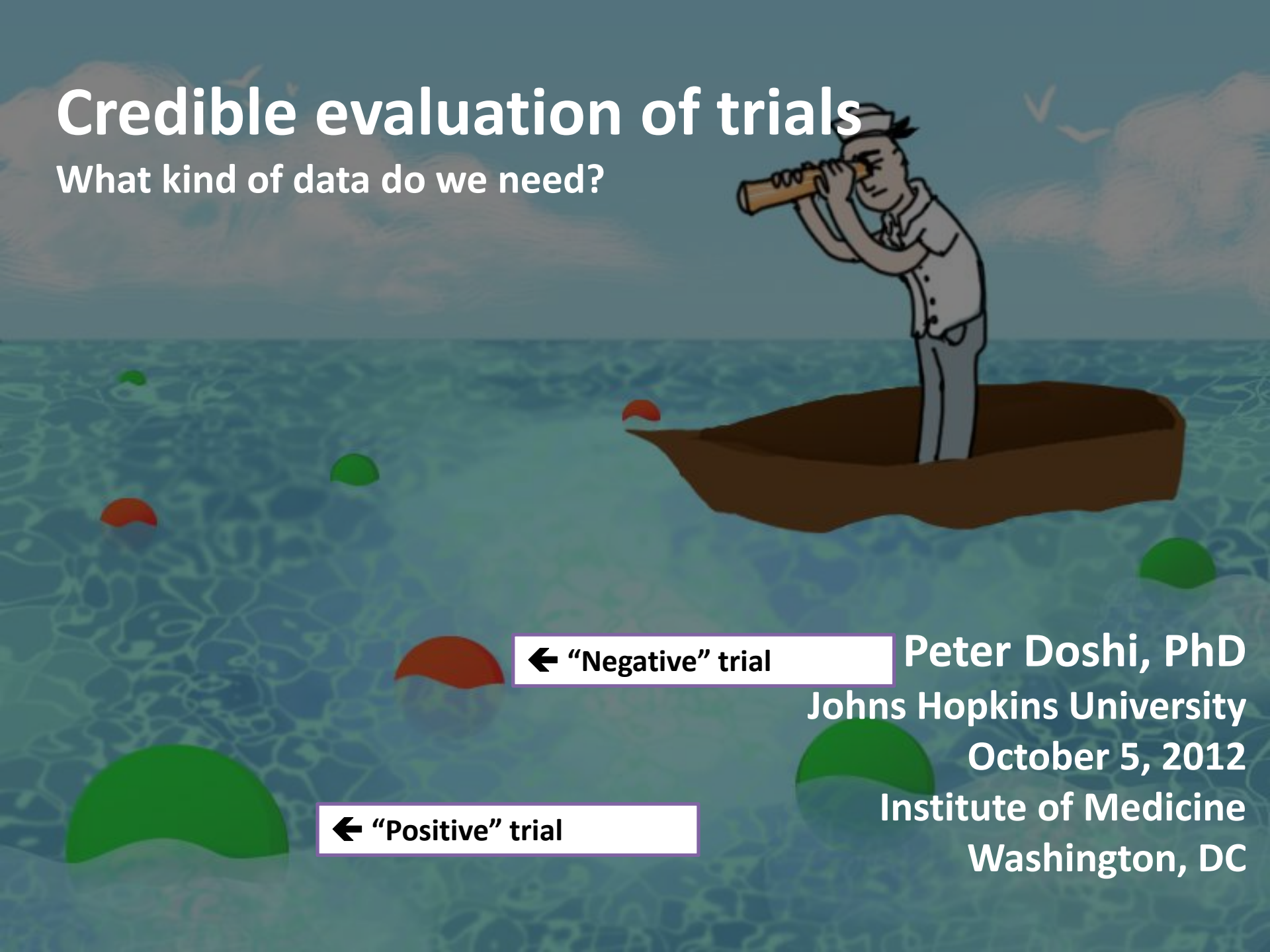
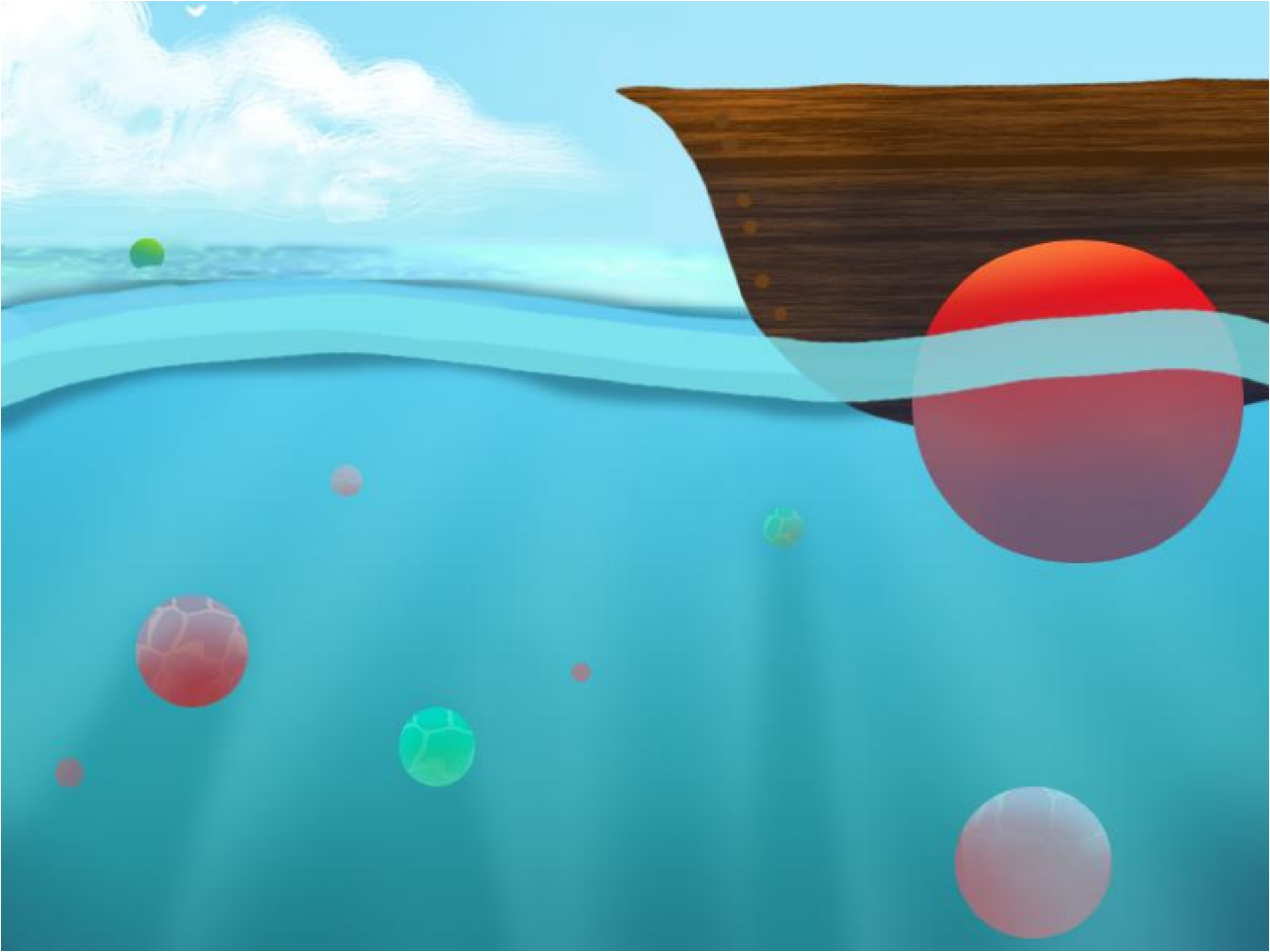
Credible evaluation of trials

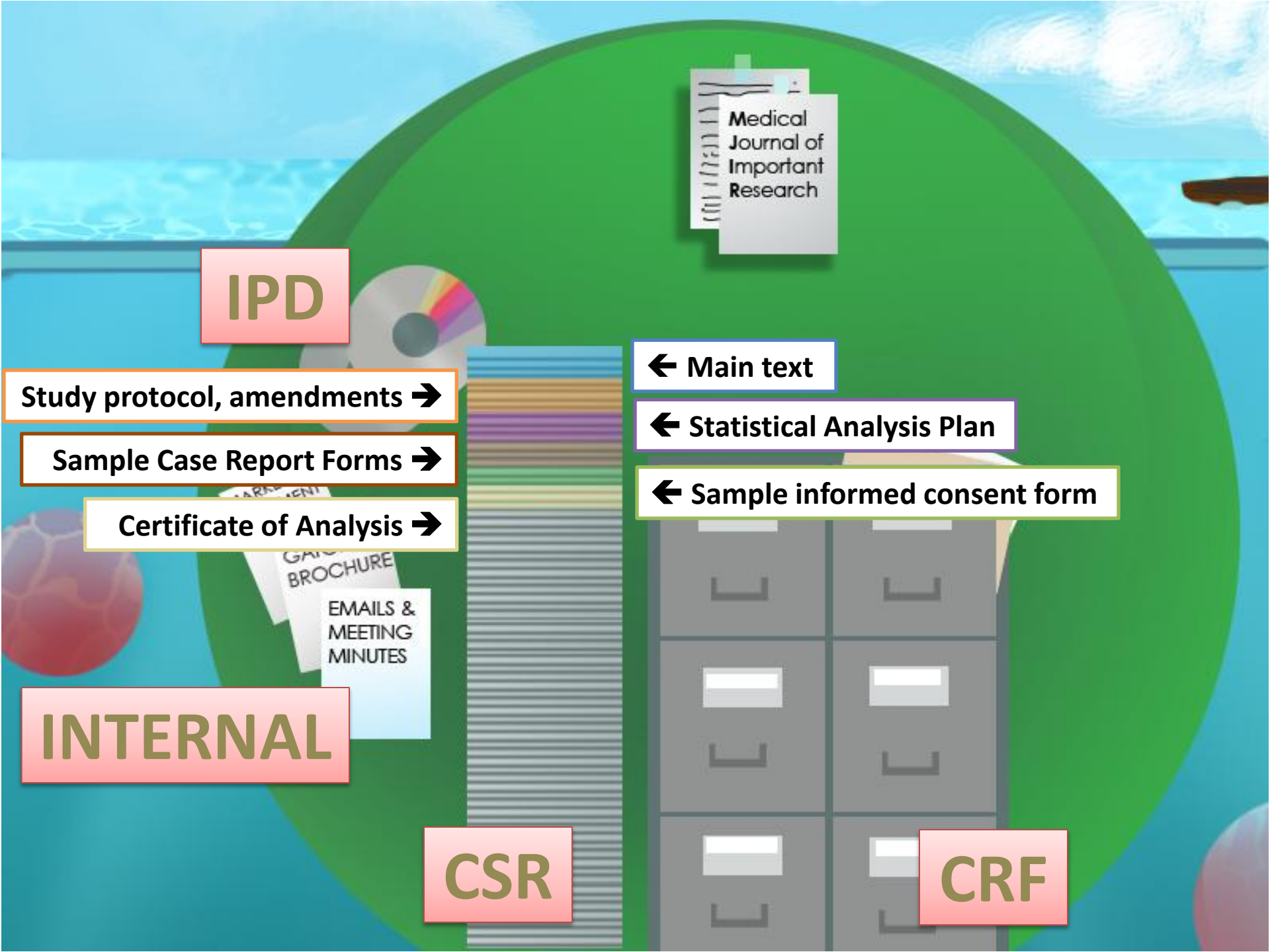
What kind of data do we need?



Peter Doshi, PhD
Johns Hopkins University
October 5, 2012
Institute of Medicine
Washington, DC




Medical
Journal of
Important
Research
MARKETING ASSESSMENT
INVESTI-
GATORS
BROCHURE
EMAILS &
MEETING
MINUTES


Medical Journal of Important Research
IPD
Study protocol, amendments
Sample Case Report Forms
Certificate of Analysis
BROCHURE
EMAILS & MEETING MINUTES
INTERNAL
Main text
Statistical Analysis Plan
Sample informed consent form
CSR
CRF

THERE ARE MANY TYPES OF TRIAL "DATA"

1. Journal publication and/or conference abstract or poster
2. Clinical Study Report (CSR)
   3. Study Protocol and amendments
   4. Sample Case Report Form (CRF)
   5. Statistical Analysis Plan (SAP)
   6. Certificate of analysis
   7. Sample Informed Consent form
8. Manual of Operations
9. Electronic Individual Participant Data (IPD)
10. Filled out Case Report Forms (completed CRFs)
    11. laboratory reports
    12. medical records and diagnostic reports
13. Investigator's Brochure (IB)
14. Sponsor documents that do not go to regulators
    14a. Marketing Assessments
    14b. Email correspondence
    14c. Meeting minutes
15. Records of the Data Monitoring Committee (aka DSMB) e.g. adjudication committee
16. Regulatory documents
    16a. Medical officer's reports
    16b. Advisory committee memoranda
    16c. Site inspection reports

What information is needed to credibly assess a trial?

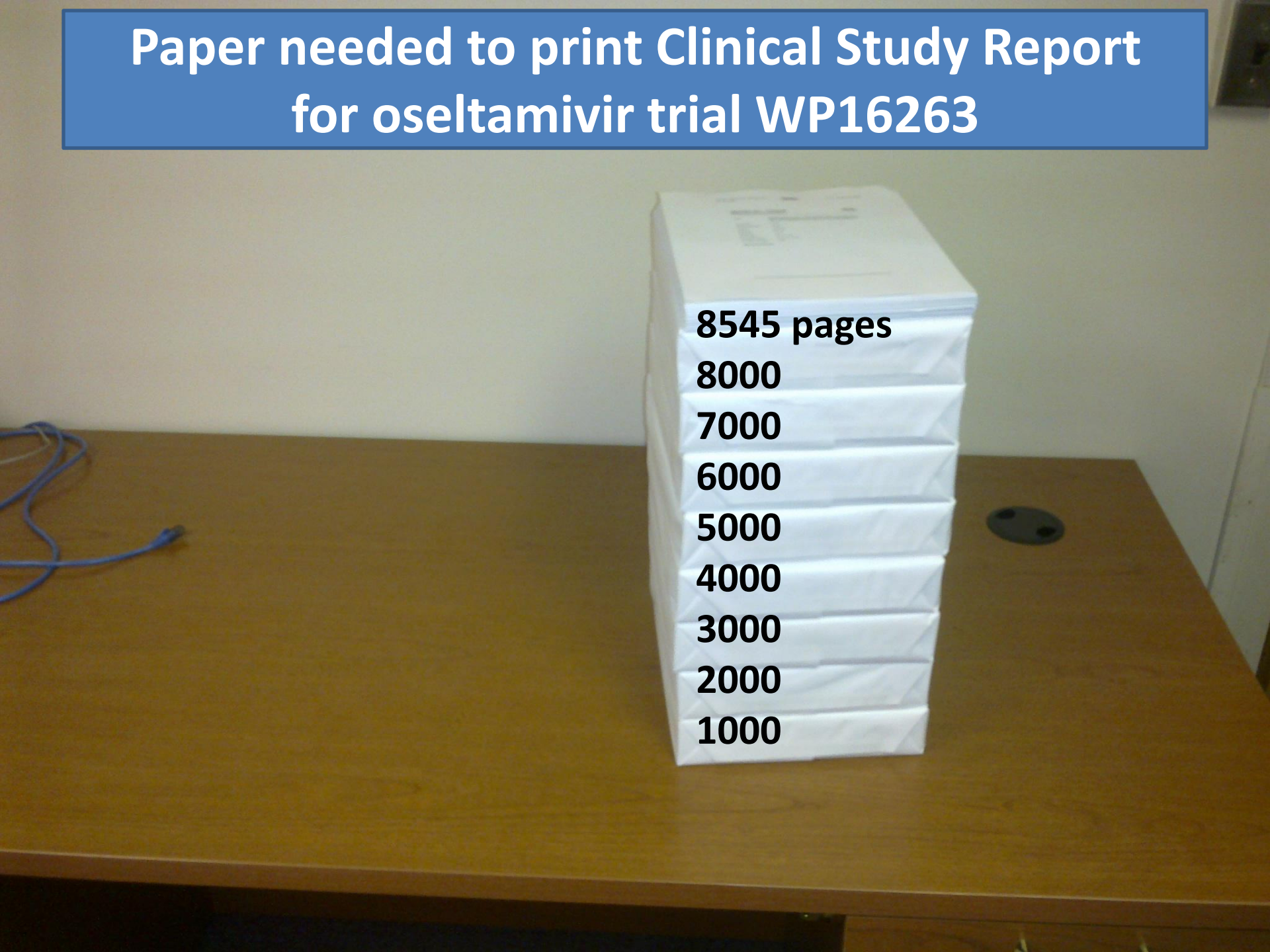
Types of data

1. MEASUREMENTS

2. ANALYSES

3. NARRATIVES

Paper needed to print Clinical Study Report for oseltamivir trial WP16263



Tamiflu® (oseltamivir phosphate)
75mg Capsules, Hard
12 mg/mL Oral Suspension

Roche

5.3.5.4.6 CSR WV15799 (W-144170)

CLINICAL STUDY REPORT MODULES

This report consists of 5 modules.

Those not supplied in this submission are obtainable from the sponsor on request.

233 pages

MODULE I: CORE REPORT

Background and Rationale
Objectives
Materials and Methods
Efficacy Results
Safety Results
Discussion
Conclusion
Appendices

190 pages

MODULE II: STUDY DOCUMENTS

Protocol and Amendment History
Blank Case Report Form (CRF)
Subject Information Sheet and Consent Form
Glossaries of Original and Preferred Terms
Randomization List
Reporting Analysis Plan (RAP)
Certificates of Analysis
List of Investigators
List of Ethics Committee

MODULE III: LISTINGS OF DEMOGRAPHIC AND EFFICACY DATA

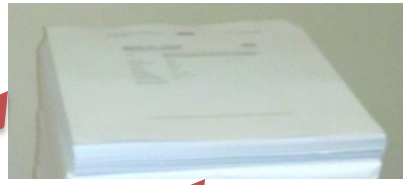
MODULE IV: LISTINGS OF SAFETY DATA

MODULE V: STATISTICAL REPORT AND APPENDICES

Statistical Analysis
Efficacy Results

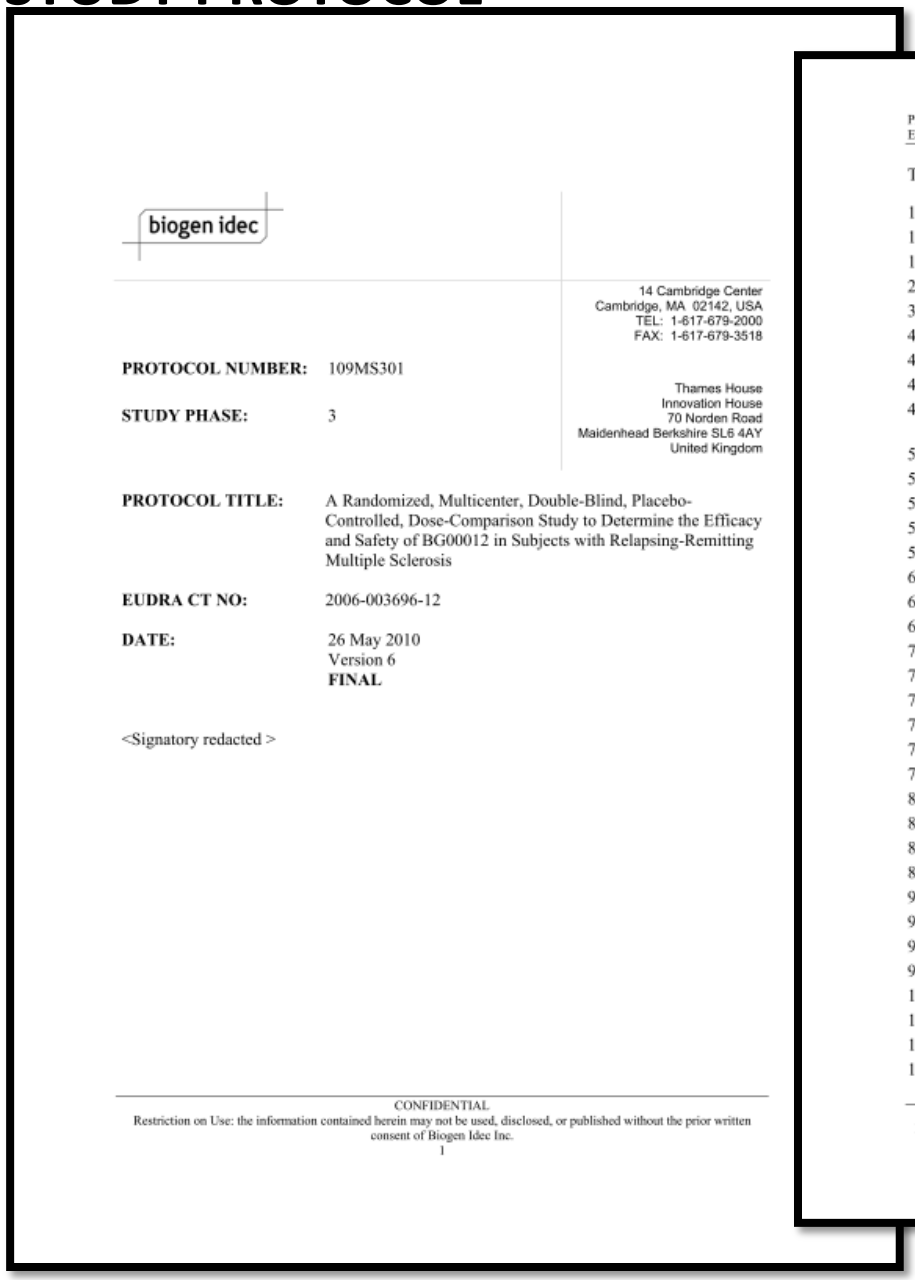
8122 pages

423 pages



8122 pages

STUDY PROTOCOL



biogen idec

14 Cambridge Center
Cambridge, MA 02142, USA
TEL: 1-617-679-2000
FAX: 1-617-679-3518

Thames House
Innovation House
70 Norden Road
Maidenhead Berkshire SL6 4AY
United Kingdom

PROTOCOL NUMBER: 109MS301

STUDY PHASE: 3

PROTOCOL TITLE: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-Comparison Study to Determine the Efficacy and Safety of BG00012 in Subjects with Relapsing-Remitting Multiple Sclerosis

EUDRA CT NO: 2006-003696-12

DATE: 26 May 2010
Version 6
FINAL

<Signatory redacted >

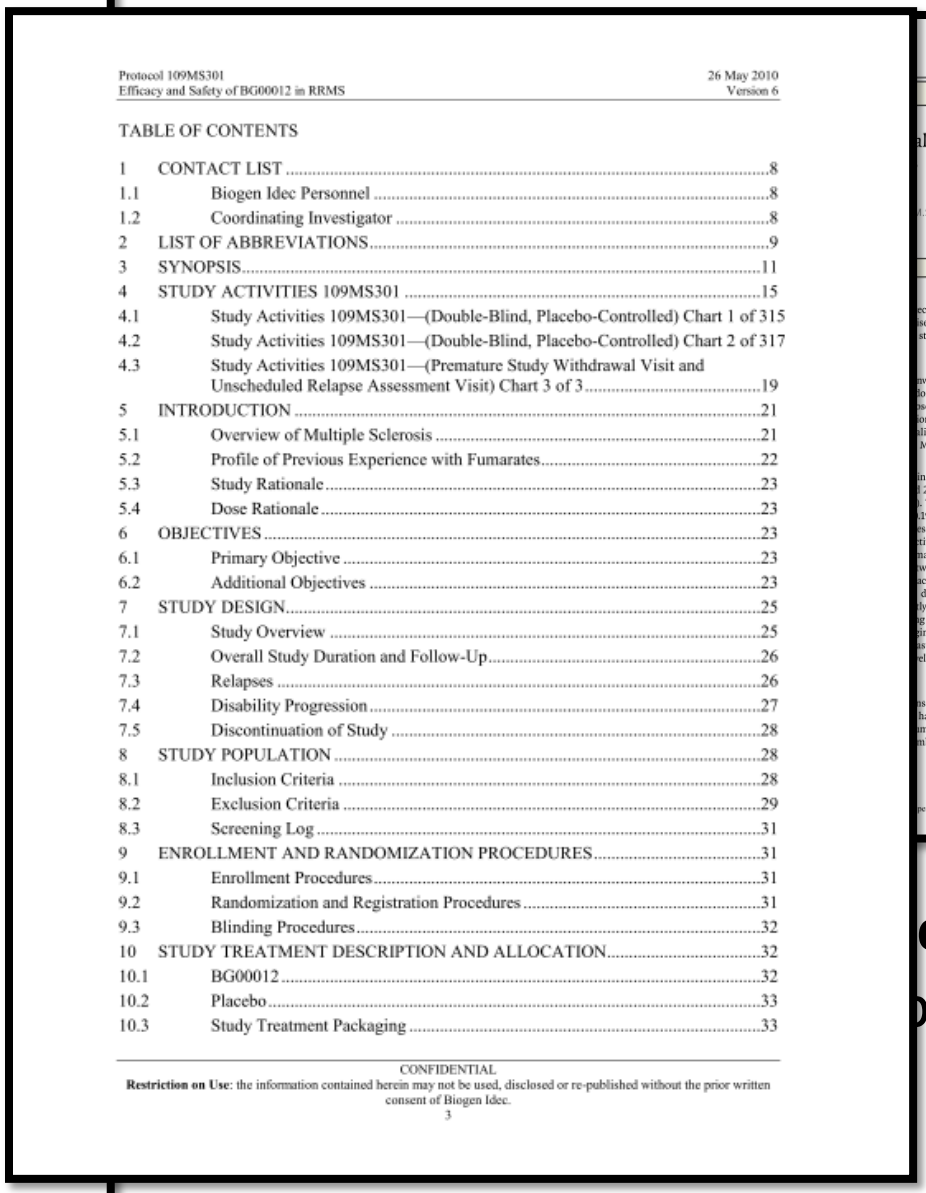


TABLE OF CONTENTS

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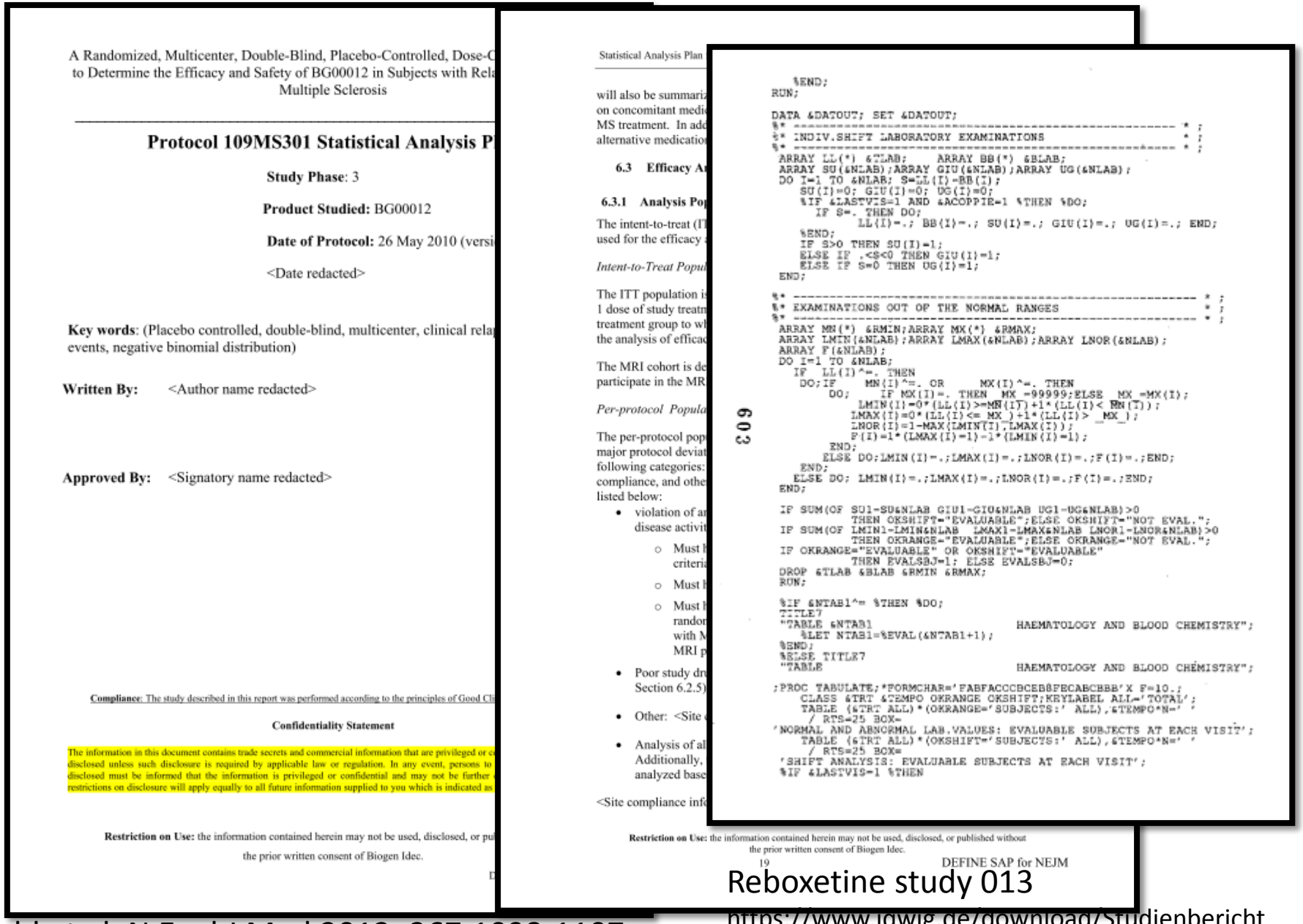
pages)

Gold et al. N Engl J Med 2012; 367:1098-1107

STATISTICAL ANALYSIS PLAN



A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Dose-C
to Determine the Efficacy and Safety of BG00012 in Subjects with Rela
Multiple Sclerosis

Protocol 109MS301 Statistical Analysis P

Study Phase: 3

Product Studied: BG00012

Date of Protocol: 26 May 2010 (versi

<Date redacted>

Key words: (Placebo controlled, double-blind, multicenter, clinical rela
events, negative binomial distribution)

Written By: <Author name redacted>

Approved By: <Signatory name redacted>

Compliance: The study described in this report was performed according to the principles of Good Cli

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or c
disclosed unless such disclosure is required by applicable law or regulation. In any event, persons to
disclosed must be informed that the information is privileged or confidential and may not be further
restrictions on disclosure will apply equally to all future information supplied to you which is indicated as

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the prior written consent of Biogen Idec.

Statistical Analysis Plan

will also be summari
on concomitant medi
MS treatment. In add
alternative medicatio

6.3 Efficacy A

6.3.1 Analysis Po

The intent-to-treat (I
used for the efficacy

Intent-to-Treat Popu

The ITT population i
1 dose of study treatm
treatment group to wh
the analysis of efficac

The MRI cohort is de
participate in the MR

Per-protocol Popula

The per-protocol pop
major protocol deviat
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compliance, and othe
listed below:

- violation of a
  disease activit
  - Must
    criteri
  - Must
  - Must
    randor
    with M
    MRI p
- Poor study dr
  Section 6.2.5)
- Other: <Site
- Analysis of al
  Additionally,
  analyzed base

<Site compliance inf

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19 DEFINE SAP for NEJM

```
   %END;
RUN;

DATA &DATOUT; SET &DATOUT;
%* ------------------------------------------------------------ * ;
%* INDIV.SHIFT LABORATORY EXAMINATIONS                          * ;
%* ------------------------------------------------------------ * ;
 ARRAY LL(*) &TLAB;     ARRAY BB(*) &BLAB;
 ARRAY SU(&NLAB);ARRAY GIU(&NLAB);ARRAY UG(&NLAB);
 DO I=1 TO &NLAB; S=LL(I)-BB(I);
    SU(I)=0; GIU(I)=0; UG(I)=0;
    %IF &LASTVIS=1 AND &ACOPPIE=1 %THEN %DO;
      IF S=. THEN DO;
            LL(I)=.; BB(I)=.; SU(I)=.; GIU(I)=.; UG(I)=.; END;
    %END;
    IF S>0 THEN SU(I)=1;
    ELSE IF .<S<0 THEN GIU(I)=1;
    ELSE IF S=0 THEN UG(I)=1;
 END;

%* ------------------------------------------------------------ * ;
%* EXAMINATIONS OUT OF THE NORMAL RANGES                        * ;
%* ------------------------------------------------------------ * ;
 ARRAY MN(*) &RMIN;ARRAY MX(*) &RMAX;
 ARRAY LMIN(&NLAB);ARRAY LMAX(&NLAB);ARRAY LNOR(&NLAB);
 ARRAY F(&NLAB);
 DO I=1 TO &NLAB;
   IF  LL(I)^=. THEN
    DO;IF    MN(I)^=. OR     MX(I)^=. THEN
       DO;    IF MX(I)=. THEN  MX_=99999;ELSE  MX_=MX(I);
           LMIN(I)=0*(LL(I)>=MN(I))+1*(LL(I)< MN(I));
          LMAX(I)=0*(LL(I)<= MX_)+1*(LL(I)> MX_);
          LNOR(I)=1-MAX(LMIN(I),LMAX(I));
          F(I)=1*(LMAX(I)=1)-1*(LMIN(I)=1);
       END;
      ELSE DO;LMIN(I)=.;LMAX(I)=.;LNOR(I)=.;F(I)=.;END;
    END;
   ELSE DO; LMIN(I)=.;LMAX(I)=.;LNOR(I)=.;F(I)=.;END;
END;

 IF SUM(OF SU1-SU&NLAB GIU1-GIU&NLAB UG1-UG&NLAB)>0
          THEN OKSHIFT="EVALUABLE";ELSE OKSHIFT="NOT EVAL.";
 IF SUM(OF LMIN1-LMIN&NLAB  LMAX1-LMAX&NLAB LNOR1-LNOR&NLAB)>0
          THEN OKRANGE="EVALUABLE";ELSE OKRANGE="NOT EVAL.";
 IF OKRANGE="EVALUABLE" OR OKSHIFT="EVALUABLE"
          THEN EVALSBJ=1; ELSE EVALSBJ=0;
 DROP &TLAB &BLAB &RMIN &RMAX;
 RUN;

 %IF &NTAB1^= %THEN %DO;
 TITLE7
 "TABLE &NTAB1                          HAEMATOLOGY AND BLOOD CHEMISTRY";
   %LET NTAB1=%EVAL(&NTAB1+1);
 %END;
 %ELSE TITLE7
 "TABLE                                 HAEMATOLOGY AND BLOOD CHEMISTRY";

;PROC TABULATE;*FORMCHAR='FABFACCCBCEB8FECABCBBB'X F=10.;
    CLASS &TRT &TEMPO OKRANGE OKSHIFT;KEYLABEL ALL='TOTAL';
    TABLE (&TRT ALL)*(OKRANGE='SUBJECTS:' ALL),&TEMPO*N=' '
      / RTS=25 BOX=
'NORMAL AND ABNORMAL LAB.VALUES: EVALUABLE SUBJECTS AT EACH VISIT';
    TABLE (&TRT ALL)*(OKSHIFT='SUBJECTS:' ALL),&TEMPO*N=' '
      / RTS=25 BOX=
'SHIFT ANALYSIS: EVALUABLE SUBJECTS AT EACH VISIT';
 %IF &LASTVIS=1 %THEN
```

603

Gold et al. N Engl J Med 2012; 367:1098-1107

Reboxetine study 013
https://www.iqwig.de/download/Studienbericht_zu_Studie_013.pdf

STUDY PROTOCOL

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis

The CLASS Study: A Randomized Controlled Trial

Fred E. Silverstein, MD
Gerald Faich, MD

Context Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a spectrum of toxic effects, notably gastrointestinal (GI) effects, because of

Main Outcome Measures Incidence of prospectively defined symptomatic upper GI ulcers and ulcer complications (bleeding, perforation, and obstruction) and other adverse effects during the 6-month treatment period.

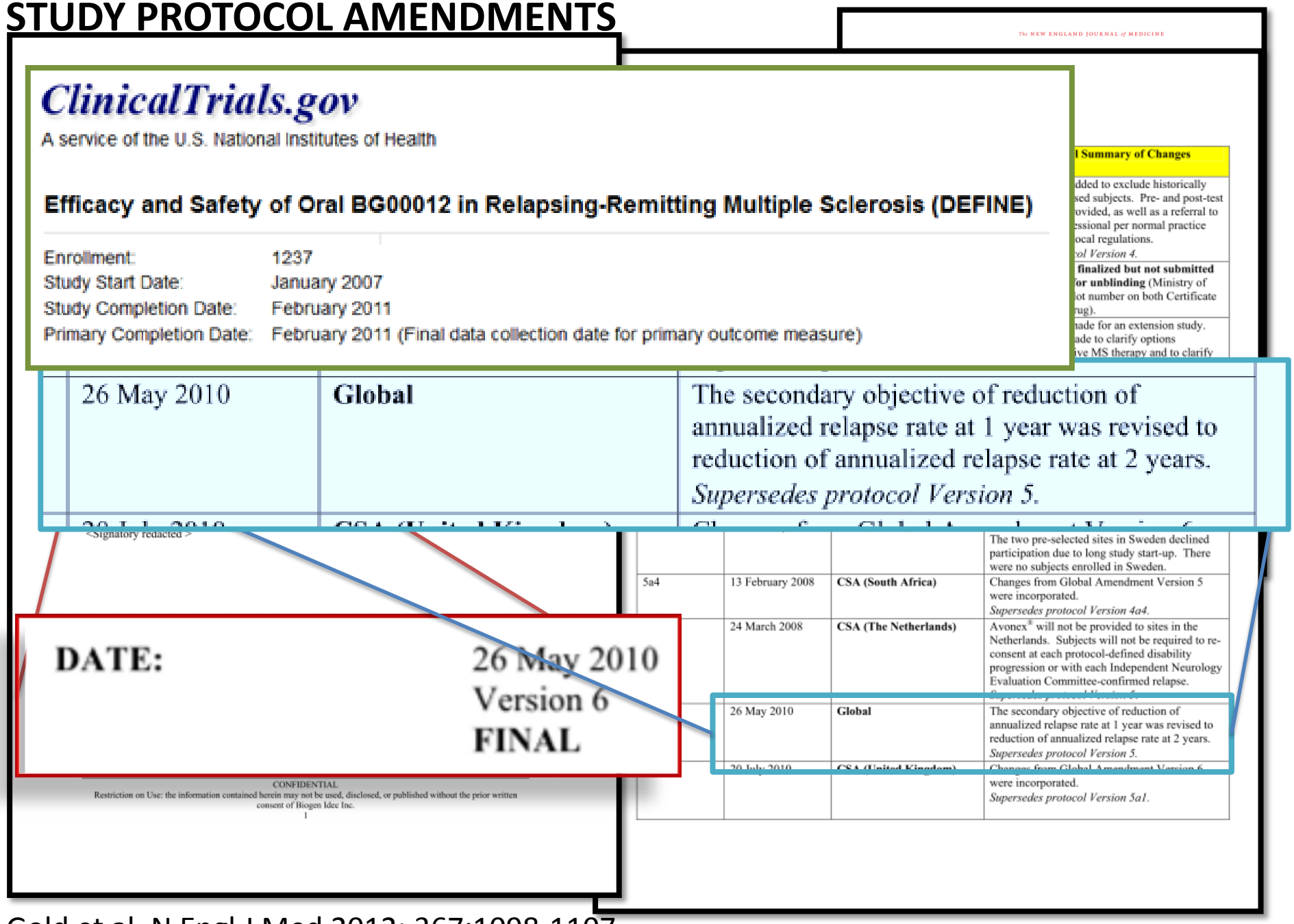
Conclusions In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages. The decrease in upper GI toxicity was strongest among patients not taking aspirin concomitantly.

JAMA. 2000;284:1247-1255 www.jama.com

"As described on the FDA Web site, **the published CLASS trial differs from the original protocol in primary outcomes, statistical analysis, trial duration, and conclusions**. In particular, the unpublished data show that by week 65, celecoxib was associated with a **similar number of ulcer complications** as diclofenac and ibuprofen."

Hrachovec JB, Mora M. *JAMA*. 2001;286(19):2398-2400.

STUDY PROTOCOL AMENDMENTS



ClinicalTrials.gov

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

Efficacy and Safety of Oral BG00012 in Relapsing-Remitting Multiple Sclerosis (DEFINE)

Enrollment:	1237
Study Start Date:	January 2007
Study Completion Date:	February 2011
Primary Completion Date:	February 2011 (Final data collection date for primary outcome measure)

26 May 2010	**Global**	The secondary objective of reduction of annualized relapse rate at 1 year was revised to reduction of annualized relapse rate at 2 years. *Supersedes protocol Version 5.*

<Signatory redacted >

DATE: 26 May 2010
Version 6
FINAL

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1

The NEW ENGLAND JOURNAL of MEDICINE

			The two pre-selected sites in Sweden declined participation due to long study start-up. There were no subjects enrolled in Sweden.
5a4	13 February 2008	**CSA (South Africa)**	Changes from Global Amendment Version 5 were incorporated. *Supersedes protocol Version 4a4.*
	24 March 2008	**CSA (The Netherlands)**	Avonex® will not be provided to sites in the Netherlands. Subjects will not be required to re-consent at each protocol-defined disability progression or with each Independent Neurology Evaluation Committee-confirmed relapse.
	26 May 2010	**Global**	The secondary objective of reduction of annualized relapse rate at 1 year was revised to reduction of annualized relapse rate at 2 years. *Supersedes protocol Version 5.*
			were incorporated. *Supersedes protocol Version 5a1.*

Gold et al. N Engl J Med 2012; 367:1098-1107

CERTIFICATE OF ANALYSIS

Tamiflu (oseltamivir phosphate) Roche

2. MATERIALS AND METHODS

2.1 Overall Study Design

This was an international, multicenter, randomized, comparison of three dose regimens of oseltamivir compar

Screening	Baseline Day	Drug Administration	Inte
Day -15 to -2	Day -1	Days 1, 2, 3, 4, 5	Day

A total of 400 subjects were required to complete the stu of four groups described below:

Treatment A: oseltamivir 75 mg b.i.d. for five

Treatment B: oseltamivir 225 mg b.i.d. for fiv

Treatment C: oseltamivir 450 mg b.i.d. for five days

Treatment D: matching placebo b.i.d. for five days

A total of 100 subjects was to be allo each treatment group.

2. Methods

2.1. Study design

This was an international, randomise multicentre, double-blind, parallel-group comparison with placebo or oral dosages of oseltamivir phosphate of 75, 225 or 450 mg b.i.d. (every 12 h) for 5 days. These dosages were chosen to maximise the likelihood of detection of electrocardiographic changes as well as other adverse effects and were based on the previously observed tolerance of dosages as high as 500 mg b.i.d. in studies in healthy adults [2]. The highest dosage for which blinding could be maintained with available formulations was 450 mg. The study took place between 22 August and 25 September 2000.

Colour white

Identity of
Ro 64-0796 negative
Dehydrocholic acid corresponds

Total of all

Content per capsule of

TAMIFLU (Oseltamivir ph
Capsules 75 mg (Oseltamivi
Ro 64-0796/V14

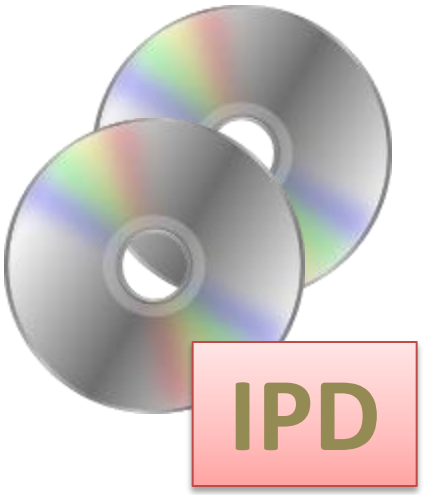
Placebo Capsules
Ro 64-0796/V16

Quality Control & Assurance

Capsule size	No. 2
Colour of the capsules	
Body	grey, opaque
Cap	light yellow, opaque

Capsule size	No. 2
Colour of the capsules	
Body	grey, opaque
Cap	ivory, opaque

INDIVIDUAL PARTICIPANT DATA (USUALLY ELECTRONIC)



Verify/Reproduce

- "Having access to the 'raw' data for each study **enables data checking, thorough exploration, and re-analysis of the data in a consistent way**.

Extend

- "IPD meta-analysis has particular benefits when the published information does not permit a good quality review, or **where particular types of analyses are required that are not feasible using summary data**."

Chapter 18 Key Points. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Wiley, 2011. www.cochrane-handbook.org

BLANK CASE REPORT FORMS

Scher et al. N Engl J Med 2012; 367:1187-1197

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Appendix C: Brief Pain Inventory (Short Form)

STUDY ID #_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

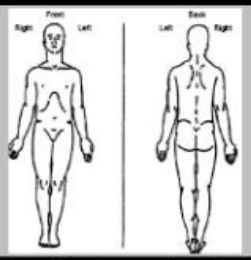
Brief Pain Inventory (Short Form)

Date: __/__/__ Time: _____
Name: _____ _____ _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

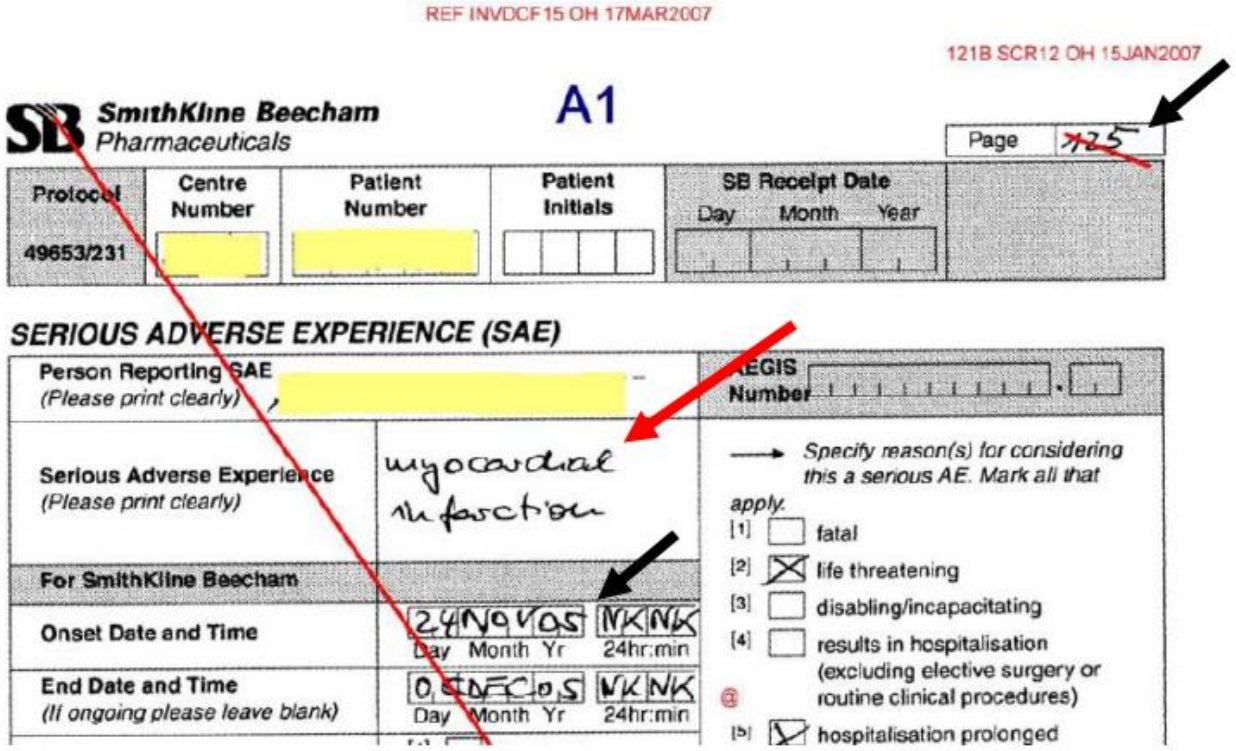
0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

COMPLETED CASE REPORT FORMS (Avandia RECORD trial)

Case A: The Missed MI



REF INVDCF15 OH 17MAR2007

121B SCR12 OH 15JAN2007

A1

SmithKline Beecham Pharmaceuticals

Page 125

Protocol	Centre Number	Patient Number	Patient Initials	SB Receipt Date Day Month Year
49653/231				

SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE (Please print clearly)

REGIS Number

Serious Adverse Experience (Please print clearly): myocardial infarction

→ Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☒ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures)
- [5] ☑ hospitalisation prolonged

For SmithKline Beecham

	Day Month Yr	24hr:min
Onset Date and Time	24NOV05	NKNK
End Date and Time (If ongoing please leave blank)	01DEC05	NKNK

This patient had PTCA on 5Dec05 and died of HF on 27Dec05.

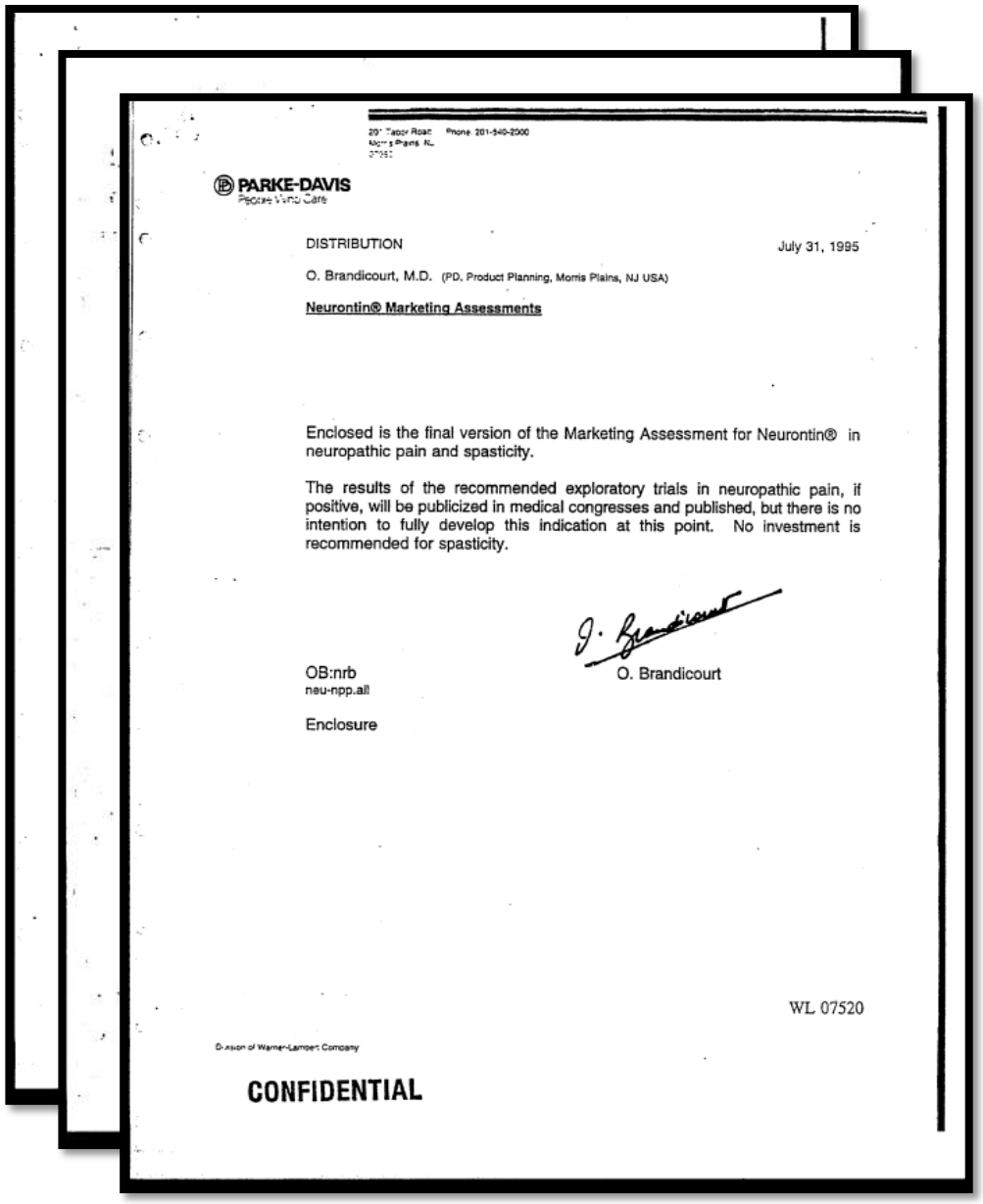
4

5

Slides by Dr. Thomas Marciniak, Division of Cardiovascular and Renal Products, FDA

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218484.pdf

MARKETING ASSESSMENTS



PARKE-DAVIS

DISTRIBUTION

July 31, 1995

O. Brandicourt, M.D. (PD, Product Planning, Morris Plains, NJ USA)

Neurontin® Marketing Assessments

Enclosed is the final version of the Marketing Assessment for Neurontin® in neuropathic pain and spasticity.

The results of the recommended exploratory trials in neuropathic pain, if positive, will be publicized in medical congresses and published, but there is no intention to fully develop this indication at this point. No investment is recommended for spasticity.

O. Brandicourt

OB:nrb
neu-npp.all

Enclosure

WL 07520

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http://dida.library.ucsf.edu/pdf/pca00a10
http://dida.library.ucsf.edu/pdf/qhb00a10

"Publication Strategy"

versus

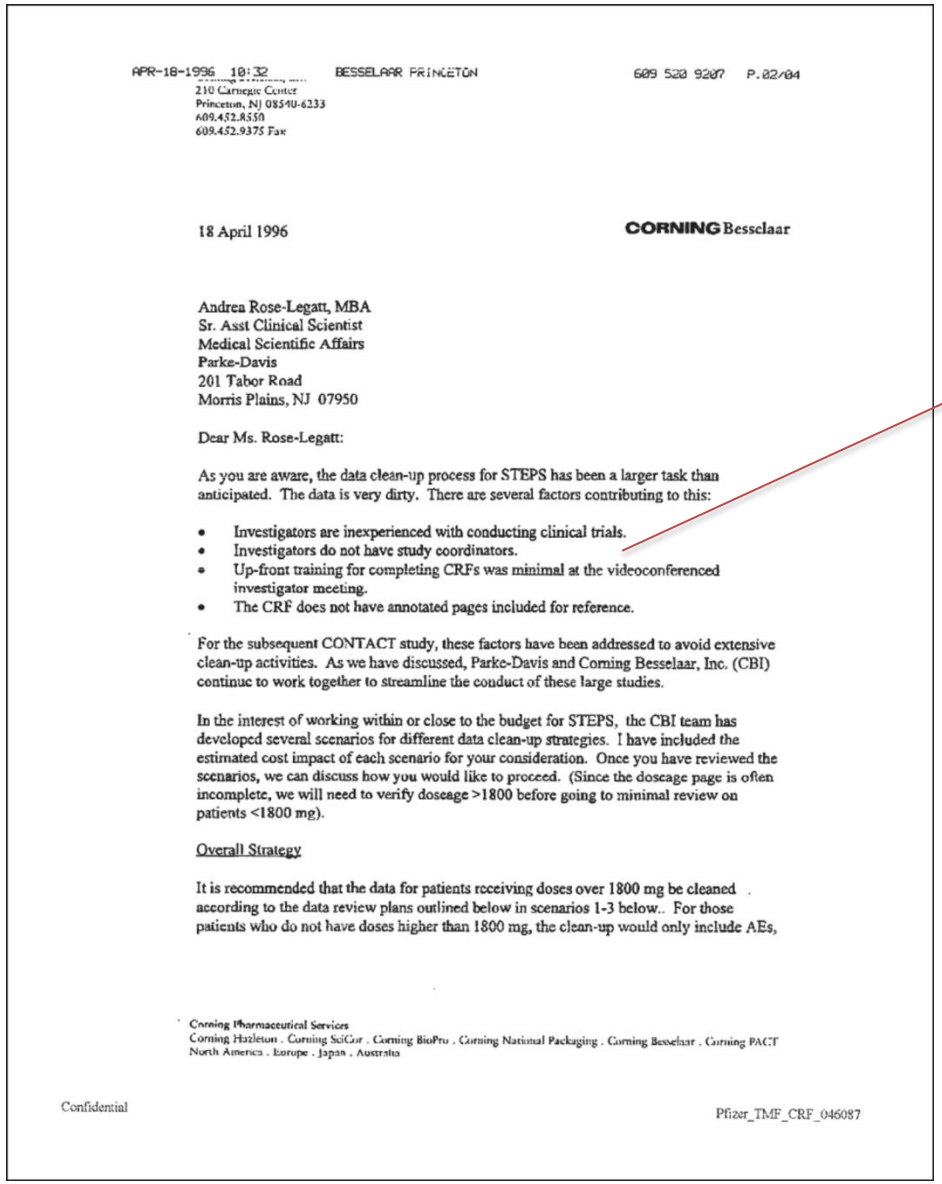
"Indication Strategy"

"**The results** of the recommended exploratory trials in neuropathic pain, **if positive, will be published** … but there is no intention to fully develop this indication at this point."

Example adapted from Vedula et al. Implementation of a publication strategy in the context of reporting biases. A case study based on new documents from Neurontin® litigation. Trials. 2012 Aug 13;13(1):136.

INTERNAL CORRESPONDENCE

Contract Research Organization to Study Sponsor



APR-18-1996 10:32 BESSELAAR PRINCETON 609 520 9207 P.02/04

210 Carnegie Center
Princeton, NJ 08540-6233
609.452.8550
609.452.9375 Fax

18 April 1996

CORNING Besselaar

Andrea Rose-Legatt, MBA
Sr. Asst Clinical Scientist
Medical Scientific Affairs
Parke-Davis
201 Tabor Road
Morris Plains, NJ 07950

Dear Ms. Rose-Legatt:

As you are aware, the data clean-up process for STEPS has been a larger task than anticipated. The data is very dirty. There are several factors contributing to this:

- Investigators are inexperienced with conducting clinical trials.
- Investigators do not have study coordinators.
- Up-front training for completing CRFs was minimal at the videoconferenced investigator meeting.
- The CRF does not have annotated pages included for reference.

For the subsequent CONTACT study, these factors have been addressed to avoid extensive clean-up activities. As we have discussed, Parke-Davis and Corning Besselaar, Inc. (CBI) continue to work together to streamline the conduct of these large studies.

In the interest of working within or close to the budget for STEPS, the CBI team has developed several scenarios for different data clean-up strategies. I have included the estimated cost impact of each scenario for your consideration. Once you have reviewed the scenarios, we can discuss how you would like to proceed. (Since the dosage page is often incomplete, we will need to verify dosage >1800 before going to minimal review on patients <1800 mg).

Overall Strategy

It is recommended that the data for patients receiving doses over 1800 mg be cleaned according to the data review plans outlined below in scenarios 1-3 below.. For those patients who do not have doses higher than 1800 mg, the clean-up would only include AEs,

Corning Pharmaceutical Services
Corning Hazleton . Corning SciCor . Corning BioPro . Corning National Packaging . Corning Besselaar . Corning PACT
North America . Europe . Japan . Australia

Confidential

Pfizer_TMF_CRF_046087

Study of Neurontin: Titrate to Effect, Profile of Safety (STEPS)

- Investigators are inexperienced with conducting trials
- Investigators do not have study coordinators
- Up-front training for completing CRFs was minimal …

Described in Krumholz SD, Egilman DS, Ross JS. Study of neurontin: titrate to effect, profile of safety (STEPS) trial: a narrative account of a gabapentin seeding trial. Arch. Intern. Med. 2011 Jun 27;171(12):1100–7.

VIEWPOINT

Clinical Trial Data as a Public Good

Marc A. Rodwin, JD, PhD
John D. Abramson, MD, MS

KNOWLEDGE OF THE BENEFITS AND RISKS OF PRESCRIPTION drugs is based mainly on published reports of clinical trials, yet the medical literature may present an incomplete and potentially biased sample of clinical trials.[1] Trials with positive results generally are published more frequently than studies that conclude that a new drug poses greater risks or is no more effective than standard therapy or a placebo. Furthermore, some articles may distort trial findings by omitting important data or by modifying prespecified outcome measures. Lack of access to detailed information about clinical trials can undermine the integrity of medical knowledge.

To increase transparency, the International Committee of Medical Journal Editors decided in 2004 that their journals would not publish results of a clinical trial unless the trial was registered prior to patient enrollment. The committee stated that registries should include data specified by the World Health Organization, although these data elements do not provide a complete picture of the clinical trials. Since 2007, US law has required researchers to register phase 2 and higher trials of drugs and biologicals on the ClinicalTrials.gov website if there is a trial site in the United States or if the trial is part of a US Food and Drug Administration (FDA) investigational new drug application. Researchers are typically required to post key results within a year of completing data collection, but studies of off-label drug uses (ie, uses other than those described in an FDA-approved drug label) are allowed 3 years to post trial results.

However, actual trial registration falls short of requirements. A review of 323 articles found that nearly 28% of the trials were unregistered. Among articles with adequately registered trials, 31% had discrepancies between outcomes reported in the registration and in the published report.[2] Moreover, no authority checks whether registration information is accurate. Even more important, current law does not require registration of sufficient information to ensure accuracy, completeness, or reasonable interpretation of the findings.

See also p 869.

The Standardized Clinical Study Report

Current policy does not consider a practical, inexpensive solution: mandatory disclosure of the standardized Clinical Study Report (CSR) for all clinical trials involving FDA-approved drugs. The FDA follows the International Conference on Harmonization Standards for Registration of Pharmaceuticals for Human Use, which requires submission of a CSR (with specified content and format) when reporting clinical trials to governmental authorities.[3] The CSR summarizes the trial, clinical end points, methods, key data, and data analysis. The CSR includes "statistical description, presentations . . . tables and figures . . . with appendices containing the protocol, sample case report forms, investigator related information, information related to the test drugs/investigational products including active control/comparators, technical statistical documentation, related publications, patient data listings, and technical statistical details such as derivations, computations, analyses, and computer output etc."[4]

A CSR includes the most pertinent information about a clinical trial in an easily analyzed format. Drug manufacturers already produce these reports to meet international and national regulatory requirements. Making CSRs publicly available would not be expensive, yet disclosure would promote research integrity, medical knowledge, and public health. Furthermore, CSRs are more likely to be reliable than other summaries. Drug manufacturers submit CSRs to public authorities when they seek marketing approval and cannot alter or delete data without potentially jeopardizing their relationships with regulatory agencies and risking criminal prosecution.

A review of the clinical trials that evaluated the efficacy of gabapentin for off-label use demonstrated the importance of disclosing CSRs.[4] In litigation involving illegal marketing, internal corporate documents for 20 clinical trials (including 18 CSRs) for off-label use of gabapentin were discovered. However, the results for only 9 of these studies were fully published and only 1 published report presented both primary outcome measures and P values consistent with the

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Rodwin MA, Abramson JD. JAMA. 2012 Sep 5;308:871-2.

EMA's "sea-change in attitude"

30 November 2010
EMA/110196/2006

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Effective date: 1 Dec
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REUTERS

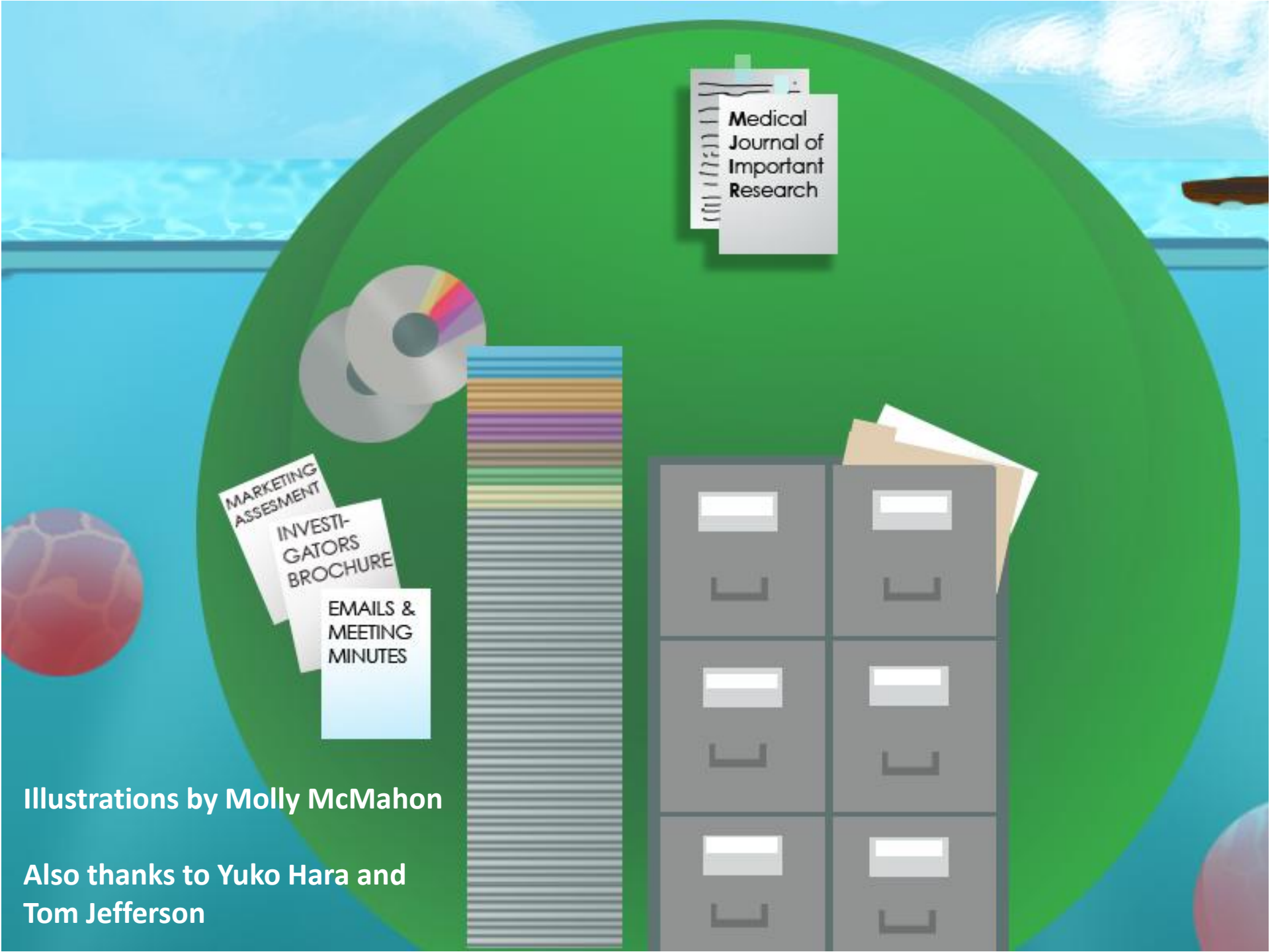
EU agency lifts lid on drug data secrets

Sun, Jul 15 2012

By Ben Hirschler

http://www.reuters.com/assets/print?aid=USBRE86E04I20120715

"**In the last 18 months, the EMA has released around 1.5 million pages of clinical trial data** - an increase of more than a hundred-fold compared to 2010 and 2009."



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