How Comparable are Clinical Trials Results Reporting on ClinicalTrials.gov versus a High-Impact Neurological Journal

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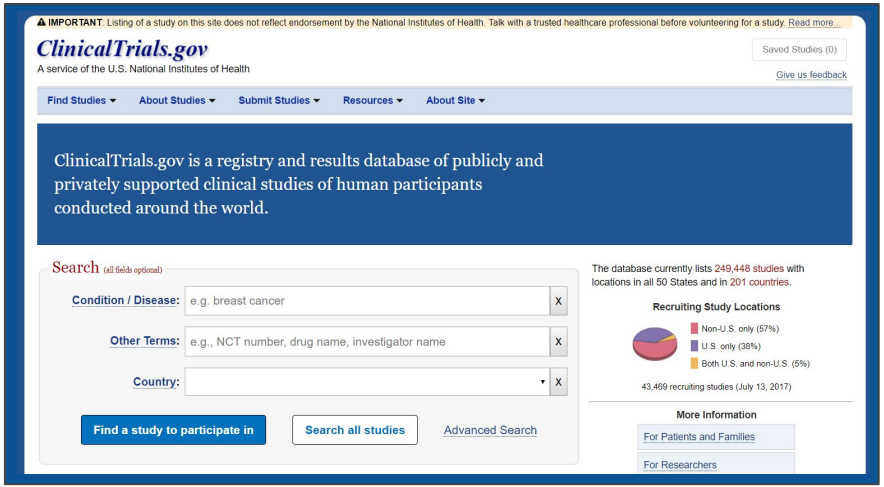
Timeline of Clinical Trials' Reporting Regulations

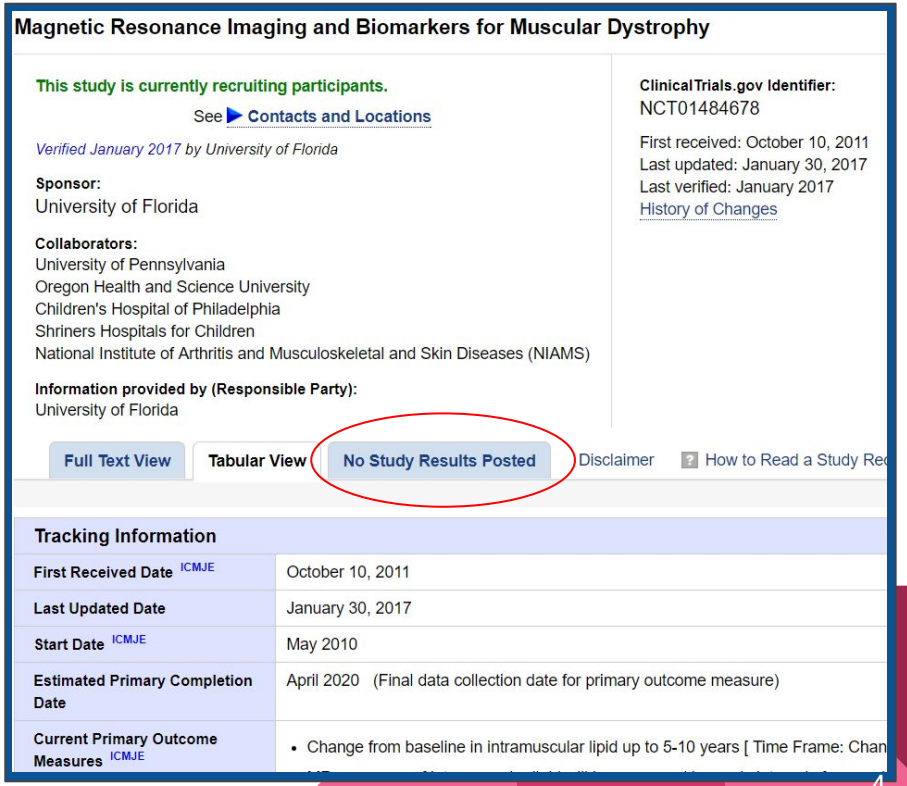
- **(1970) Initializations of Registrar Programs**
- **(1997) FDA Modernization Act**
- **(2000) ClinicalTrials.gov Officially Available**
- **(2005; 2007) International Committee of Medical Journal Editors' Regulations**
    - To Publish: Must Register!
- **(2007) U.S. Congress**
    - Results Required Within **12 Months of Completion** (Interventions)
        - Defined As Collection of Primary Endpoint on Final Study Subject

Background on ClinicalTrials.gov

- **“What is ClinicalTrials.gov?”**
  - Database on Clinical Trials, Drugs, Devices, Diseases, etc.
  - Registered at Beginning, Updated Throughout (P.I. or Sponsor)
- **“Who Uses ClinicalTrials.gov?”**
  - **Patients**, **Public**, various Healthcare Professionals, the IRB
- **“Why Should I Register and Submit Results?”**
  - Fulfill Ethical Obligations (IRB Approval, Informed Consent)
  - Reduce Publication Bias
  - Limit Falsification, Fabrication

Understanding ClinicalTrials.gov

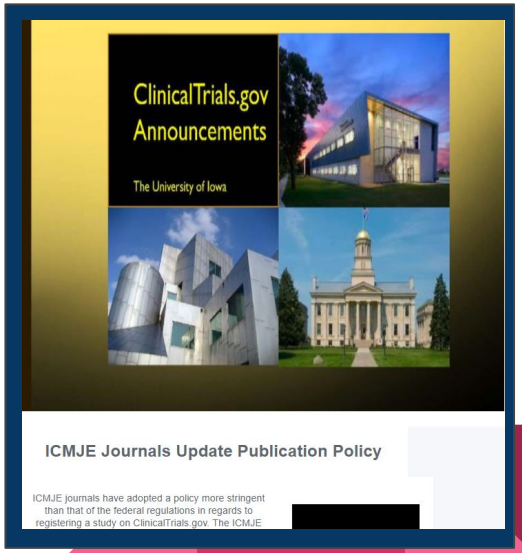




Updates to Clinical Trials' Regulations

- **International Committee of Medical Journal Editors' Regulations (ICMJE) UPDATE (June 2017)**
  - July 1, 2018: ICMJE Journals with Results MUST CONTAIN **Data Sharing Statement**
  - July 1, 2019: Data Sharing Statement Required in ClinicalTrials.gov

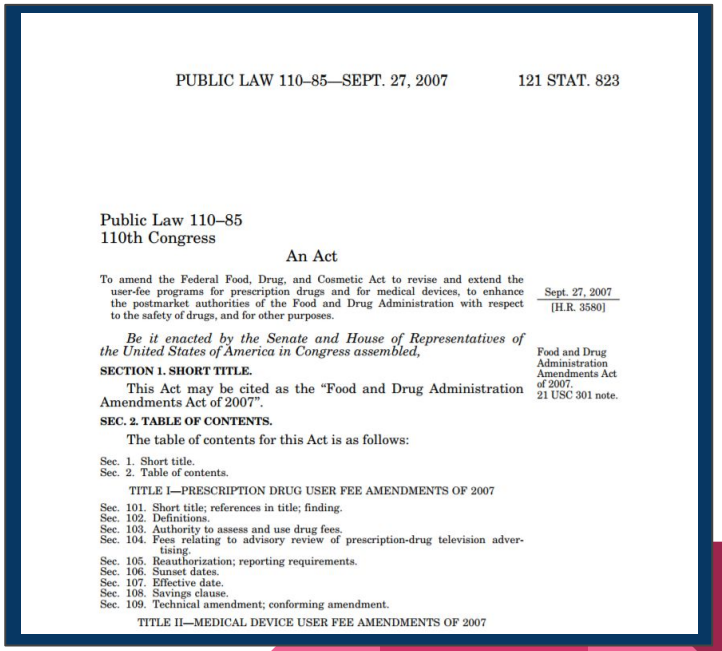
ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS



Penalties for Not Uploading to ClinicalTrials.gov

- **Civil Monetary Penalties (Potentially $10,000/day)**
- **Withholding of Grants (Typically Federally Funded Studies)**

As of today, July 20, 2017, we are unaware of any significant enforcement of these penalties (or any) for failing to report results on ClinicalTrials.gov.



PUBLIC LAW 110–85—SEPT. 27, 2007 121 STAT. 823

Public Law 110–85
110th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and for medical devices, to enhance the postmarket authorities of the Food and Drug Administration with respect to the safety of drugs, and for other purposes.

Sept. 27, 2007
[H.R. 3580]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Food and Drug Administration Amendments Act of 2007.
21 USC 301 note.

SECTION 1. SHORT TITLE.

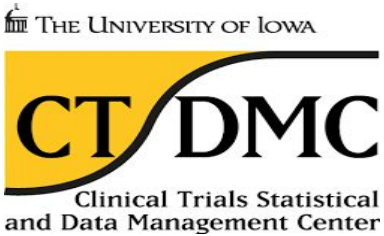
This Act may be cited as the "Food and Drug Administration Amendments Act of 2007".

SEC. 2. TABLE OF CONTENTS.

The table of contents for this Act is as follows:

Background on *Neurology*

- **"What is *Neurology*?"**
  - Official Journal of American Academy of Neurology (AAN)
  - "The Most Widely Used and Highly Cited Peer-Reviewed Neurology Journal"
- **"Why Did We Choose Neurology?**
  - **University of Iowa Clinical Trials Statistical and Data Management Center** → Neurological Focus
  - Manageable, Contained Study



Understanding ClinicalTrials.gov vs. *Neurology*

Descriptive Information	
Brief Title ICMJE	MK0974 (Telcagepant) for Migraine Prophylaxis in Patients With Episodic Migraine (0974-049)
Official Title ICMJE	A Phase IIa, Multicenter, Randomized, Placebo-controlled Clinical Trial to Study the Safety and Efficacy of MK0974 for Migraine Prophylaxis in Patients With Episodic Migraine
Brief Summary	A study to assess the safety and efficacy of MK0974 for preventing migraines in patients with episodic migraine.
Detailed Description	*Not Provided*
Study Type ICMJE	Interventional
Study Phase	Phase 2
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Participant, Investigator Primary Purpose: Treatment
Condition ICMJE	Migraine
Intervention ICMJE	• Drug: Telcagepant 140 mg Other Name: MK-0974 • Drug: Telcagepant 280 mg Other Name: MK-0974 • Drug: 140 mg telcagepant placebo • Drug: 280 mg telcagepant placebo
Study Arms	• Experimental: Telcagepant 140 mg

Measured Values

	Telcagepant 140 mg	Telcagepant 280 mg	Placebo
Participants Analyzed [Units: Participants]	248	247	125
Change From Baseline in Mean Monthly Headache Days [Units: Days per month] Mean (95% Confidence Interval)	-3.4 (-3.9 to -2.8)	-3.6 (-4.1 to -3.1)	-2.4 (-3.2 to -1.7)

ARTICLES

Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention

Tony W. Ho, MD
Kathryn M. Connor, MD
Ying Zhang, PhD
Eric Pearlman, MD, PhD
Janelle Koppenhaver, MA
Xiaoyin Fan, PhD
Christopher Lines, PhD
Lars Edvinsson, MD
Peter J. Goadsby, MD
David Michelson, MD

ABSTRACT

Objective: To evaluate whether the calcitonin gene-related peptide (CGRP) receptor antagonist telcagepant might be effective for migraine prevention.

Methods: In this randomized, double-blind, placebo-controlled, multicenter trial (ClinicalTrials.gov NCT00797667), patients experiencing 3–14 migraine days during a 4-week baseline were randomized to telcagepant 140 mg, telcagepant 280 mg, or placebo twice daily for 12 weeks. Efficacy was assessed by mean monthly headache days and migraine/probable migraine days (headache plus ≥1 associated symptom).

Results: The trial was terminated following a recommendation from the Safety Monitoring Board due to hepatotoxicity concerns. At termination, the planned 660 patients had been randomized, 656 had been treated with ≥1 dose of study medication, and 14 had completed the trial. The

the 4-week period prior to screening. Due to potential interactions with telcagepant, patients taking potent and moderate CYP3A4 inhibitors, potent CYP3A4 inducers, or specific CYP3A4 substrates within 1 month of screening were ineligible, and these medications were not permitted during the study.

Design. This randomized, double-blind, placebo-controlled, parallel-group phase 2 study (Merck Protocol 049) was performed at 91 investigative sites in the United States from December 2008 to April 2009. The study was designed to test Class I hypotheses that at least one telcagepant dose regimen

Statistical analyses. The planned endpoints were intended to evaluate change from baseline to the end of 12 weeks. There were 2 primary efficacy endpoints: mean monthly headache days and mean monthly migraine/probable migraine days. All patients who were randomized, took ≥1 dose of study medication, and had ≥1 postrandomization efficacy measurement were included in the treatment group to which they were randomized. The primary efficacy hypotheses were tested using a constrained longitudinal data analysis method[19] that included both baseline and postbaseline mean monthly headache days (migraine/probable

The Roots of the Research: Becker, 2015

- **“Reporting Of Results In ClinicalTrials.gov And High-Impact Journals: A Cross-Sectional Study”**
  - Jessica E. Becker, Yale School of Medicine (M.D. Thesis)
- **Clinical Trial Selection Parameters**
  - Medline-Indexed Journal
  - July 1, 2010 --> June 30, 2011 **(n = 4,586)**
  - Impact Factor >= 10 (Web of Knowledge) **(n = 831)**
  - Results Reported as of January 2012 (Data Collection Begun) **(n = 149)**
  - Only FDA Mandated Main Trial Results **(n = 96)**

Becker's Results (Becker, 2015)

- **95 of 96 Articles HAD A DISCREPANCY**
  - 30% Discordant Trial Cohort Descriptions
  - 28% Discordant Intervention Definitions
  - **28% Discordant Primary Outcome or Results**
    - **29% of Those LED TO DIFFERENCES IN INTERPRETATION**
  - 95% Discordant Secondary Outcome or Results
  - 50% Discordant Adverse Effects

Results Information	Trials Reporting, No. (%)		Comparison of Reported Information among Trials Reporting in Both Sources, No. (%)		
	ClinicalTrials.gov	Publication	Concordant	Discordant	Could Not Be Compared
Cohort Characteristics					
Enrollment No.	96 (100)	96 (100)	94 (98)	2 (2)	0 (0)
Completion Rate	90 (94)	90 (94)	70 (78)	20 (22)	0 (0)
Sample Age Distribution	96 (100)	96 (100)	56 (58)	6 (6)	34 (35)
Sample Sex Distribution	96 (100)	96 (100)	85 (89)	9 (9)	2 (2)
Trial Intervention	96 (100)	96 (100)	65 (68)	15 (16)	16 (17)
Efficacy Endpoints					
Primary*	91 (95)	91 (95)	81 (61)	21 (16)	30 (23)
Secondary†	89 (93)	94 (98)	338 (55)	53 (9)	228 (37)

Becker's Comparisons (Journals/ClinicalTrials.gov)

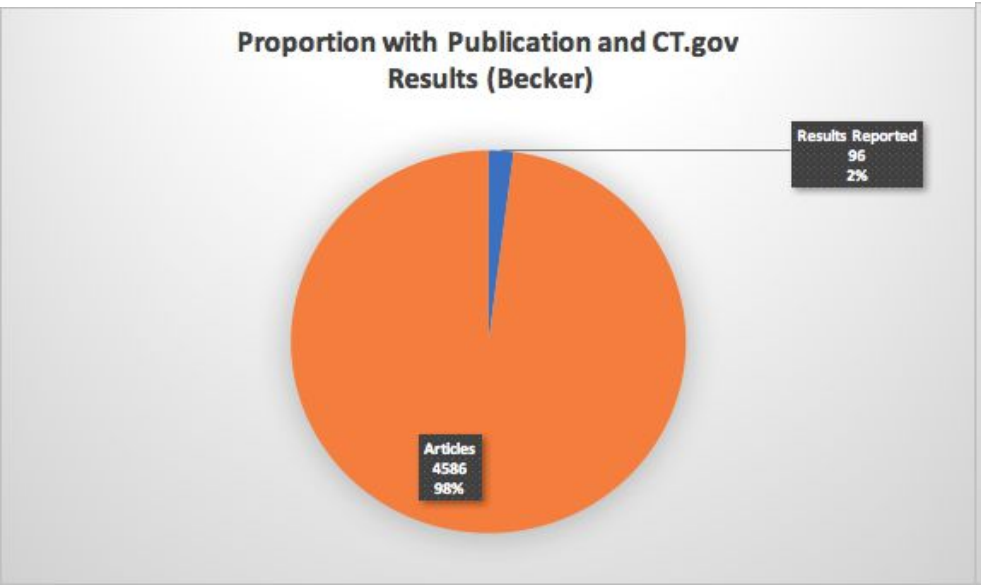
- Cohort Characteristics
- Trial Intervention
- Primary and Secondary Efficacy Endpoint Definitions and Results
- Adverse Effects

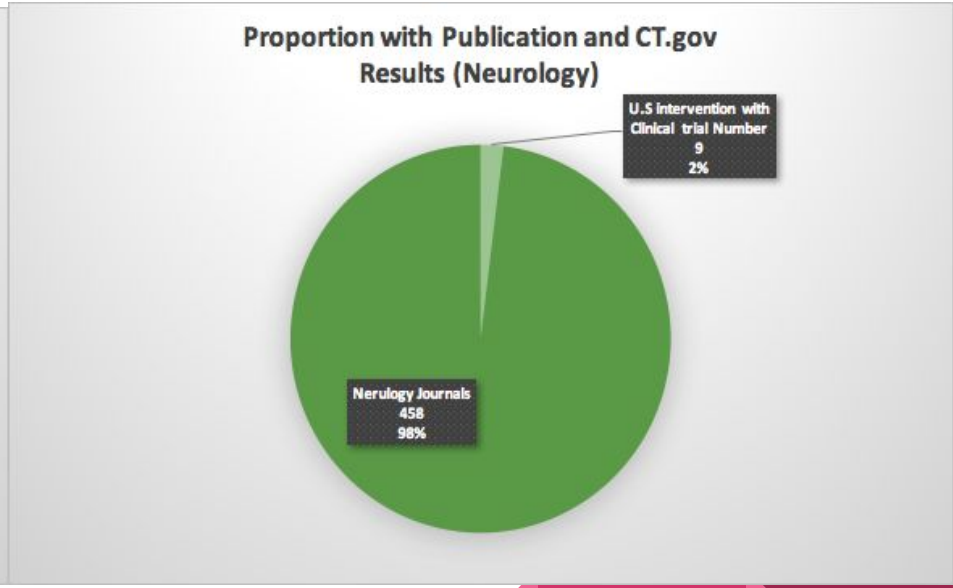
The Standard of "Numerically Equal" (Becker 2015) -- What Does this Mean?

This Study's Parameters

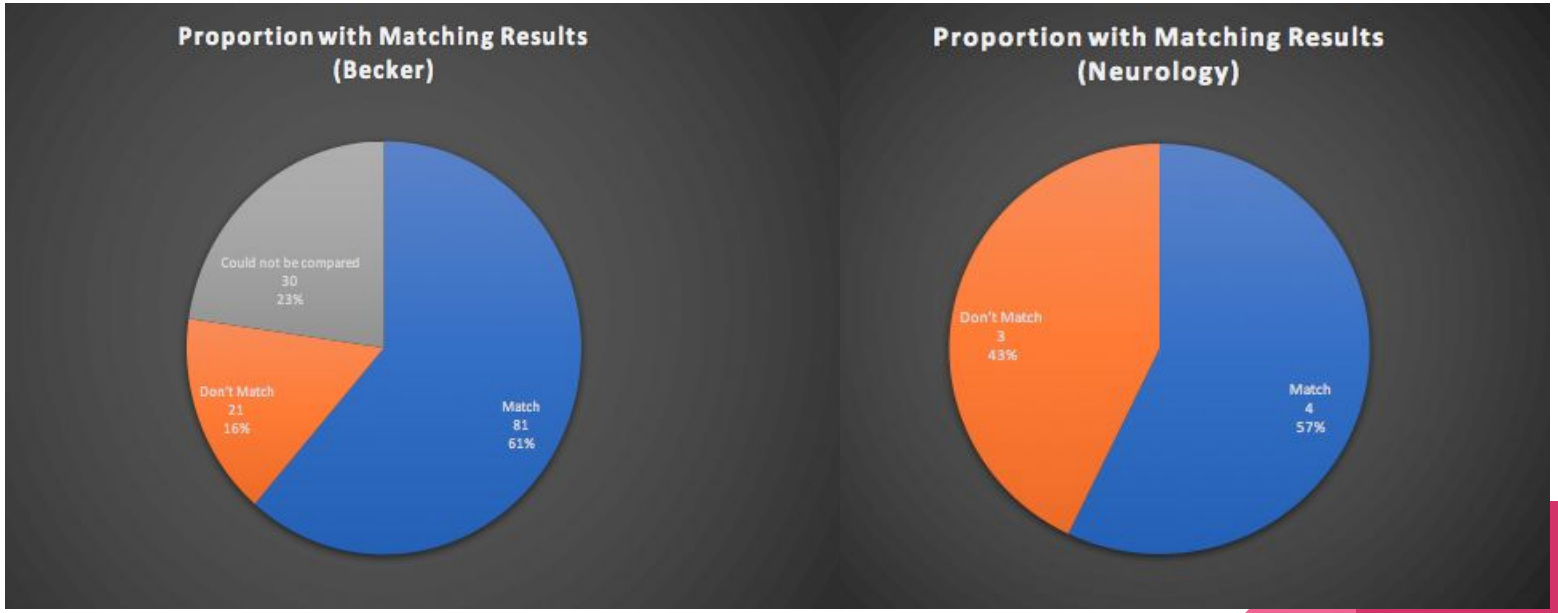
- **Clinical Trial Selection Parameters**
  - Medline-Indexed Journal *(Neurology)*
  - ~~July 1, 2010 --> June 30, 2011~~ January 1, 2014 → December 31, 2014 **(n = 467)**
  - ~~All Reported Data Elements Included (Lead Funder, Design, Condition Studied, etc.)~~
  - ~~Impact Factor >= 10 (Web of Knowledge)~~
  - ~~Results Reported as of January 2012 (Data Collection Begun)~~
  - ~~Only FDA Mandated Main Trial Results~~
  - Interventional Studies **(n = 43)**
  - United States **(n = 20)**
  - Results Published at ClinicalTrials.gov **(n = 9)**
  - *Neurology* Article is **Primary** Record of Clinical Trial Results **(n = 7)**

Proportion Comparisons (Dual Results)





Proportion Comparisons (Match vs. Not Match)



Additional Observations

1. **Observations about the Two Records Excluded (n = 9 - 2)**
    a. Clinical Trial Finished in 2004, Posted in 2017? --- Motivations behind Posting Results?
2. **Observations about the Four Records that Matched**
    a. ENTIRELY Different Authors between ClinicalTrials.gov and *Neurology*
    b. Slight Differences -- Difficult to Report Primary Endpoints in Two Different Formats (i.e. Neurology and ClinicalTrials.gov)
        i. **EXAMPLE: "MS Activity in RESTORE"**
3. **Observations about the Three Records that Didn't Match**
    a. Trial Stopped Early, Differences in Data Analysis, Interim Results NEVER UPDATED

An Example of a “Match”: Food for Thought

- **“MS Disease Activity in RESTORE”**
  - Match or No Match? → Unclear, Required Multiple Discussions
  - Multiple Tables in *Neurology* Combined and Re-Ordered *Approximated* ClinicalTrials.gov Results
    - Are the Results Based on the Same Data? **YES**
    - Could a Typical Reader/Researcher Replicate the Results in *Neurology* SOLELY from ClinicalTrials.gov?

      HIGHLY UNLIKELY
- **Becker’s “Numerically Equal” Standard**
  - What is True “Reproducibility?”
  - What Does it Mean to Report Results Accurately (a “Match”)?
  - To What Extent Must Results Be Easily Interpretable?

Table 2 Patients with disease recurrence during the randomized treatment period

	All patients, n (%) (95% CI)	High disease activity, n (%) (95% CI)[a]	Low disease activity, n (%) (95% CI)
Patients with MRI disease recurrence[b]			
Total	49/167 (29) (22.6-36.9)	23/68 (34) (22.8-46.3)	26/99 (26) (17.9-36.1)
Natalizumab	0/45 (0) (0-7.9)	0/19 (0) (0-17.6)	0/26 (0) (0-13.2)
Placebo	19/41 (46) (30.7-62.8)	11/19 (58) (33.5-79.7)	8/22 (36) (17.2-59.3)
Other therapies			
IM IFN-β-1a	1/14 (7) (0.2-33.9)	0/4 (0) (0-60.2)	1/10 (10) (0.3-45.5)
GA	8/15 (53) (26.6-78.7)	5/7 (71) (29.0-96.3)	3/8 (38) (8.5-75.5)
MP	21/52 (40) (27.0-54.9)	7/19 (37) (16.3-61.6)	14/33 (42) (25.5-60.8)
Patients with relapse			
Total	25/167 (15) (9.9-21.3)	14/68 (21) (11.7-32.1)	11/99 (11) (5.7-19.0)
Natalizumab	2/45 (4) (0.5-15.1)	2/19 (11) (1.2-33.1)	0/26 (0) (0-13.2)
Placebo	7/41 (17) (7.2-32.1)	2/19 (11) (1.2-33.1)	5/22 (23) (7.8-45.4)
Other therapies			
IM IFN-β-1a	4/14 (29) (8.4-58.1)	2/4 (50) (6.8-93.2)	2/10 (20) (2.5-55.6)
GA	4/15 (27) (7.8-55.1)	3/7 (43) (9.9-81.6)	1/8 (13) (0.3-52.7)
MP	8/52 (15) (6.9-28.1)	5/19 (26) (9.1-51.2)	3/33 (9) (1.9-24.3)

	Natalizumab	Intravenous Placebo	Interferon β-1a	Glatiramer Acetate	Methylprednisolone
Participants Analyzed [Units: Participants]	45	41	14	15	52
Time Course to Return of Radiological and/or Clinical Evidence of Multiple Sclerosis Activity, as Measured by the Percentage of Subjects Who Met Magnetic Resonance Imaging (MRI) and/or Clinical Relapse Rescue Criteria. [Units: Percentage of subjects meeting criteria]	4.7	60.5	28.6	53.3	54.8

Takeaways for Statisticians and Clinicians

- **Timely Reporting is Difficult**
  - The Level of Difficulty Would Probably Surprise the General Public
- **The “Bar” for Reporting Outcomes and Publically Sharing Data is Being Raised All the Time**
- **Studies on Frequentist, Accurate Reporting of Clinical Trials Can Raise Awareness of the Challenges and Inherent Behaviors of Self-Reporting**

Acknowledgments

- **Iowa Summer Institute in Biostatistics --** Gideon K. D. Zamba, PhD., Miles Dietz-Castel, Terry Kirk, Joe Cavanaugh, PhD.
- **Advisor:** Eric Foster, PhD.
- **Sponsored by the National Heart Lung and Blood Institute (NHLBI), Grant # HL131467**

NIH National Heart, Lung, and Blood Institute

The University of Iowa

Questions?