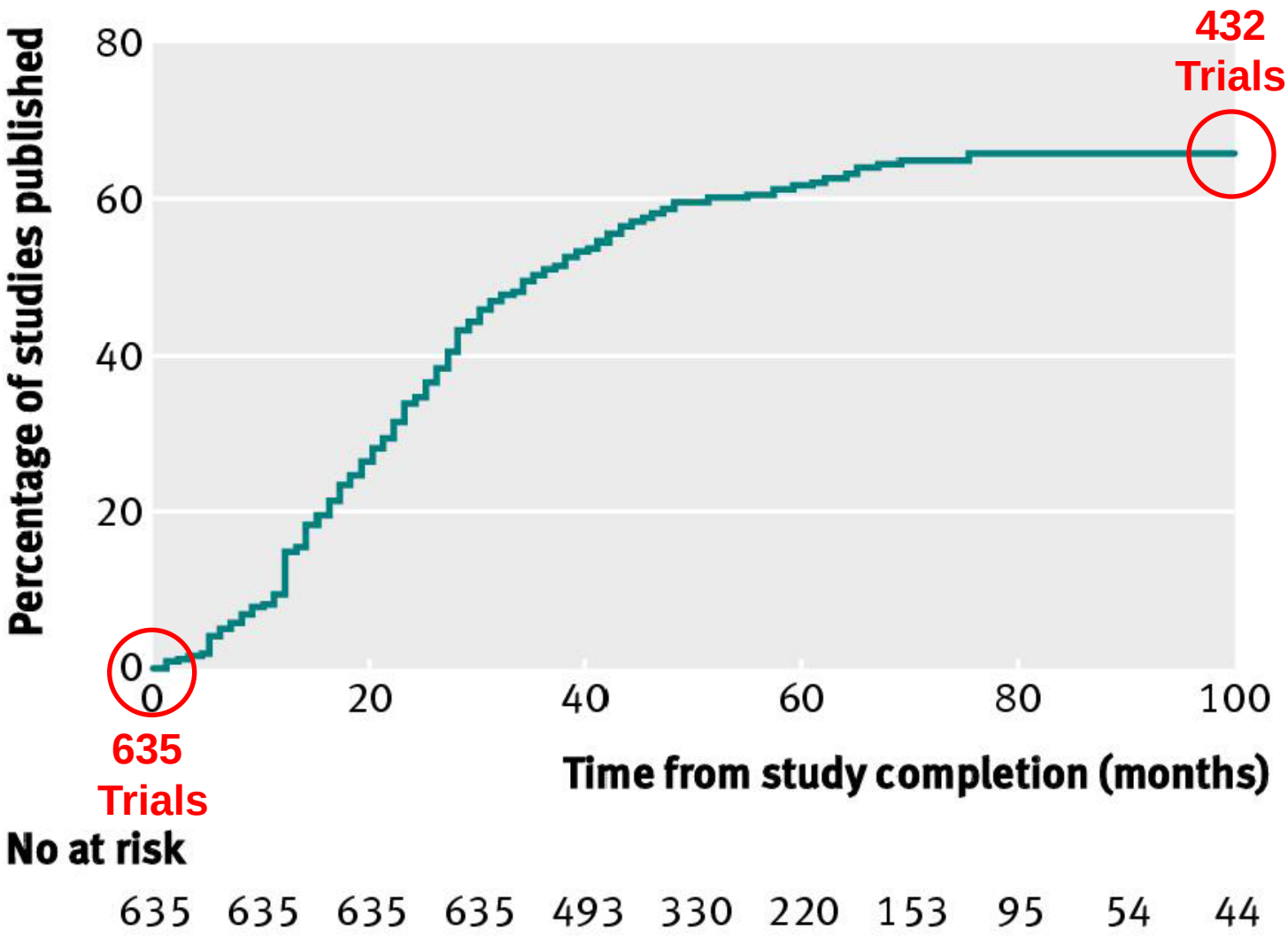
Systematic, Searchable Sources of Data
(Beyond those submitted by sponsor)

- PubMed
- ClinicalTrials.gov
- Other registries

Problems with Published Literature

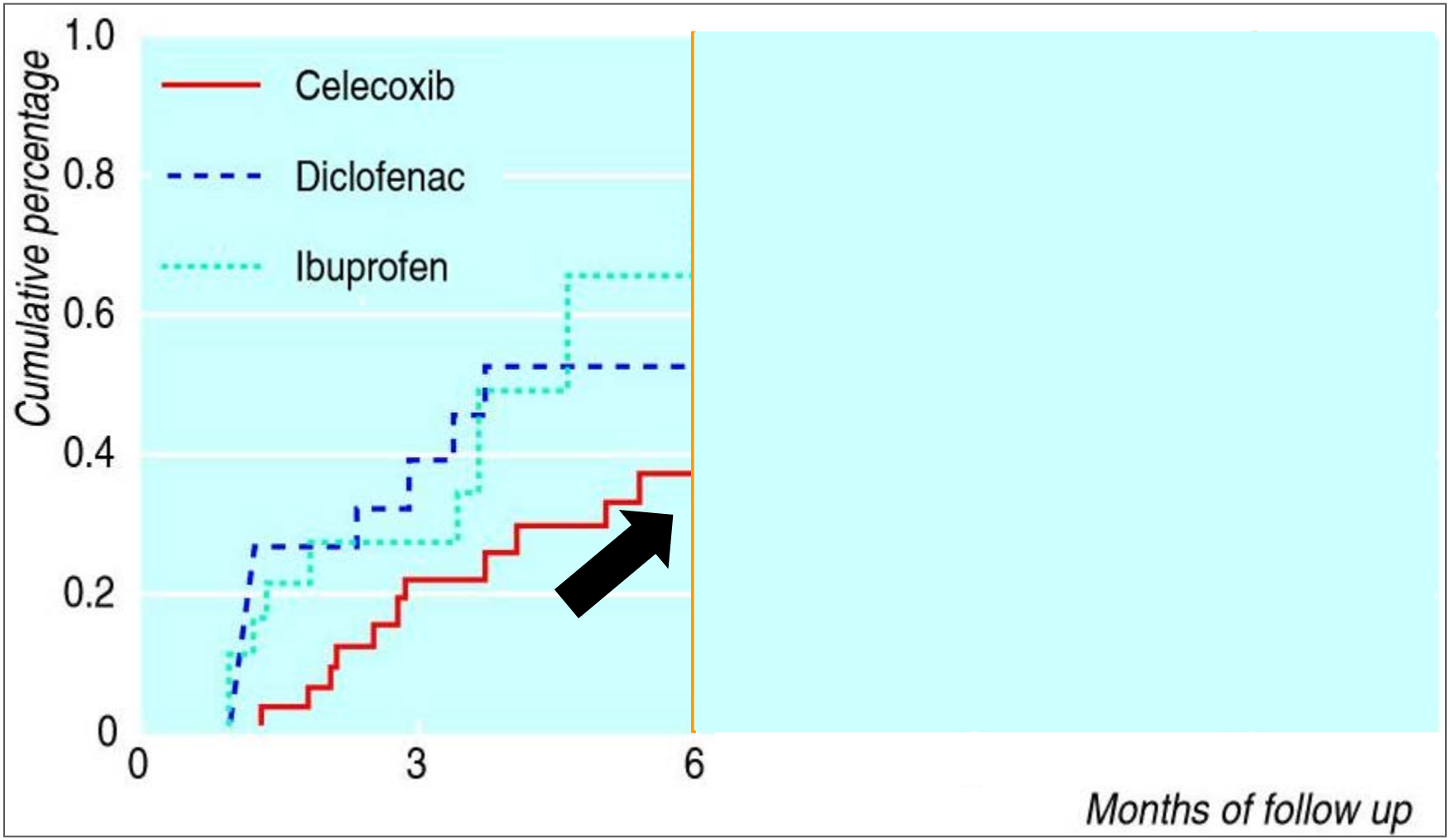
- Missing many trials
- Incomplete reporting of trials that are published
  - Prespecified outcome measures may be omitted
  - AEs omitted
- Lack of fidelity to protocol for some analyses; e.g.
  - Unacknowledged changes to outcome measures
  - Deviations from analysis plan

Fig 2 Cumulative percentage of studies published in a peer reviewed biomedical journal indexed by MEDLINE during 100 months after trial completion among all NIH funded clinical trials registered within ClinicalTrials.gov



Ross et al. *BMJ* 2012;344:d7292.

Kaplan-Meier estimates for ulcer complications according to traditional definition. Results are truncated after 12 months, no ulcer complications occurred after this period. (Adapted from Lu 2001.)



Jüni P, Rutjes AW, Dieppe PA. *BMJ*. 2002 Jun 1;324(7349):1287-8.

Trial Registration and Results Reporting

- Registration (prior to trial initiation)
  - Public list of all relevant trials with key protocol details
- Results Reporting
  - Structured, curated summary data
    - Ensures minimum data set: (participant flow, baseline characteristics, prespecified outcome measures, AEs)
    - Independent of journal publication

ClinicalTrials.gov

- Registry: Over 160,000 studies
  - 500 new studies/week
  - 18% (over 29,000) observational studies
- Results database: Over 11,000 studies
  - 100 new sets of results/week
- International in scope
  - Fewer than half are in US only
- All phases, all study models, all intervention types

Content of ClinicalTrials.gov Record

- One record per trial
- Registration section
  - Submitted at trial initiation
  - Summarizes information from trial protocol
    - Condition
    - Interventions
    - Outcomes
    - Design, etc
  - Includes recruitment information (e.g., eligibility, locations)
- Results section
  - Submitted after trial completion
  - Summarizes trial results
    - Participant flow
    - Baseline characteristics
    - Outcome measures (including statistical analyses)
    - Adverse events

Key Policies

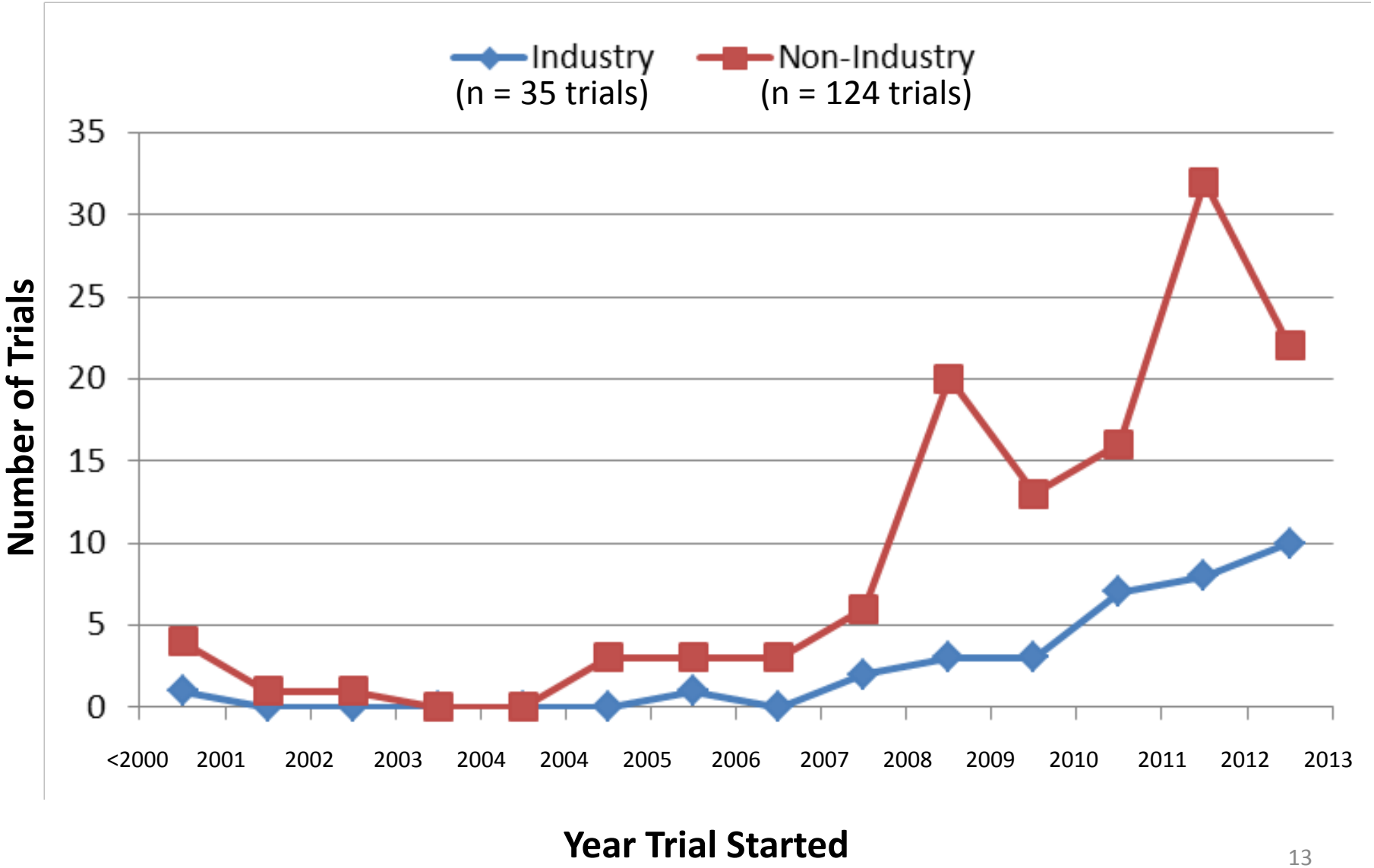
- ICMJE (Registration only)
  - Interventional trials
    - All intervention types
  - All phases; all jurisdictions; enforced by journal editors
- FDAAA (Registration and Results)
  - Interventional trials
    - Drugs, biologics, devices
  - Not phase 1
  - US FDA jurisdiction (e.g., IND/IDE or US site)
  - Specific enforcement mechanisms
- EMA (Registration and Results)

“Invisible” Trials

- Not all trials legally required to register
  - E.g., non-IND studies with no US sites
- Registration only helps if there is an accessible, searchable database
- Features of search engine determine the utility
  - Even best search engines have challenges with drug and device names, other features of trials
- Many registries around the world
  - Varying quality of search engines
  - No systematic de-duplication

Not All Trials are Registered

Number of Trials First Registered in 2014 at ClinicalTrials.gov and Listed as "Completed" or "Terminated" by Start Year



Not All Registered Trials Can Be Found

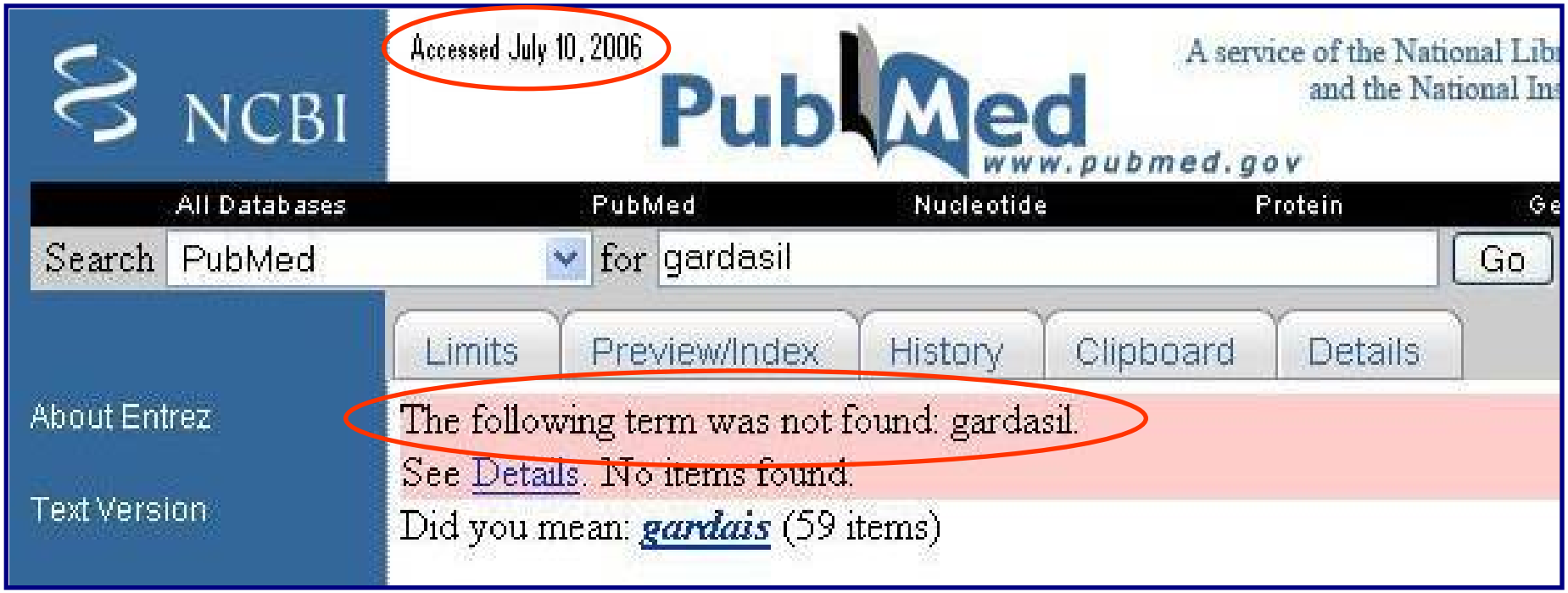
Drug Serial #s = "Hidden" Trials

ClinicalTrials.gov Gardasil® Search

Gardasil® was approved on June 8, 2006

PubMed Gardasil® Search

One month after approval (and promotion)



Study NCT00378560

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Linking patients to medical research

Developed by the National Library of Medicine

Home | Search | Listings | Resources | Help | What's New | About

Gardasil (V501) Study in Adult Women

This study is currently recruiting patients.

Verified by Merck September 2006

Sponsored by:	Merck
Information provided by:	Merck
ClinicalTrials.gov Identifier:	NCT00378560

Purpose

A study to evaluate the efficacy, immunogenicity, safety and tolerability of Gardasil (V501) in adult women.

Condition	Intervention	Phase
Papillomavirus Infections	Vaccine: V501, Gardasil, human papillomavirus (types 6,11,16,18) recombinant vaccine / Duration of Treatment: 7 Months Vaccine: Placebo (unspecified) / Duration of Treatment: 7 Months	Phase II

Names/Identifiers Are Critical

- Search engines depend on known names, lists of synonyms, and hierarchies: e.g., Paxil
  - Aropax
  - Asimia
  - brl-29060
  - fg-7051
  - Ldmp
  - Paroxetine
  - Pexeva
  - Seroxat
- "Code" names, without "de-coders," lead to "hidden" trials
- Non-specific names may also prevent the search engine from retrieving a useful list of trials
- Biologic, device, and other irregular intervention names challenge the system:
  - Vaccine: ALVAC-HIV MN120TMG (vCP205)
  - Device: IT LEISH (rK39); Device: galyfilcon AP 8.3 BC; Device: BD/33G

Naming Drugs

- After Approval
  - Generic name (USAN, USP), links to chemical structure
- Before Approval
  - Chemical structure (name, drawing)
  - Company serial number
    - No public record or oversight
    - No guaranteed one-to-one correspondence

Does the Search Engine Enable You to Find the Trials You Want?

- Spelling correction and relaxation of search terms
- Use of synonymy
- Fielded search
- Use of hierarchy from MeSH
- Relevancy ranking

There Are Many Trial Registries of Varying Quality

Insufficient Coordination Leads to "World Chaos"

Protocol Registration Status

TransparentCT®
THE INTERNATIONAL CLINICAL TRIAL DISCLOSURE KNOWLEDGE BASE

Mandatory for Registrant to Post (in effect)	Non-voluntary Post by EC or Government (in effect)	Mandatory for Registrant to Post (pending)	Non-voluntary Post by EC or Government (pending)	Legislation / Regulations (ongoing activity)	Voluntary Registry (in effect)
Argentina ReNIS	Argentina EFC	Kenya	Croatia	Canada	Africa
Austria NIS[1]	Chile	Mexico	Italy Integrated Platform	China	Australia/New Zland
Brazil[2]	Colombia[6]	Switzerland[8]	Spain[9]	Poland	China CFDA
Euro. Union EU PAS	Czech Republic		Zimbabwe		China ChiCTR
India	Euro. Union EU CTR				Cuba
Israel[3]	France				Euro. Union ENCePP
Malaysia	Germany PharmNet.Bund				Germany DRKS
New Zealand[4]	Korea MFDS				Hong Kong
Philippines[5]	Netherlands CCMO				Iran
South Africa	Norway				Japan
Taiwan	Peru				Korea CRiS
United States	Russia				Netherlands NTR
	Serbia				Poland INFARMA
	Singapore				Sri Lanka
	Slovakia[7]				Taiwan PMS[10]
	Venezuela				Tanzania[11]
					Thailand
					United Kingdom[12]

- This table is not intended to be exhaustive
- It is not guaranteed to be accurate
- Red indicates changes since April 2012
- Last updated April 2013

[1] Non-interventional studies
[2] Register Phase 1 - 4 trials in ReBEC
[3] Register in ClinicalTrials.gov
[4] Required for ethics approval (WHO/CTgov)
[5] Register Phase 1 - 4 trials in PHRR
[6] Posts PDF lists of trials
[7] Replaced database with PDF file
[8] In any WHO/ICMJE registry plus national database
[9] NCA loads XML; sponsor adds summary
[10] Post-marketing studies
[11] In public user test phase (since Jul 2011)
[12] NRES, ISRCTN, and PROSPERO

World Health Organization

International Clinical Trials Registry Platform
Search Portal

Home | Advanced Search | Search Tips | UTN | ICTRP website | Contact us

Example: liver cancer OR breast cancer NOT genetic | Search | Search tips

Welcome

- The Clinical Trials Search Portal provides access to a central database containing the trial registration data sets provided by the registries listed on the right. It also provides links to the full original records.
- To facilitate the unique identification of trials, the Search Portal bridges (groups together) multiple records about the same trial. More information
- Please note: This Search Portal is not a clinical trials registry. How to register a trial
- For mobile users, please use this link http://apps.who.int/trialsearch/ictrpmob.aspx. It can be opened from any smartphone
- It is now possible to export the results of the search into XML. More information
- Crawling the ICTRP database now requires a username/password. To request access to the crawling pages please send an email to ictrpinfo@who.int

Data Providers

Data sets from data providers are updated every Tuesday evening according to the following schedule:
Every week:

- Australian New Zealand Clinical Trials Registry, last data file imported on **3 February 2014**
- ClinicalTrials.gov, last data file imported on **3 February 2014**
- EU Clinical Trials Register (EU-CTR), last data file imported on **3 February 2014**
- ISRCTN, last data file imported on **3 February 2014**

Every 4 weeks:

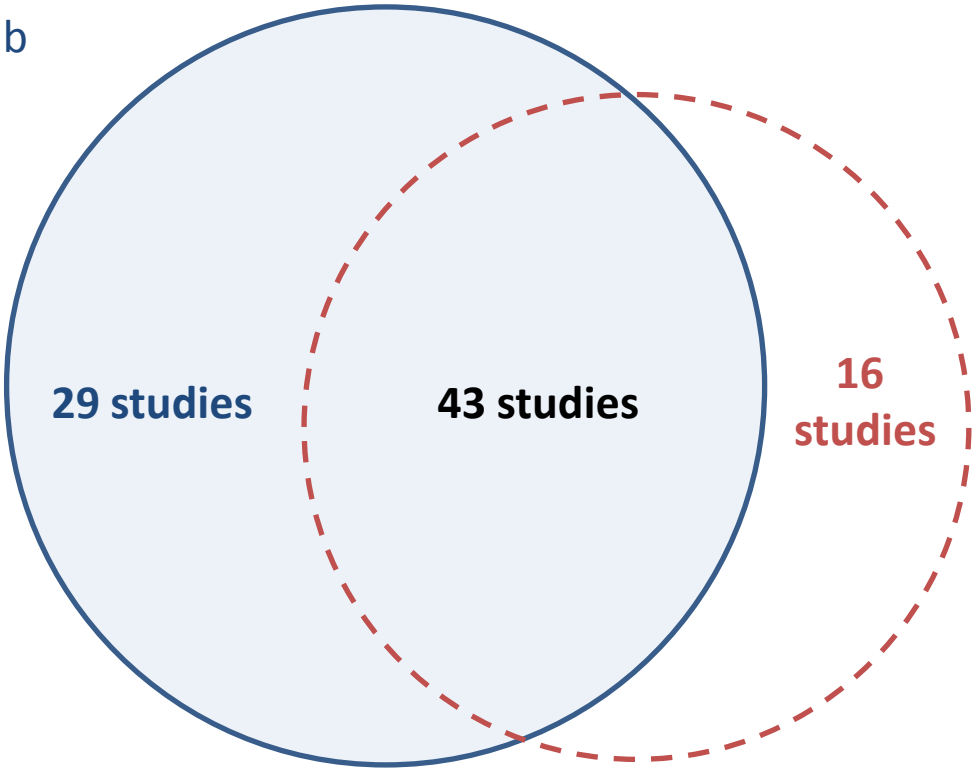
- Brazilian Clinical Trials Registry (ReBec), last data file imported on **3 February 2014**
- Chinese Clinical Trial Registry, last data file imported on **2 February 2014**
- Clinical Trials Registry - India, last data file imported on **3 February 2014**
- Clinical Research Information Service - Republic of Korea, last data file imported on **3 February 2014**
- Cuban Public Registry of Clinical Trials, last data file imported on **3 February 2014**
- German Clinical Trials Register, last data file imported on **3 February 2014**
- Iranian Registry of Clinical Trials, last data file imported on **2 February 2014**
- Japan Primary Registries Network, last data file imported on **2 February 2014**
- Pan African Clinical Trial Registry, last data file imported on **3 February 2014**
- Sri Lanka Clinical Trials Registry, last data file imported on **2 February 2014**
- The Netherlands National Trial Register, last data file imported on **3 February 2014**
- *New* Thai Clinical Trials Register (TCTR), last data file imported on **3 February 2014**

88 Registered Clinical Studies of Tysabri: ClinicalTrials.gov & WHO Search Portal

ClinicalTrials.gov Search
Intervention = "Tysabri"
Synonyms Searched:

- Natalizumab
- Antegren
- Anti-vla4

WHO Search Portal Search
Intervention = "Tysabri" OR "Natalizumab"



Names for 3 SSRI Drugs Recognized by ClinicalTrials.gov Search Engine

Zoloft

- Altruline
- Aremis
- Besitran
- Gladem
- Lustral
- Sealdin
- Sertraline

Prozac

- Fluoxetine
- Lilly 110140
- Rapiflux
- Reconcile
- Sarafem
- Selfemra

Paxil

- Aropax
- Asimia
- Brisdelle
- brl-29060
- fg 7051
- Ldmp
- Paroxetine
- Pexeva
- Seroxat

Case Study – the GAS Study

- Registered in (at least) three registries
  - ISRCTN, ClinicalTrials.gov, ANZCTR
- Three different PIs (US, UK, Aus); three different "sponsors."
- ANZCTR and ClinicalTrials.gov records have same title; ISRCTN lists ANZCTR as secondary ID
- WHO portal lists two records, but does not recognize them as duplicates; does not have the ISRCTN record

On WHO Portal Site:
Basic Search for “The GAS Study”

World Health Organization

INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM
SEARCH PORTAL

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Back to Search

1 trial found for: the GAS study

Show 10 records per page

Recruitment status	Main ID	Public Title	Date of Registration
Recruiting	ACTRN12606000441516	A multi-site randomised controlled trial comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants	16/10/2006

On WHO Portal Site: Title Field Search for "Neurodevelopmental Outcome"

World Health Organization

INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM

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Back to Search | Sort by: Date of registration | 10 records for 7 trials found! (What is this?)

Show 10 records per page

Recruitment status	Main ID	Public Title	Date of Registration
Recruiting	NCT00809055	Magnetic Resonance Imaging (MRI) and Neurodevelopmental Outcomes in Preterm Infants Following Administration of High-Dose Caffeine	15/12/2008
Recruiting	NCT00756600	A Multi-Site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in Infants	18/09/2008
Recruiting	NCT00713635	Prenatal Effects of Congenital Heart Disease (CHD) on Neurodevelopmental Outcome	09/07/2008
Recruiting	NCT00464100	Near-Infrared Spectroscopy (NIRS) Neurodevelopmental Outcomes	18/04/2007
Recruiting	ACTRN12606000441516	A multi-site randomised controlled trial comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants	16/10/2006
Recruiting	NTR364	Effect of early fatty acid status on neurodevelopmental outcome at 9 years.	12/09/2005
Recruiting	NTR306	The effect of treatment of neonatal electrographic seizures, detected with the continuous cerebral function monitoring, with respect to occurrence of postneonatal epilepsy and neurodevelopmental outcome.	09/09/2005

Problems with Published Studies

- Incomplete reporting of Outcome Measures
  - Unacknowledged changes
  - Omissions
- Unacknowledged changes to Analysis Population
  - "missing participants"
- Incomplete reporting of AEs, e.g.,
  - Only "attributable" or "clinically significant"

Full Text View | Tabular View | Study Results | Related Studies

Brief Descriptive Title of Clinical Trial

Study Recruitment Status

Information provided by Organization

Study Type:	Interventional
Study Design:	Randomized, Double Masked, Placebo Control, Parallel Assignment
Interventions:	Drug: Drug A; Drug: Drug B

Participant Flow

Recruitment Details – Key information relevant to the recruitment process for the overall study, such as dates of the recruitment.

Pre-Assignment Detail – Significant events and approaches for the overall study following participant enrollment, but prior to assignment.

Overall Study

	Drug A	Drug B	Placebo
STARTED			
COMPLETED			
Not Completed			
Lost to Follow-up			
Adverse Event			

Baseline Characteristics

	Drug A	Drug B	Placebo	Total
Number of Participants				
Age				
Gender				
Female				
Male				

Outcome Measures

Primary Outcome Measure

Measure Name	
Measure Description	
Time Frame	

Population Description – Explanation of how the number of participants for analysis was determined.

Measured Values

	Drug A	Drug B	Placebo
Number of Subjects			
Primary Outcome Measure			

Statistical Analysis for Primary Outcome Measure

Groups	
Method	
P-Value	
Mean Difference	
95% Confidence Interval	

Additional Details About the Analysis – e.g., null hypothesis, power calculation, and whether the p-value is adjusted for multiple comparisons

More Information

Certain Agreements – Information about restrictions on the ability of the principal investigator to disseminate trial data after trial completion

Limitations and Caveats – Limitations of the study, such as early termination leading to small numbers of subjects analyzed

Results Point of Contact – Phone and/or email for additional information about the results

4 Scientific Modules

- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Adverse Events
- Other, including "Certain Agreements"

Collapse Section

Serious Adverse Events

	Intravitreal Aflibercept Injection (IAI) (Baseline to Week 24)	Sham Treatment (Baseline to Week 24)	IAI to IAI (Week 24 to Week 100)	Sham Treatment to IAI (Week 24 to Week 100)
Total # participants affected/at risk	**6/114 (5.26%)**	**6/74 (8.11%)**	**20/110 (18.18%)**	**14/60 (23.33%)**
Blood and lymphatic system disorders				
Anaemia * A [1]				
# participants affected/at risk	1/114 (0.88%)	0/74 (0%)	0/110 (0%)	1/60 (1.67%)
Neutropenia * A [2]				
# participants affected/at risk	0/114 (0%)	0/74 (0%)	0/110 (0%)	1/60 (1.67%)
Pernicious anaemia * A [3]				
# participants affected/at risk	0/114 (0%)	0/74 (0%)	0/110 (0%)	1/60 (1.67%)
Cardiac disorders				
Acute myocardial infarction * A [4]				
# participants affected/at risk	0/114 (0%)	1/74 (1.35%)	0/110 (0%)	0/60 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA Version 13.1
[1] Non-Ocular AE
[2] Non-Ocular AE
[3] Non-Ocular AE
[4] Non-Ocular AE

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PLOS | MEDICINE

Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals

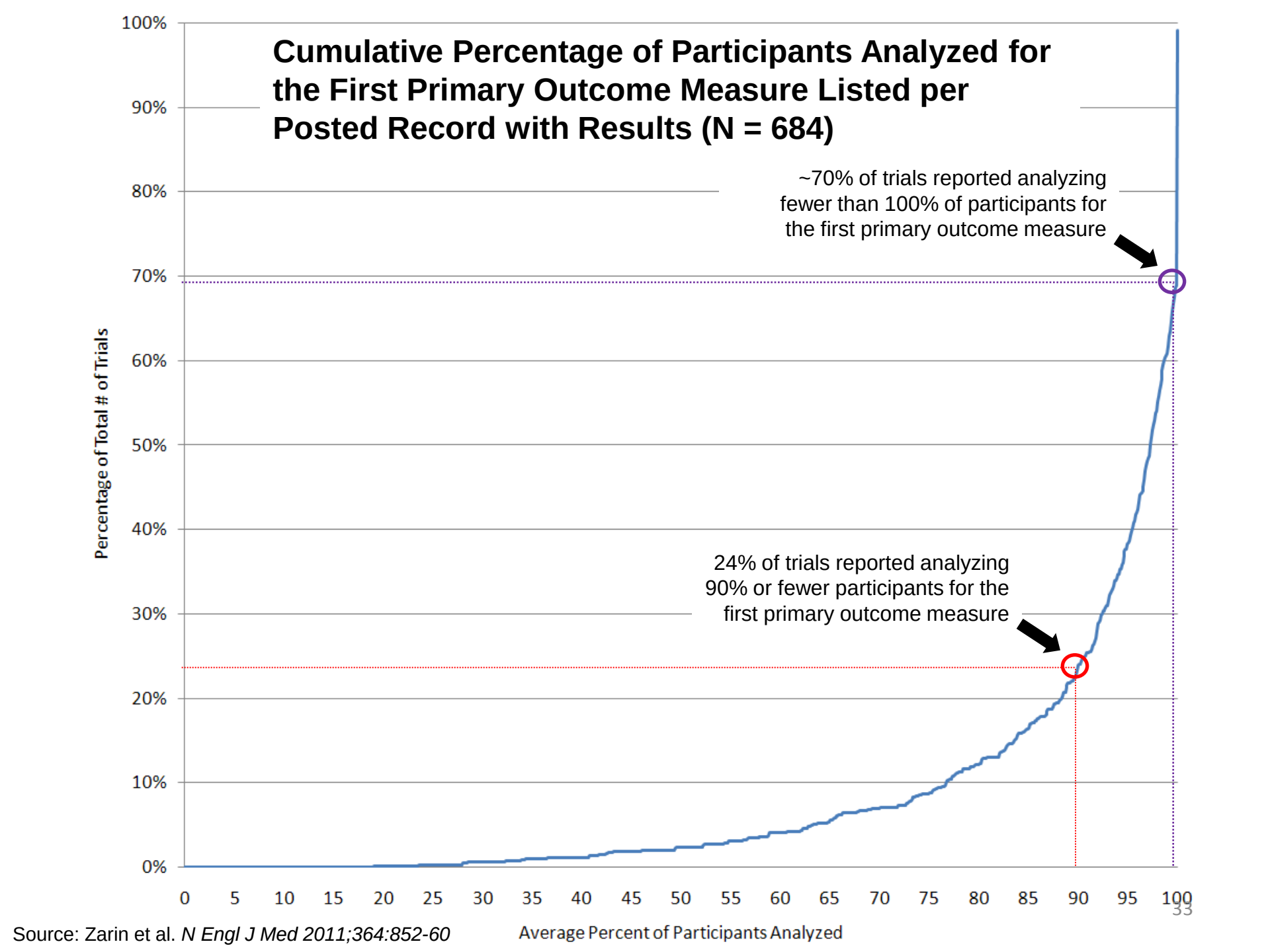
Carolina Riveros[1,2,3], Agnes Dechartres[1,2,3]*, Elodie Perrodeau[1,3], Romana Haneef[1,3], Isabelle Boutron[1,2,3,4], Philippe Ravaud[1,2,3,4,5]

1 INSERM U738, Paris, France, **2** Université Paris Descartes—Sorbonne Paris Cité, Paris, France, **3** Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France, **4** French Cochrane Centre, Paris, France, **5** Mailman School of Public Health, Columbia University, New York, New York, United States of America

Findings: "Reporting was significantly more complete at ClinicalTrials.gov than in the published article for the flow of participants (64% versus 48% of trials, p,0.001), efficacy results (79% versus 69%, p = 0.02), adverse events (73% versus 45%, p,0.001), and serious adverse events (99% versus 63%, p,0.001)."

Conclusions: "Our results highlight the need to search ClinicalTrials.gov for both unpublished and published trials. Trial results, especially serious adverse events, are more completely reported at ClinicalTrials.gov than in the published article."

PLoS Med. 2013 10(12): e1001566



Source: Zarin et al. *N Engl J Med 2011;364:852-60*

BMJ open
accessible medical research

Haphazard reporting of deaths in clinical trials: a review of cases of ClinicalTrials.gov records and matched publications–a cross-sectional study

Amy Earley,[1] Joseph Lau,[2] Katrin Uhlig,[1,3]

To cite: Earley A, Lau J, Uhlig, K. Haphazard reporting of deaths in clinical trials: a review of cases of ClinicalTrials.gov records and matched publications–a cross-sectional study. *BMJ Open* 2013;**3**:e001963. doi:10.1136/bmjopen-2012-001963

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-001963).

ABSTRACT

Context: A participant death is a serious event in a clinical trial and needs to be unambiguously and publicly reported.

Objective: To examine (1) how often and how numbers of deaths are reported in ClinicalTrials.gov records; (2) how often total deaths can be determined per arm within a ClinicalTrials.gov results record and its corresponding publication and (3) whether counts may be discordant.

Design: Registry-based study of clinical trial results reporting.

Setting: ClinicalTrials.gov results database searched in July 2011 and matched PubMed publications.

Selection criteria: A random sample of ClinicalTrials.gov results records. Detailed review of records with a single corresponding publication.

ARTICLE SUMMARY

Article focus

- We hypothesised that the lack of clear expectations for reporting all deaths in clinical trials give rise to discrepancies in the number of deaths reported across reports of a trial.

Key message

- There is a lack of clarity, consistency and agreement in reporting of deaths in clinical trials which highlights the need for unambiguous templates to standardise reporting of total number of deaths per arm in ClinicalTrials.gov records and more explicit reporting guidelines for peer-reviewed publications.

Strengths and limitations of this study

BMJ Open. 2013 Jan 18;3(1).

Some Suggestions

- Enforce registration and use NCT # in communications
- Ask sponsors for listings of all trials, along with registration numbers
- Signal seriousness of registration details; follow-up on discrepancies
- Consider methods of disseminating “code names” and other informal naming conventions

Weight-Loss Efficacy of Lorcaserin (Belviq) and Phentermine plus Extended-Topiramate (Qsymia) at 1 Year.*		
Drug, Study, and Treatment	Mean Percentage Change in Body Weight (Mean Efficacy Criterion)	Proportion of Pa ≥5% of Bod (Categorical Effi
Belviq†		
Studies 1 and 2 combined‡		
10 mg BID	−5.8	47
Placebo	−2.5	23
Study 3		
10 mg BID	−4.5	38
Placebo	−1.5	16
Qsymia§		
Study 1		
15 mg/92 mg	−10.9	67
Placebo	−1.6	17
Study 2		
7.5 mg/46 mg	−7.8	62
15 mg/92 mg	−9.8	70
Placebo	−1.2	21

Unambiguous Identification of Obesity Trials

TO THE EDITOR: Colman et al. (Oct. 25 issue)[1] describe trial results underlying approval of two weight-management drugs by the Food and Drug Administration. However, their table included noninformative terms (e.g., "study 1") without citing publications or ClinicalTrials.gov records. The materials that were referenced[2,3] used only acronyms (e.g., BLOOM) and internal identifiers (e.g., OB-301) — neither of which could be linked to the terms in the table. Using ClinicalTrials.gov (www.clinicaltrials.gov), we identified six studies of lorcaserin for obesity[4] and nine studies of phentermine and topiramate for obesity[5] (as of October 15, 2012). Only Colman et al. could confirm the likely matches (Table 1).

This is an important example of why listing ClinicalTrials.gov identifiers (NCT numbers) would provide unambiguous access to trial-design infor-

Table 1. Different Identifiers for the Same Clinical Studies.*

Drug, Identifier Used by Colman et al., and Identifier Used in References Cited by Colman et al.	Probable ClinicalTrials.gov Identifier	Publication (PubMed Identifier) Associated with Probable ClinicalTrials.gov Identifier
Belviq		
Studies 1 and 2 combined		
BLOOM	NCT00395135	Smith et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010; 363:245-56 (20647200)
BLOSSOM	NCT00603902	Fidler et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab 2011; 96:3067-77 (21795446)
Study 3		
BLOOM-DM	NCT00603291	O'Neil et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20:1426-36 (22421927)
Qsymia		
Study 1		
OB-302	NCT00554216	NA
Study 2		
OB-303	NCT00553787	Gadde et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial. Lancet 2011;377:1341-52 (21481449)

* BLOOM denotes Behavioral Modification and Lorcaserin for Overweight and Obesity Management, BLOOM-DM Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus, BLOSSOM Behavioral Modification and Lorcaserin Second Study for Obesity Management, and NA not applicable.

Source: Zarin DA, Tse T. N *Engl J Med*. 2013; 368:580-1