A Conceptual Framework of Clinical Research Transparency

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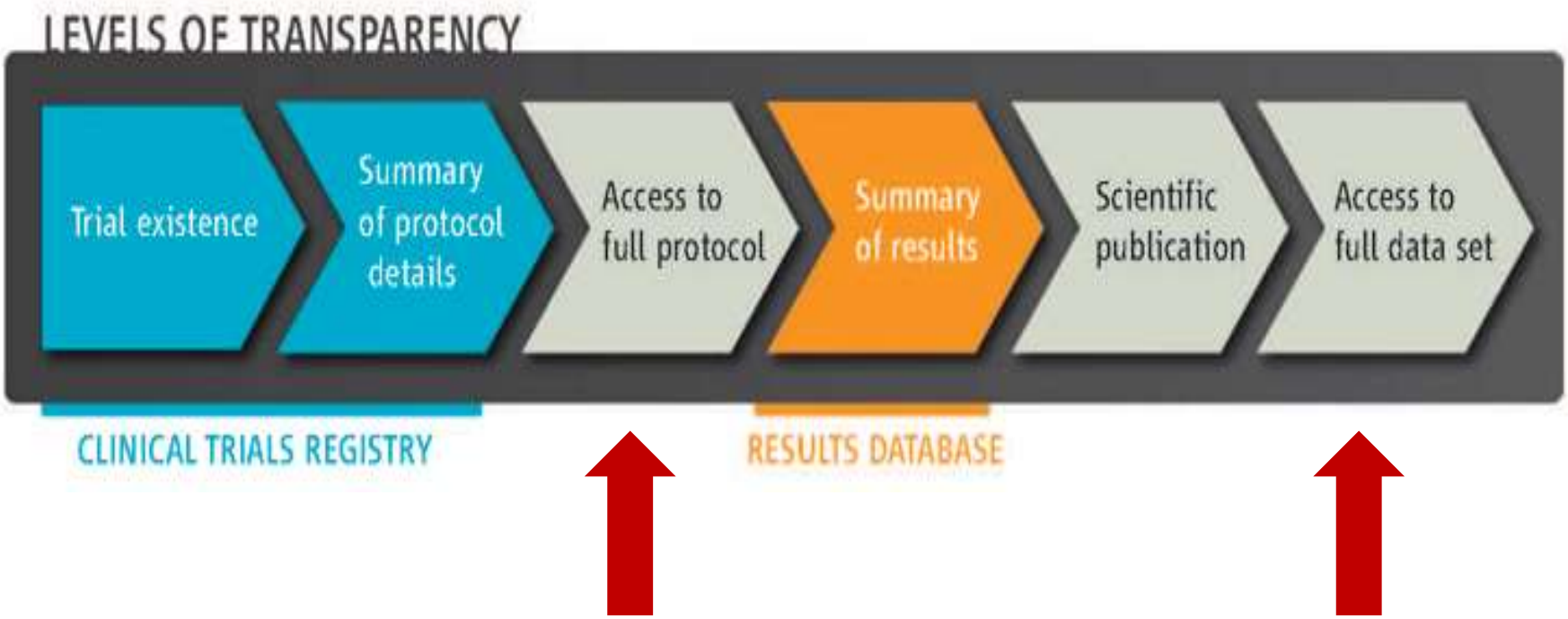
Overview

Levels of Transparency Circa 2008

Zarin DA, Tse T. *Science*. 2008.

Levels of Transparency
Where We Are Headed Today



Clinical Study Reports (CSRs)
Individual Participant-Level Data (IPD)

Zarin DA, Tse T. *Science*. 2008.

Types of Clinical Trial Data

- Participant Level Data
  - Uncoded data
  - Abstracted
  - Coded
  - Computerized
  - Edited/cleaned
  - Analyzable
- Summary (aggregated) Data
  - Analyzed/summary
    - CSRs
    - Summary Results Database

Three Key Problems

- Not all trials are published
- Publications do not always include all prespecified outcome measures
- Unacknowledged changes are made to the trial protocol that would affect the interpretation of the findings
  - e.g., changes to the prespecified outcome measures

Current Status

- Registration
  - Has reached a cultural tipping point
  - > 350 new trials/week at ClinicalTrials.gov
  - Provides a window into the “CRE”; many published analyses of data
- Summary Results Reporting
  - Still in early stages—incomplete adherence to policies
  - 100 trials/week; 50% without publications
  - Early stages of research

Lessons from ClinicalTrials.gov

- Registration
  - Inconsistent adherence to protocols
  - Continued evidence of selective publication
  - Evidence of selective reporting of outcomes
- Results Database
  - Lack of clarity about who is in charge of the science
  - Data analysis practices are not always rigorous
  - Subjects (and data) are commonly left out of analyses

arm, open, non-randomized

Categories		Oncology	Other specialties
Interventional Model	Single arm	65%	31%
	Parallel	32%	56%
	Crossover/Factorial	3%	13%
Allocation	Non-Randomized	64%	23%
	Randomized	36%	77%
Masking	Open	88%	47%
	Double Blind	9%	39%
	Single Blind	3%	13%

Initial Assumptions About ClinicalTrials.gov Requirements

- Required data are generated routinely after a clinical trial
  - Required reporting based on the protocol for each trial
  - Required data would be necessary to understand the results of the trial
  - Required data would be necessary to write a journal article
- Burden of reporting would be mainly due to data entry and time requirements

Our Initial Assumptions Were Wrong!

- Protocol may be vague, or may not be followed
- Summary Data NOT always readily available, even for trials that had been published
  - For many trials, nobody could explain the structure or analysis
- There is not an objective, easy to describe route from initial participant level data to the summary data—Many people and many judgments are involved

Summary Data: Journal vs. ClinicalTrials.gov

- 110 matched “pairs” of ClinicalTrials.gov results entries and publications
- 82% had at least one important discrepancy, e.g.
  - 24% in data for primary outcome measure
    - Numerator
    - Denominator
  - 30% in Serious Adverse Event data

Status of Publication Bias?

Restoring Invisible and Abandoned Trials (RIAT)

BMJ

BMJ 2013;346:f2865 doi: 10.1136/bmj.f2865 (Published 13 June 2013)

ANALYSIS

Restoring invisible and abandoned trials: a call for people to publish the findings

OPEN ACCESS

Unpublished and misreported studies make it difficult to determine the true value of a treatment. **Peter Doshi and colleagues** call for sponsors and investigators of abandoned studies to publish (or republish) and propose a system for independent publishing if sponsors fail to respond

Peter Doshi *postdoctoral fellow*[1], Kay Dickersin *professor, director*[2 3 4], David Healy *professor of psychiatry*[5], S Swaroop Vedula *postdoctoral fellow*[6], Tom Jefferson *researcher*[7]

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore; [3]Center for Clinical Trials, Johns Hopkins Bloomberg School of Public Health ; [4]US Cochrane Center, Baltimore; [5]Bangor University, Bangor, UK; [6]Johns Hopkins University, Baltimore; [7]Cochrane Collaboration, Rome, Italy

RIAT 116 CSRs Listed in Table 1

Tables

Table 1| **Clinical study reports in our possession**

Trial identifiers	No of participants	Year completed*	Published
Amgen epoetin alfa study 930107	1265	1997§	Yes[36,37]
AstraZeneca quetiapine study 015	331	1995	
AstraZeneca quetiapine study 041	532	2002	
AstraZeneca quetiapine study 049	542	2003	Yes[66]
AstraZeneca quetiapine study 135	509	2005	
AstraZeneca quetiapine study 125	574	2005	Yes[67]
AstraZeneca quetiapine study 127	1953	2006	
AstraZeneca quetiapine study 126	1461	2006	
Bristol-Myers Squibb clopidogrel study CAPRIE	19185	1996	Yes[68]
Bristol-Myers Squibb clopidogrel study CURE	12562	2000	Yes[69]
Bristol-Myers Squibb clopidogrel study CLARITY	3491	2005	Yes[70,71]
Bristol-Myers Squibb clopidogrel study COMMIT	45852	2005	Yes[72]
Bristol-Myers Squibb clopidogrel study PICOLO	92	2006	Yes[73]
Bristol-Myers Squibb aripiprazole study CN138135	480	2006	Yes[74]
GSK H5N1 pandemic influenza vaccine studies H5N1-008, H5N1-011 EXT 008	5075	2006	Yes[75]
GSK paroxetine study 329	275	1998	Yes[76]
GSK paroxetine study 377	286	1998	Yes[77]
GSK paroxetine study 453	339	1998	Yes[78]
GSK paroxetine study 511	125	1999	Yes[79]
GSK paroxetine study 701	206	2001	Yes[80]
GSK paroxetine study 704	207	2001	Yes[81]
GSK paroxetine study 715	62	2001	Yes[82]
GSK paroxetine study 676	322	2001	Yes[83]
GSK paroxetine study 716	265	2002	Yes[84]
GSK zanamivir study 167-101	319	2000	
GSK zanamivir study 167T3-11	145	2001	
GSK zanamivir study JNAI-01	116	1995	Yes[85]
GSK zanamivir study JNAI-04	50	1996	
GSK zanamivir study JNAI-07	333	1999	
GSK zanamivir study NAI30008	525	2000	Yes[86]
GSK zanamivir study NAI30009	471	1999	Yes[87]
GSK zanamivir study NAI30010	1158	1999	Yes[88]
GSK zanamivir study NAI30011	466	2000	
GSK zanamivir study NAI30012	358	2001	
GSK zanamivir study NAI30015	588	2001	Yes[89]
GSK zanamivir study NAI30020	334	2001	
GSK zanamivir study NAI30028	266	2001	
GSK zanamivir study NAI30031	1291	2001	Yes[90]
GSK zanamivir study NAI30034	3363	2001	Yes[91]
GSK zanamivir study NAIA2005	220	1995	Yes[92]
GSK zanamivir study NAIA2006	64	1995	Yes[93]
GSK zanamivir study NAIA2010	257	1997	Yes[94]
GSK zanamivir study NAIA3002	777	1998	Yes[95]
GSK zanamivir study NAIA3003	1116	2000	Yes[96]

Table 1 (continued)

Trial identifiers	No of participants	Year completed*	Published	No of pages†	Level of access to trial data: Trial protocol	IPD	CRFs
GSK zanamivir study NAIA3004	489	2000	Yes[97]	391	No	No	No
GSK zanamivir study NAIA3005	1137	1998	Yes[98]	358	No	No	No
GSK zanamivir study NAIA32006	1256	1998	Yes[99]	527	No	No	No
GSK zanamivir study NAIA32009	577	1998	Yes[100]	364	No	No	No
GSK zanamivir study NAIB2005	198	1995	Yes[101]	372	No	No	No
GSK zanamivir study NAIB2006	115	1995		240	No	No	No
GSK zanamivir study NAIB2007	554	1996		461	No	No	No
GSK zanamivir study NAIB3001	465	1997	Yes[102]	465	No	No	No
GSK zanamivir study NAIB3002	356	1998	Yes[103]	454	No	No	No
GSK zanamivir study PE-01	44	1996		392	No	No	No
Merck rofecoxib study 078	1457	2003		392	Yes	No	No
Novartis Fluad study V87P1	486	2007	Yes[104]				
Novartis Fluad study V87P6	471	2008	Yes[105]				
Pfizer atorvastatin study 881060	326	1998					
Pfizer gabapentin study 879-251	87	1998					
Pfizer gabapentin study 945-215**	165	1997	Yes[106]				
Pfizer gabapentin study 945-259	117	1997	Yes[107]				
Pfizer gabapentin study 945-220	145	1998	Yes[108]				
Pfizer gabapentin study 945-217	157	1999					
Pfizer gabapentin study 1032-001	483	1999					
Pfizer gabapentin study 945-224**	325	1999					
Pfizer gabapentin study 945-306**	307	2000	Yes[109]				
Pfizer gabapentin study 1035-001	329¶	2000					
Pfizer gabapentin study 1032-004	206	2000					
Pfizer gabapentin study 1032-002	282	2000					
Pfizer gabapentin study 1035-002	206	2000					
Pfizer gabapentin study 1032-003	212	2000					
Pfizer gabapentin study 945-271**	120	2001	Yes[110]				
Pfizer gabapentin study 945-411**	339	2001	Yes[111]				
Pfizer gabapentin study 945-278**	121	2002	Yes[112]				
Pfizer gabapentin study A945-1002**	389	2003					
Pfizer gabapentin study 945-291	42	2004	Yes[113]				
Pfizer reboxetine study 9	50	1989					
Pfizer reboxetine study 91	56	1990	Yes[114]				
Pfizer reboxetine study 8	258	1991‡					
Pfizer reboxetine study 33a	50	1991					
Pfizer reboxetine study 17	256	1992					
Pfizer reboxetine study 15	326	1992					
Pfizer reboxetine study 13	358	1993					
Pfizer reboxetine study 16	168	1993	Yes[115]				
Pfizer reboxetine study 26	347	1994					
Pfizer reboxetine study 49	212	1998					
Pfizer reboxetine study 50	460	1999					
Pfizer reboxetine study 45	350	1999					
Pfizer reboxetine study 34	128	2000					
Pfizer reboxetine study 47	774	2000	Yes[116]				
Pfizer reboxetine study 46	767	2000					

Table 1 (continued)

Trial identifiers	No of participants	Year completed*	Published	No of pages†	Level of access to trial data: Trial protocol	IPD	CRFs
Pfizer reboxetine study 52	325	2000	Yes[117]	92	No	No	No
Pfizer reboxetine study 43	359	2001	Yes[121]	80	No	No	No
Pfizer reboxetine study 32	85	2001		88	No	No	No
Pfizer reboxetine study 96	34	2001		52	No	No	No
Pfizer reboxetine study 71	69	2002		316	No	No	No
Pfizer sertraline study 206	12	1983		721	Yes	Yes	No
Roche oseltamivir studies WV15673 WV15697	1562	1998	Yes[118]	804	Yes	No	No
Roche oseltamivir study WV15670	726	1998	Yes[119]	1032	Yes	No	No
Roche oseltamivir study WV15671	629	1998	Yes[120]	1018	Yes	No	No
Roche oseltamivir study NP15757	59	1998	Yes[121]	445	Yes	No	No
Roche oseltamivir study WV15720	60	1998		525	Yes	No	No
Roche oseltamivir study WV15708	395	1998		661	Yes	No	No
Roche oseltamivir study WV15707	27	1998		459	Yes	No	No
Roche oseltamivir study M76001	1459	1998		1514	Yes	No	No
Roche oseltamivir study WV15799	962	1999	Yes[122]	900	Yes	No	No
Roche oseltamivir study WV15825	572	1999	Yes[123]	575	Yes	No	No
Roche oseltamivir study WV15758	698	1999	Yes[124]	1126	Yes	No	No
Roche oseltamivir studies WV15812 WV15872	404	1999		683	Yes	No	No
Roche oseltamivir studies WV15759 WV15871	335	1999	Yes[125]	1121	Yes	No	No
Roche oseltamivir studies WV15876 WV15819 WV15878	741	2000		973	Yes	No	No
Roche oseltamivir study WP16263	400	2000	Yes[126]	8546	Yes	Yes	No
Roche oseltamivir study WV16193	809	2001	Yes[127]	894	Yes	No	No
Roche oseltamivir study NV16871	328	2004		614	Yes	No	No
Rowbotham arthroscat study MA-CT-10-002	80	2010		4924	Yes	Yes	Part
Takeda pioglitazone study PNFP-001	408	1998	Yes[128]	2486	Yes	No	No

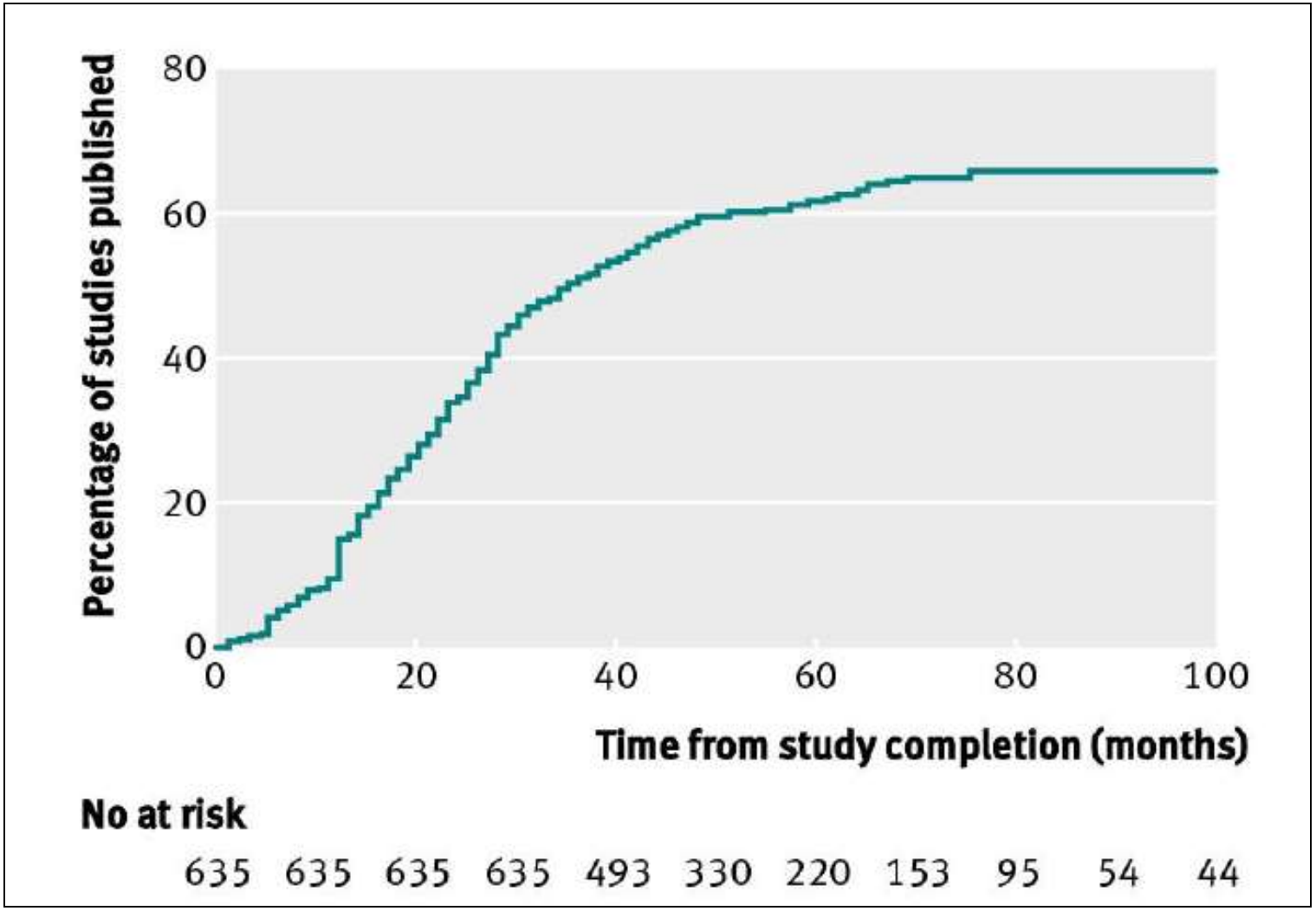
CSR=clinical study report; CRFs=case report forms; IPD=individual participant data
*Date of last participant follow-up (if known).
†No of pages in our possession. Not all reports were complete.
‡Date of CSR (date of last participant follow up is unknown).
§Scheduled end date documented in the CSR (the trial was stopped early).
¶We also have an addendum comprising 101 patients, completed in March 2006

Doshi P et al. *BMJ* 2013; 346:f2865

39% Table 1 CSRs Not Published

- 45 of 116 (39%) Trials Marked as “Not Published”
  - Involve data from nearly 12,500 human volunteers

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

Summary Data

- Decision makers (other than FDA) rely on summary data
  - Clinical decision making
  - Policy decision making (e.g., payors)
- Characteristics of Summary Data
  - Convenient
  - Assume they are accurate reflection of underlying participant level data—(assume little room for subjectivity)
- Basis of statistical analyses
- Basis of point estimates

However…

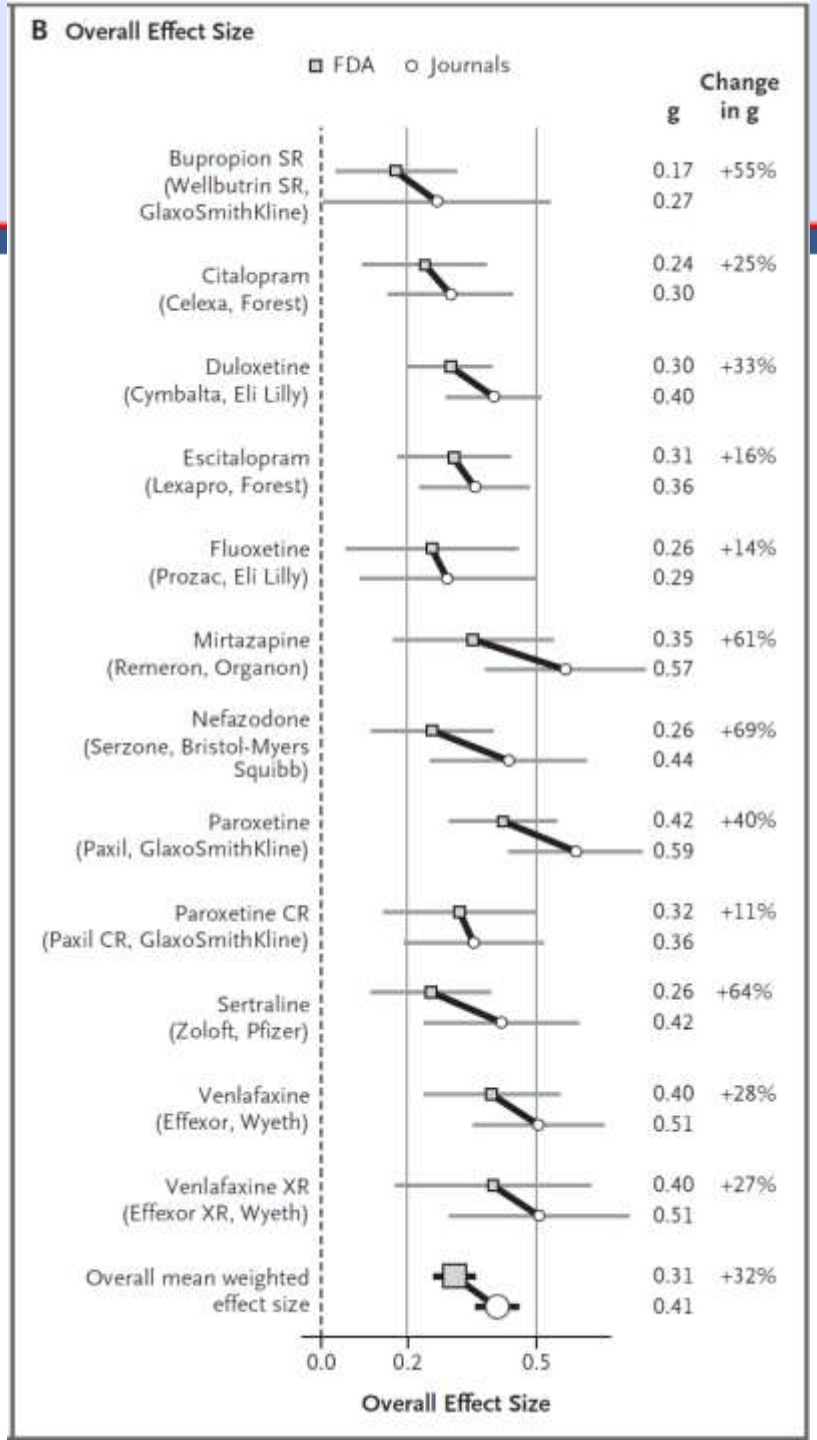
Summary Data May Not Always be Accurate Reflection of Participant Level Data

This is a big problem!

Figure 3. Mean Weighted Effect Size According to Drug, … and Data Source.

Values for effect size are expressed as Hedges's g (the difference between two means divided by their pooled standard deviation). Effectsize values of 0.2 and 0.5 are considered to be small and medium, respectively.

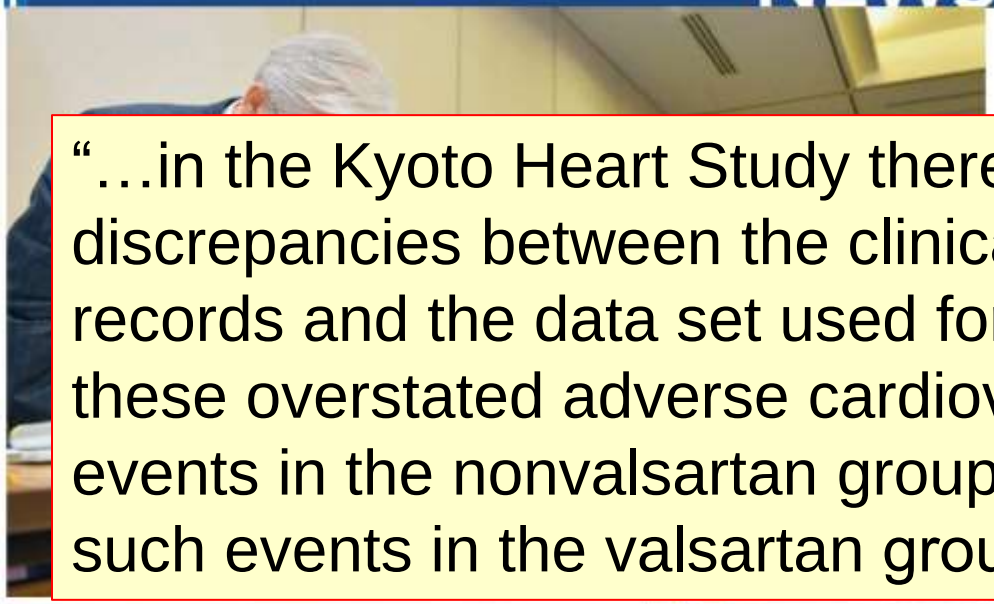
Overall effect-size values (i.e., based on data from the FDA for published and unpublished studies combined), as compared with effect-size values based on data from corresponding published reports… For each drug, the effect-size value based on published literature was higher than the effect-size value based on FDA data, with increases ranging from 11 to 69%. For the entire drug class, effect sizes increased by 32%.



Source: *N Engl J Med* 2008;358:252-60

KYOTO Heart Study (NCT00149227)

NEWS & ANALYSIS



"…in the Kyoto Heart Study there were 34 discrepancies between the clinical medical records and the data set used for analysis; these overstated adverse cardiovascular events in the nonvalsartan group and missed such events in the valsartan group."

JAPAN

Tampered Data Cast Shadow on Drug Trial

TOKYO—In a scandal reverberating across Japan's biomedical research landscape, a university in Kyoto last week acknowledged data manipulation in a university-run clinical trial for a blockbuster hypertension drug, valsartan. Japanese media have turned the episode

The 4-year study followed 3000 patients given valsartan or alternative medications. A main outcome, reported on 31 August 2009 in the *European Heart Journal*, was that valsartan, which reduces blood pressure by blocking the receptor for the hormone angiotensin, "pre-

FASTTRACK
ESC HOT LINE

morbidity and mortality in
nsive patients with high
KYOTO HEART Study

Björn Dahlöf, and Hiroaki Matsubara

Conclusion

Keywords

Introduction

Retracted

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 31, 2011 VOL. 364 NO. 13

Boceprevir for Untreated Chronic HCV Genotype 1 Infection

Fred Poordad, M.D., Jonathan McCone, Jr., M.D., Bruce R. Bacon, M.D., Savino Bruno, M.D., Michael P. Manns, M.D., Mark S. Sulkowski, M.D., Ira M. Jacobson, M.D., K. Rajender Reddy, M.D., Zachary D. Goodman, M.D., Ph.D., Navdeep Boparai, M.S., Mark J. DiNubile, M.D., Vilma Sniukiene, M.D., Clifford A. Brass, M.D., Ph.D., Janice K. Albrecht, Ph.D., and Jean-Pierre Bronowicki, M.D., Ph.D., for the SPRINT-2 Investigators*

Results: "In the nonblack cohort [n=938], a sustained virologic response was achieved:

- in **125** of the **311** patients (40%) in group 1,
- in **211** of the **316** patients (67%) in group 2 (P<0.001), and
- in **213** of the **311** patients (68%) in group 3 (P<0.001)"

BAC
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METHODS

We conducted a double-blind study in which previously untreated adults with HCV

Los
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B.);
Azienda Ospedaliera Fatebenefratelli e Oftalmico, Milan (S.B.); Medical School of Hannover, Hannover, Germany (M.P.M.);

ORIGINAL CONTRIBUTION

Effect of Adenosine-Regulating Agent Acadesine on Morbidity and Mortality Associated With Coronary Artery Bypass Grafting

The RED-CABG Randomized Controlled Trial

Mark F. Newman, MD
T. Bruce Ferguson, MD
Jennifer A. White, MS
Giuseppe Ambrosio, MD
Joerg Koglin, MD
Nancy A. Nussmeier, MD
Ronald G. Pearl, MD, PhD
Bertram Pitt, MD

Context Ischemia/reperfusion injury remains an important cause of morbidity and mortality after coronary artery bypass graft (CABG) surgery. In a meta-analysis of randomized controlled trials, perioperative and postoperative infusion of acadesine, a first-in-class adenosine-regulating agent, was associated with a reduction in early cardiac death, myocardial infarction, and combined adverse cardiac outcomes in participants undergoing on-pump CABG surgery.

Objective To assess the efficacy and safety of acadesine administered in the perioperative period in reducing all-cause mortality, nonfatal stroke, and severe left ventricular dysfunction (SLVD) through 28 days.

Design, Setting, and Participants The Reduction in Cardiovascular Events by Aca-

Results: "The primary outcome occurred in:

- **75** of **1493** participants (5.0%) in the placebo group and
- **76** of **1493** (5.1%) in the acadesine group

(odds ratio, 1.01 [95% CI, 0.73-1.41])."

We Need Reliable Summary Data

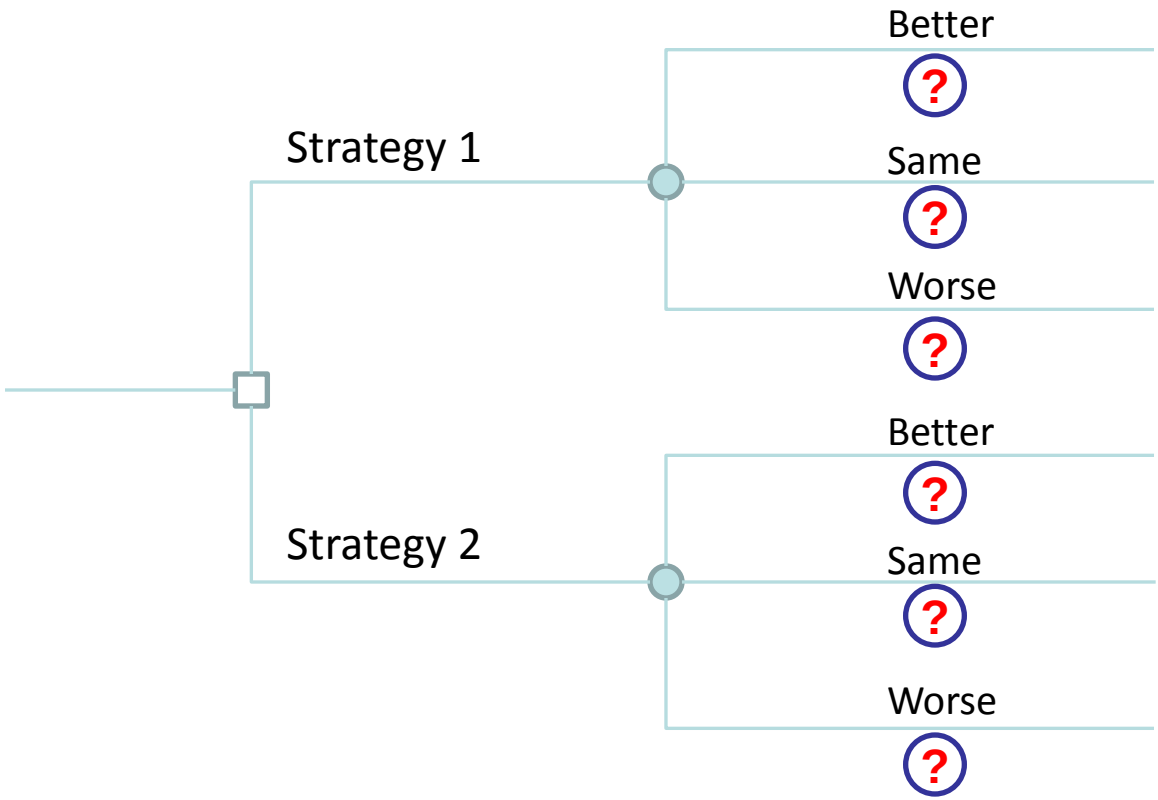
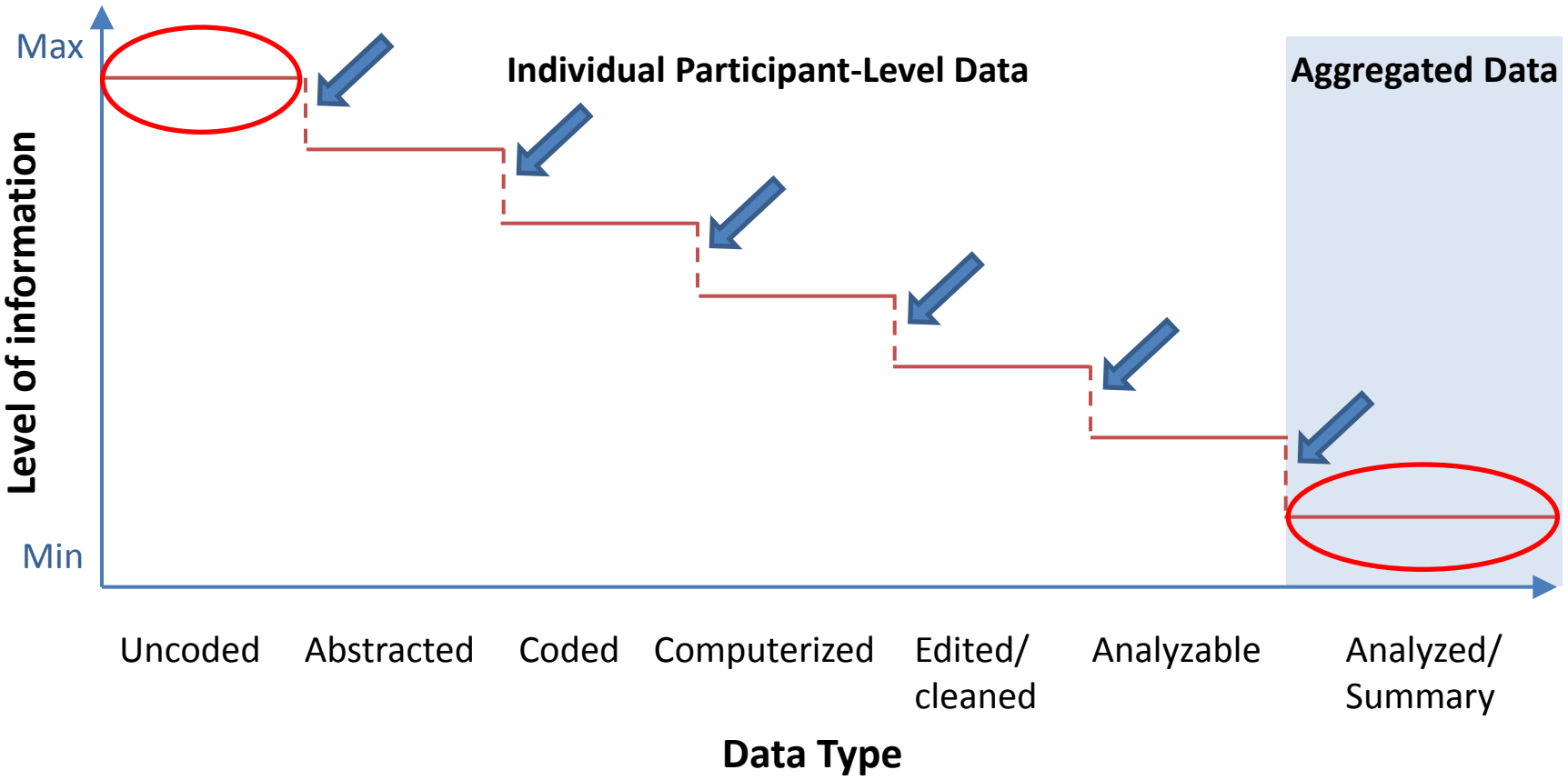


Figure. Information loss as clinical trials data progress from raw uncoded data to summary data



Documents that may help to explain the journey

- Protocol and Amendments
- Investigator Brochure
- Statistical Analysis Plan (SAP)
- Informed Consent Form(s)
- DSMB Reports
- Clinical Study Reports
- AE Reports
- Other ??

Points to Consider

- Decision makers will always need summary data
- The “journey” from initially collected participant-level data to summary data is not completely objective or reliable
- Structured curated data help to mitigate against acts of commission and acts of omission
- Participant-level data might allow for
  - Audit/accountability function
  - Subgroup and other analyses not possible with summary data
  - Pooling of data leading to potential new discoveries
- Non-systematic data release could also generate a new kind of “disclosure bias”

Key Questions to Ask About New Data Disclosure Policies

1. Is “IPD” discussion distracting us from need to ensure summary results of all trials?
2. What is the scope of trials for which participant-level data will be made accessible?
   - Is the policy chipping away at “censored” studies, or adding detail to already exposed studes?
3. Which data (e.g., type, format) and supporting materials will be accessible? (Be precise.)
4. What is the process for obtaining access?
5. How transparent is that process?

Some Additional Thoughts

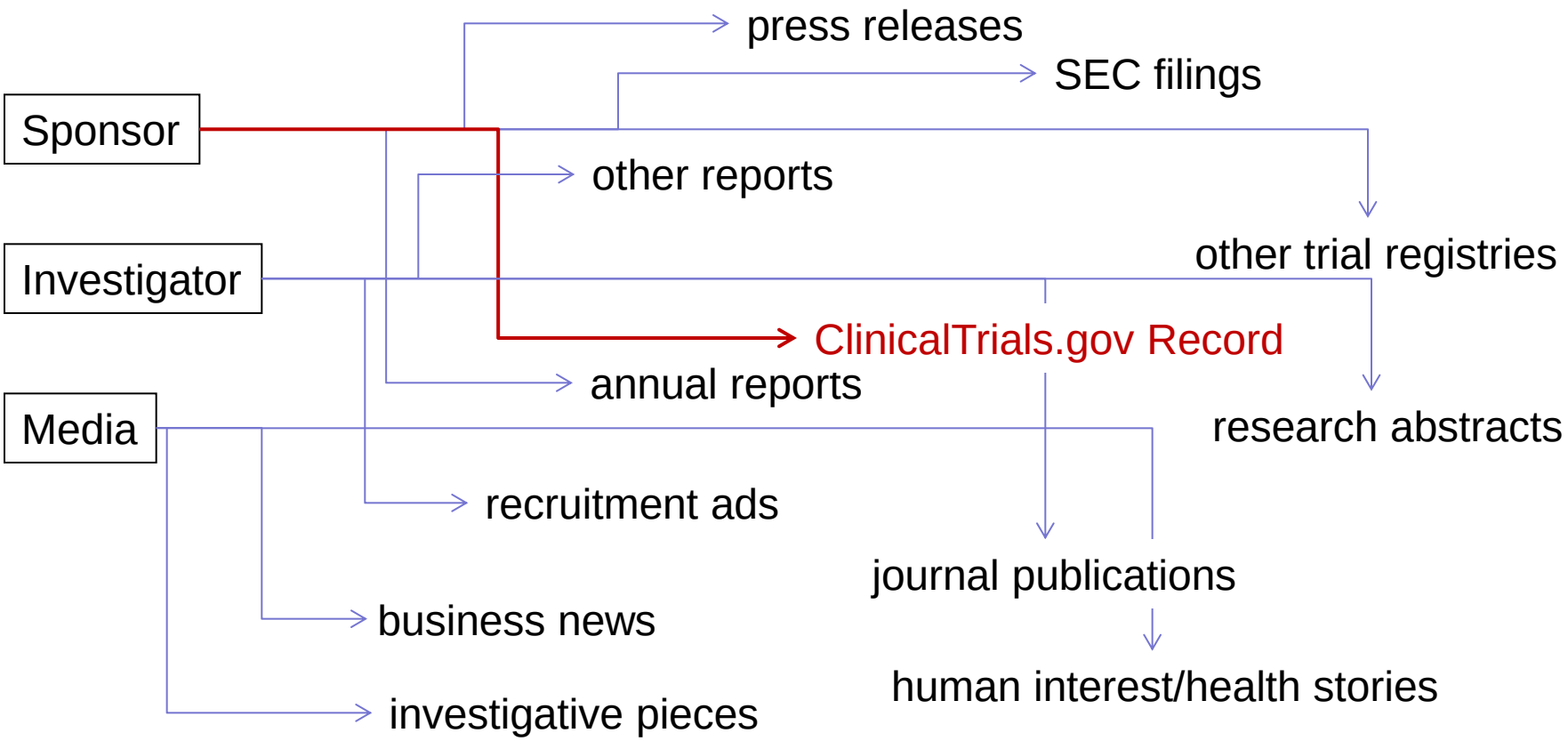
- ClinicalTrials.gov has not solved anything. It is a tool! Trial sponsors must use it—room for improvement
  - Missing trials
  - Suboptimal reporting
- Commit to providing summary data for all trials
- Need to ensure transparency of all analyses (primary and secondary)
- Need to respect trial reporting
  - Academic and other credit
  - Resource requirements

Potential Role for ClinicalTrials.gov

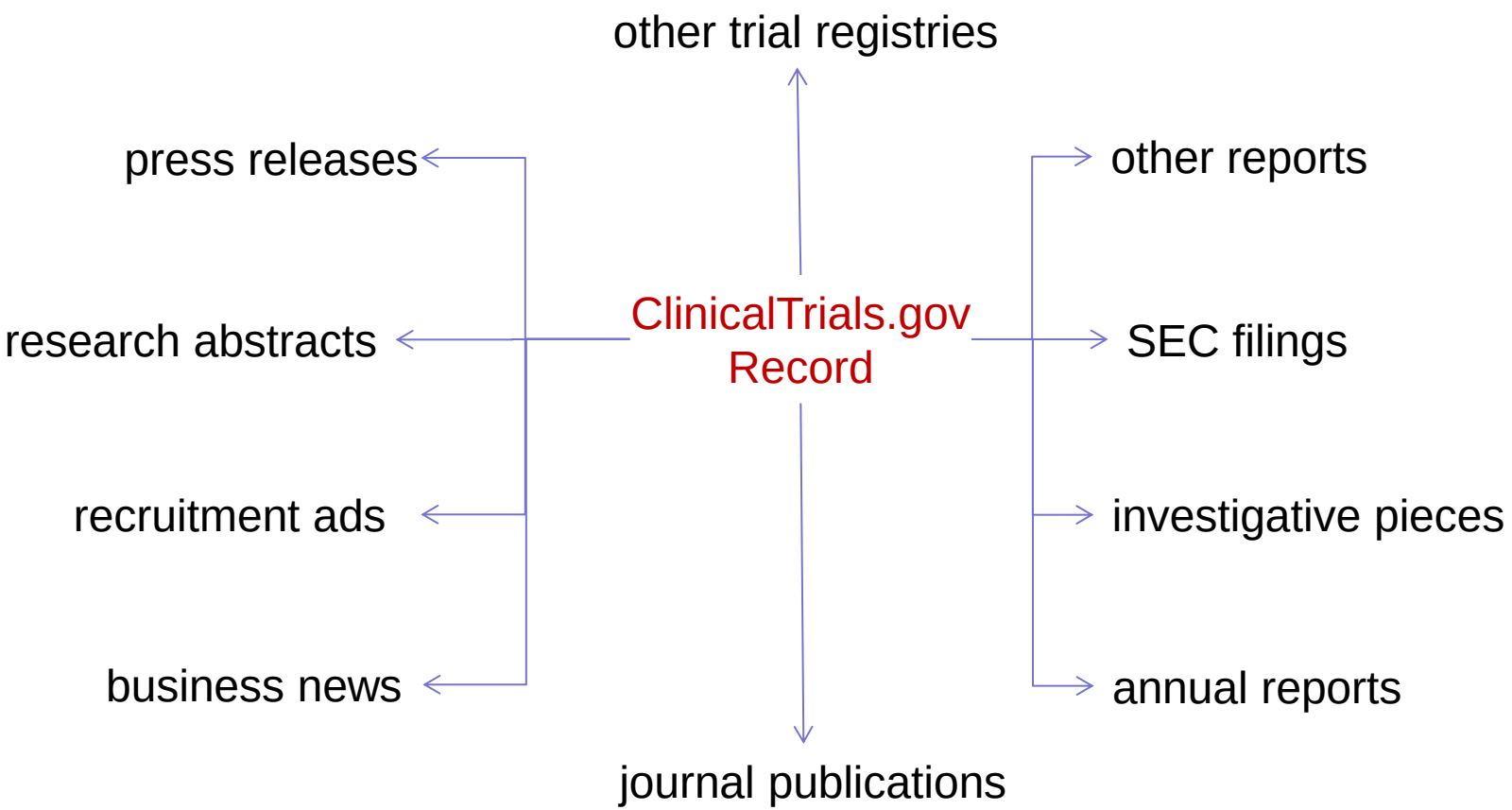
- Provide framework and access to key trial information
  - Registration
  - Results
  - Links
  - Documents
- Provide context for available information
  - List of all trials for given topic
  - Documentation of what information is available for each trial
  - Help to avoid “disclosure biases” of all sorts

"Informational Chaos"
Diffuse, hard-to-access information about a single study

Sample Routes of Dissemination of Information about a Single Study



ClinicalTrials.gov: Informational Scaffold



Big Challenges for Discussion

- Trial participation is legitimate societal need that warrants sacrifice from human volunteers, BUT

- Many trials are being done that will not contribute to medical knowledge (i.e., not useful)
  - Do not address an important question
  - Design cannot support a valid answer
  - Redundant—answer already known
  - No public report of results
- Current system cannot distinguish between “useful” and “not useful” trials.

Big Challenge for Discussion

- Drug and device companies want to protect their investments by keeping data confidential, BUT

- The natural consequence is that other sponsors will need to do their own trials to answer the same questions
  - People do not want to be in trials for which the answer is already known