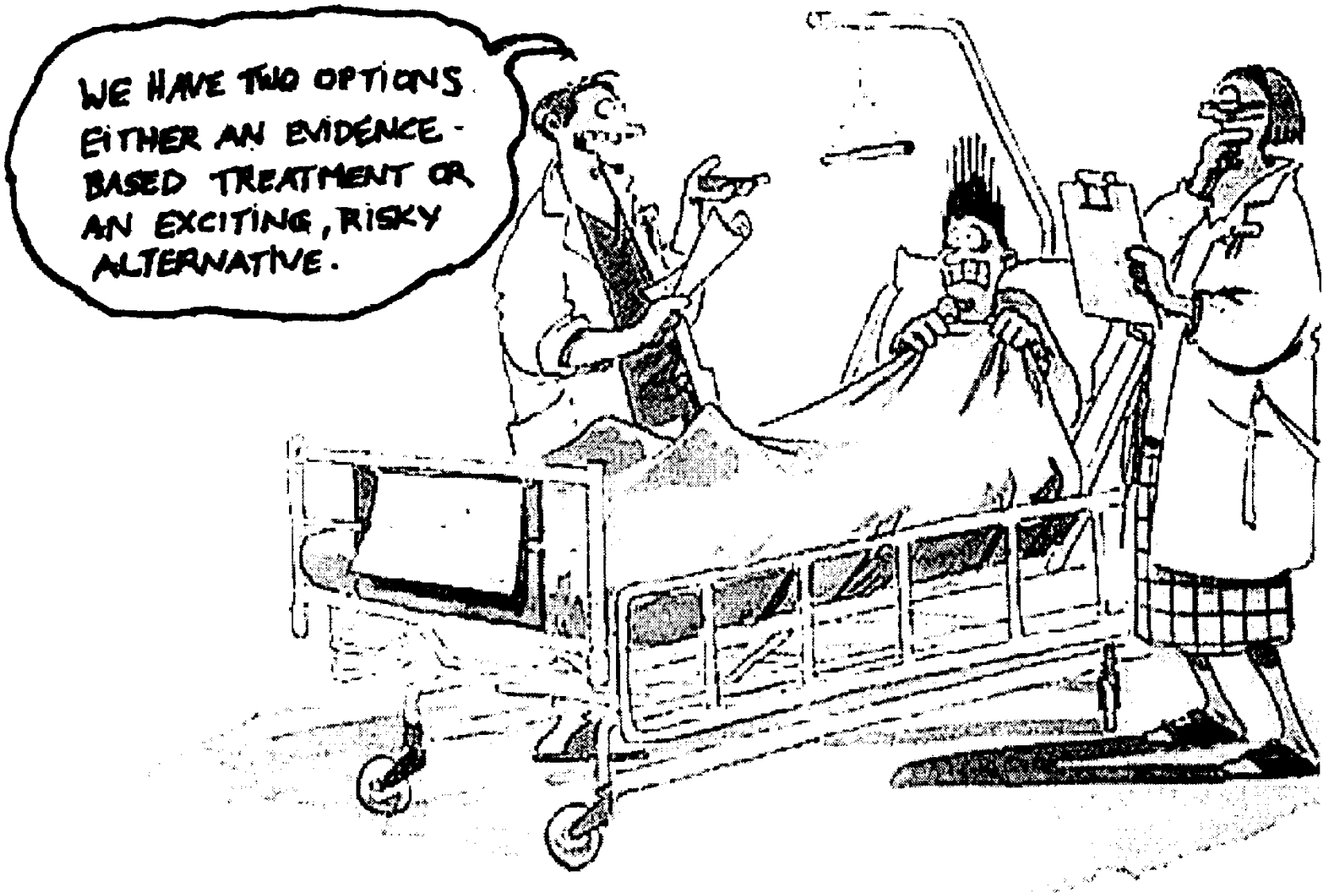
The Limits of Summary Data Reporting: Lessons from ClinicalTrials.gov

Deborah A. Zarin, M.D.
Director, ClinicalTrials.gov
October 2012

Disclaimer

Why Do We Do Clinical Trials?


WE HAVE TWO OPTIONS. EITHER AN EVIDENCE-BASED TREATMENT OR AN EXCITING, RISKY ALTERNATIVE.

Evidence Based Medicine (EBM)

- Clinical and policy decisions should be informed by evidence regarding the benefits, risks and other burdens associated with all possible alternatives.
- Clinical trials are a key component of the body of scientific evidence that must be used to make decisions.
- Most decision makers depend on summary data from journal articles

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

ClinicalTrials.gov

- Registry (est. 2000)
  - At trial inception
  - Contains key protocol details
  - >130,000 trials
- Results Database (est. 2008)
  - After trial completion
  - Summary results
  - >7000 trials

Types of Clinical Trial Data

- Participant Level Data
  - Uncoded data
  - Abstracted
  - Coded
  - Computerized
  - Edited/cleaned
  - Analyzable
- Summary Data
  - Analyzed/summary

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)

ClinicalTrials.gov and Levels of "Transparency"

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

The Results Database

- FDAAA enacted in September 2007
- Results Database launched in Sept 08
- Design based on statutory language and informed by CONSORT and other relevant standards
- Requires reporting of “minimum data set” that was specified in the trial protocol
- Tabular format for data with minimal narrative
- EMA is developing a DB based on our model

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

Review Criteria Overview

- Complete and meaningful entries
  - [“Zarin scale” without further detail; “IOP” without explanation]
- Logic and internal consistency
  - [number of participants must be consistent across modules; time to event must be measured in a unit of time]
- Apparent validity
  - [624 years cannot be the mean age]

Initial Assumptions about ClinicalTrials.gov Data 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

Which of These Data are NOT Used for Writing Journal Articles?

- # Started and Completed Each Arm of Trial
- Age and gender of participants*
- Each prespecified outcome measure*
- Adverse events that were collected*

* Summary statistics only

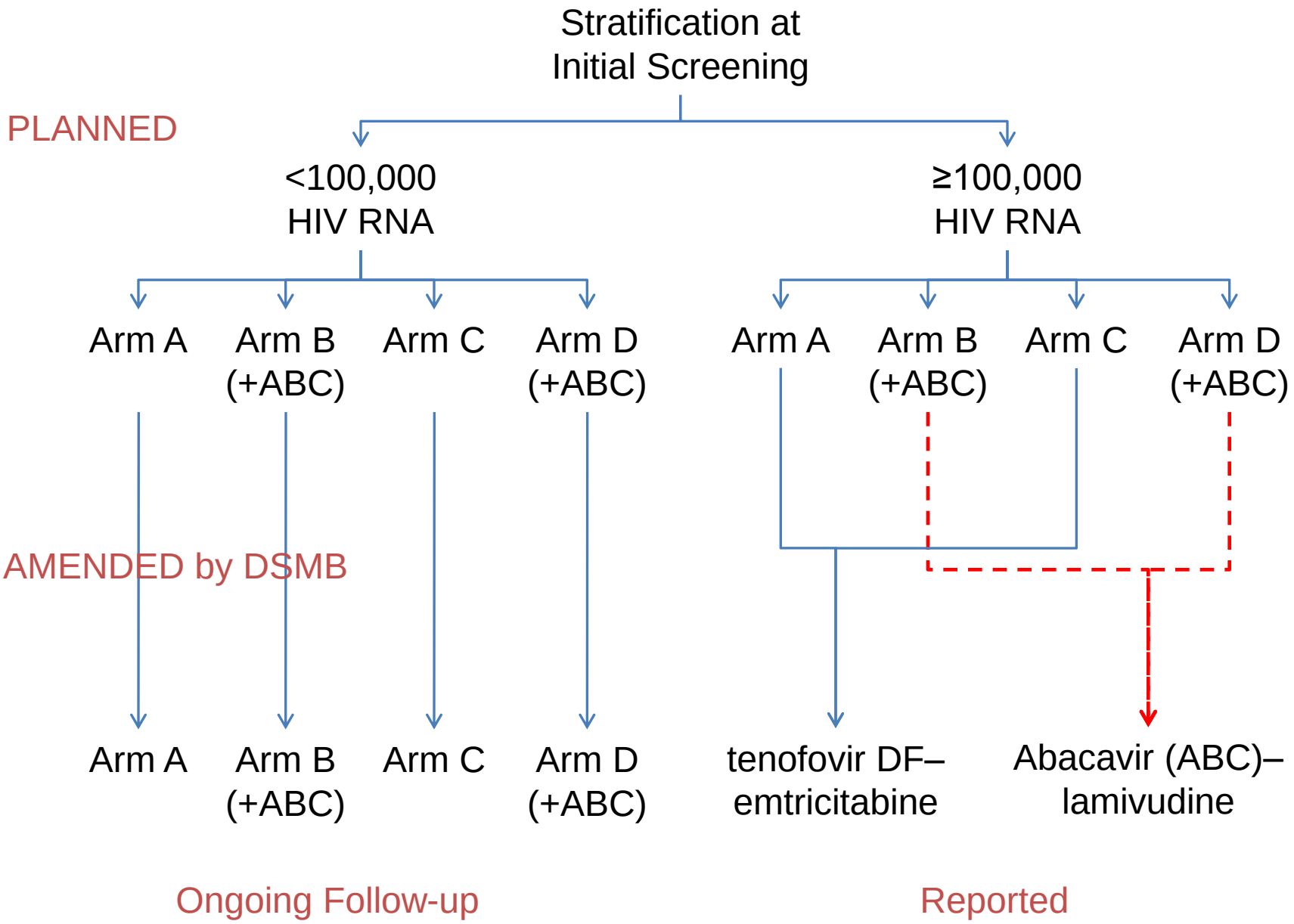
Structural Changes to Studies

- Arms come and go
- Participants come and go
- Participant Flow and Baseline Characteristics Tables describe different population than the Outcomes Tables
- Data providers cannot explain the "denominators"

Table 1. Baseline Characteristics of the Patients.*

Variable	Abacavir–Lamivudine (N = 398)	Tenofovir DF–Emtricitabine (N = 399)	Total (N = 797)
Sex — no. (%)			
Male	331 (83)	345 (86)	676 (85)
Female	67 (17)	54 (14)	121 (15)
Age — yr			
Median	38	40	39
Interquartile range	32–45	32–46	32–45
Age group — no. (%)			
16–19 yr	3 (1)	2 (1)	5 (1)
20–29 yr	77 (19)	68 (17)	145 (18)
30–39 yr	143 (36)	121 (30)	264 (33)
40–49 yr	121 (30)	142 (36)	263 (33)
50–59 yr	41 (10)	54 (14)	95 (12)
>59 yr	13 (3)	12 (3)	25 (3)
Race or ethnic group — no. (%)†‡			
White	170 (43)	202 (51)	372 (47)
Black	112 (28)	94 (24)	206 (26)
Hispanic	103 (26)	93 (23)	196 (25)
Asian or Pacific Islander	5 (1)	5 (1)	10 (1)
Native American or Alaskan Native	1 (<1)	1 (<1)	2 (<1)
Mixed race	7 (2)	3 (1)	10 (1)

Arms	Assigned Interventions
1: Experimental Participants will receive EFV, FTC/TDF, and placebo for ABC/3TC for 96 weeks	Drug: Efavirenz 600 mg tablet taken orally daily Drug: Emtricitabine/Tenofovir disoproxil fumarate 200 mg emtricitabine/300 mg tenofovir disoproxil fumarate tablet taken orally daily Drug: Abacavir/Lamivudine placebo Placebo tablet taken orally daily
2: Experimental Participants will receive EFV, placebo for FTC/TDF, and ABC/3TC for 96 weeks	Drug: Abacavir/Lamivudine 600 mg abacavir/300 mg lamivudine tablet taken orally daily Drug: Efavirenz 600 mg tablet taken orally daily Drug: Emtricitabine/Tenofovir disoproxil fumarate placebo Placebo tablet taken orally daily
3: Experimental Participants will receive RTV-boosted ATV, FTC/TDF, and placebo for ABC/3TC for 96 weeks	Drug: Atazanavir 300 mg tablet taken orally daily Drug: Emtricitabine/Tenofovir disoproxil fumarate 200 mg emtricitabine/300 mg tenofovir disoproxil fumarate tablet taken orally daily Drug: Ritonavir 100 mg tablet taken orally daily Drug: Abacavir/Lamivudine placebo Placebo tablet taken orally daily
4: Experimental Participants will receive RTV-boosted ATV, placebo for FTC/TDF, and ABC/3TC for 96 weeks	Drug: Abacavir/Lamivudine 600 mg abacavir/300 mg lamivudine tablet taken orally daily Drug: Atazanavir 300 mg tablet taken orally daily Drug: Ritonavir 100 mg tablet taken orally daily Drug: Emtricitabine/Tenofovir disoproxil fumarate placebo Placebo tablet taken orally daily


Stratification at
Initial Screening
PLANNED
<100,000
HIV RNA
≥100,000
HIV RNA
Arm A
Arm B
(+ABC)
Arm C
Arm D
(+ABC)
Arm A
Arm B
(+ABC)
Arm C
Arm D
(+ABC)
AMENDED by DSMB
Arm A
Arm B
(+ABC)
Arm C
Arm D
(+ABC)
tenofovir DF–
emtricitabine
Abacavir (ABC)–
lamivudine
Ongoing Follow-up
Reported

Examples of Incoherent Entries

- 823.32 mean hours sleep/day
- “time to survival”
- 36 eyeballs in study of 14 people
- “mean time to seizure” = 18 people

Serious Adversary Events

?

	Drug	Placebo	Drug (All)	Placebo (All, Pre-CO)	Placebo (CO, Post-DB)
Total # participants affected/at risk	**153/297 (51.52%)**	**164/302 (54.3%)**	**191/297 (64.31%)**	**185/302 (61.26%)**	**26/47 (55.32%)**
Blood and lymphatic system disorders					
Neutrophils					
# participants affected/at risk	1/297 (0.34%)	0/302 (0%)	1/297 (0.34%)	0/302 (0%)	0/47 (0%)
Blood and lymphatic system disorders					
Hemoglobin					
# participants affected/at risk	8/297 (2.69%)	6/302 (1.99%)	11/297 (3.7%)	7/302 (2.32%)	0/47 (0%)

?

Examples of Changed Outcome Measures

- Quality of life scale is replaced by a depression scale
- One month data is replaced by 3 month data
- “# people with an event” is replaced by “time to event”
- “all cause mortality” is replaced by “time to relapse”

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

The ClinicalTrials.gov Results Database — Update and Key Issues

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., Robert M. Califf, M.D., and Nicholas C. Ide, M.S.

ABSTRACT

BACKGROUND

The ClinicalTrials.gov trial registry was expanded in 2008 to include a database for reporting summary results. We summarize the structure and contents of the results database, provide an update of relevant policies, and show how the data can be used to gain insight into the state of clinical research.

METHODS

We analyzed ClinicalTrials.gov data that were publicly available between September 2009 and September 2010.

RESULTS

As of September 27, 2010, ClinicalTrials.gov received approximately 330 new and 2000 revised registrations each week, along with 30 new and 80 revised results submissions. We characterized the 79,413 registry and 2178 results of trial records

Summary Data: Journal vs. ClinicalTrials.gov

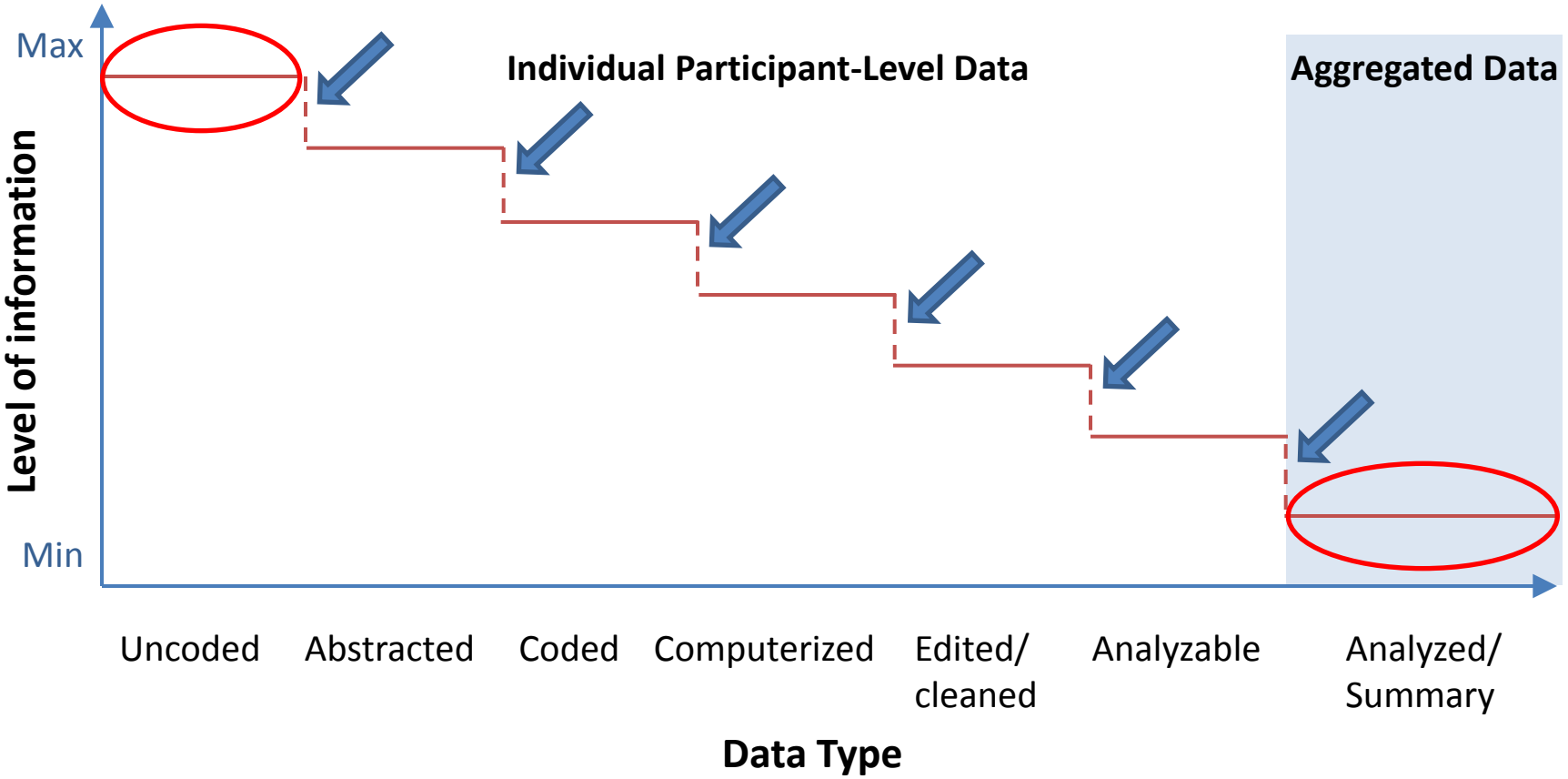
- 110 matched “pairs” of ClinicalTrials.gov results entries and publications
- 82% had at least one important discrepancy, e.g.
  - 24% in data for primary outcome measure
    - Numerator
    - Denominator
  - 30% in Serious Adverse Event data

Example of Discrepancy:

Maximal Walking Distance at 12 weeks

	ClinicalTrials.gov	Publication
Treatment 1	618 meters	775 meters
Treatment 2	572 meters	721 meters

Not a Straight Line from Uncoded Data to Summary Data



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

This is a big problem!

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
Peg
wit
50%
hib

METHODS

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

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

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.

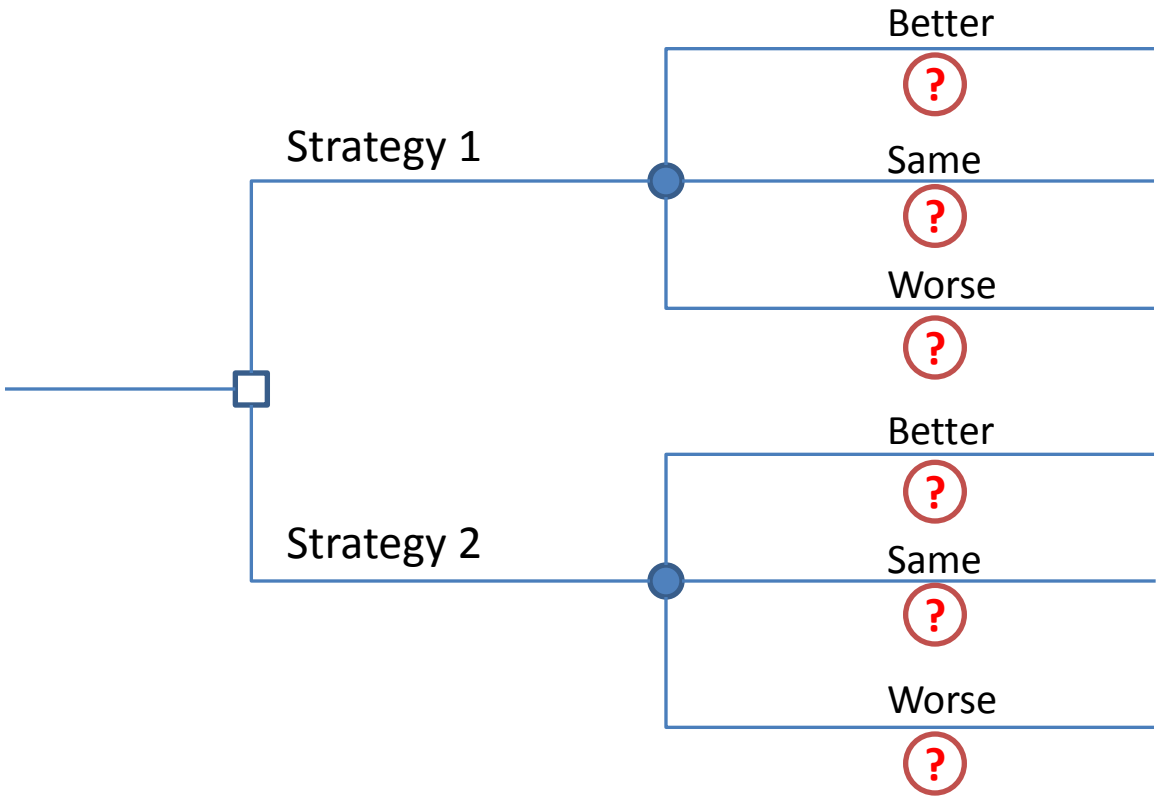
Design, Setting, and Participants The Reduction in Cardiovascular Events by Aca-

Results: "The primary outcome occurred in:

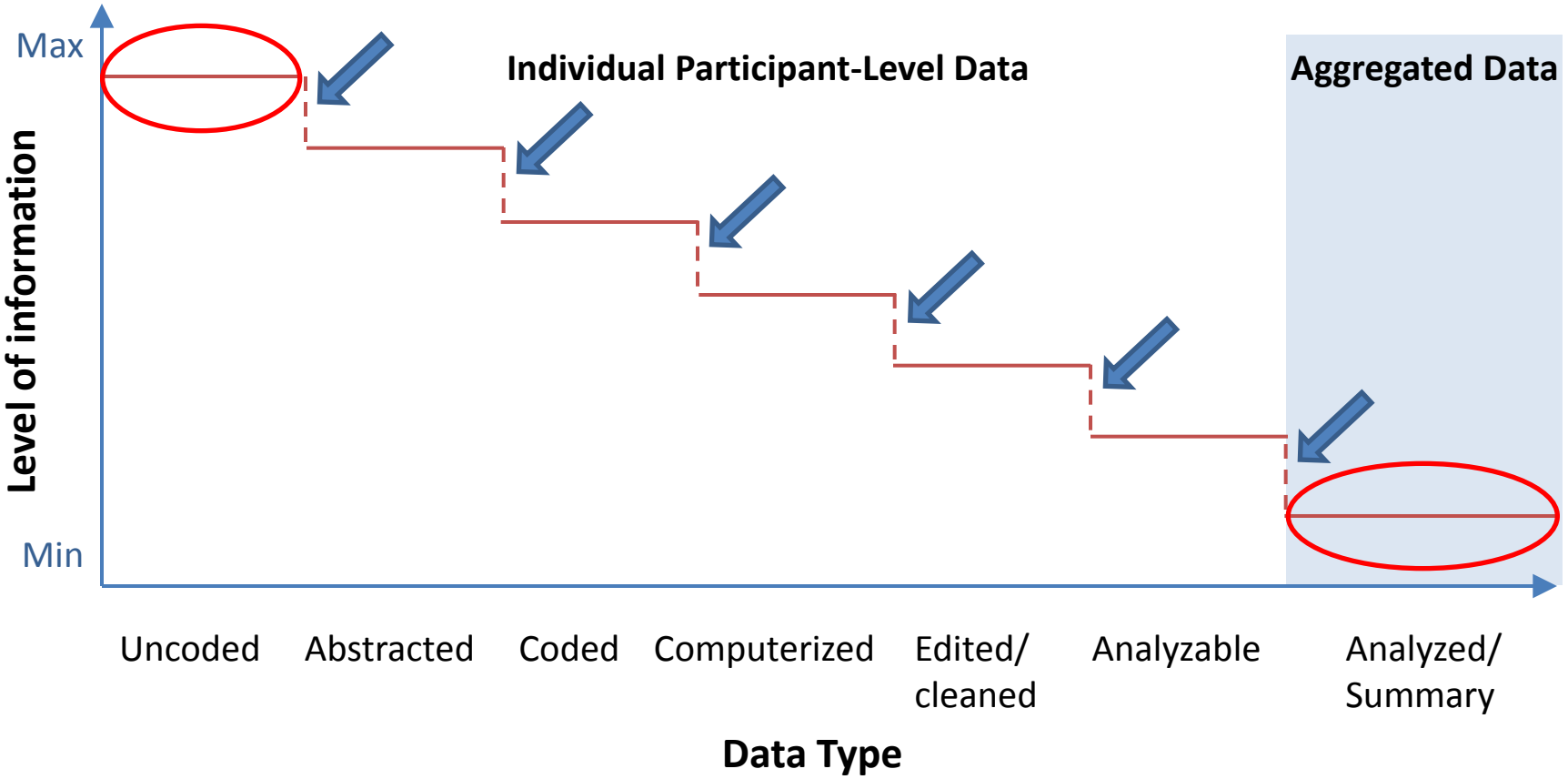
- **75** of **1493** participants (5.0%) in the placebo group and
- **76** of **1493** (5.1%) in the acadesine group

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

We Need Reliable Summary Data



Process is Not Transparent!



The NEW ENGLAND JOURNAL of MEDICINE

Believe the Data

Jeffrey M. Drazen, M.D.

Better care for our patients comes largely from clinical research. Such research is possible because of a union between a critically posed research question and the altruism of patient participants. One would therefore think that the translation of research findings into clinical actions would depend solely on the importance of the research question and the quality of the data used to answer it. An article by Kesselheim and colleagues in this issue of the *Journal* provides evidence that this assumption is not entirely true.[1]

The article describes research into the medical sociology of how internists use clinical information. The investigators also randomly varied the attributed source of support for each study. Of the abstracts submitted to each participant, one abstract listed the National Institutes of Health (NIH) as the source of support, one listed no support source, and one listed a fictitious pharmaceutical company as supporting both the study and the principal investigator. When the data were analyzed according to funding source, the investigators found that for studies of equivalent rigor the internists put much less faith in those supported by the pharmaceutical industry than in those supported by the NIH.

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 ??

In Sum:

- The “journey” from initially collected participant level data to summary data is not completely objective
- Greater transparency could help to inspire trust
- Greater transparency could also help “the field” engage in internal quality improvement