Critical Analysis of Clinical Trials
Assessing Therapeutic Value

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“Any astronomer can predict just where every star will be at half past eleven tonight. He can make no such prediction about his daughter.”

James Truitt Adams

Evidence-Based Medicine
What it Is

1. Critical evaluation of the medical literature in order to help define the true value of different therapeutic interventions
   • An explicit assessment of current best evidence regarding treatment
2. Provides an aid in medical decision making
3. It cannot, however, be the sole guide to physician behavior
   • Individual clinical expertise must be integrated with research evidence

Torpy JM et al. JAMA. 2006; 296(9): 1192.
Evidence-Based Medicine
What it Isn’t

1. Expert consensus regarding treatment
2. Based on anecdotal information
3. Based on marketing campaigns
4. Encourage a ‘cook-book’ approach to medicine or the strict adherence to guidelines

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Estimating the Treatment Effect
Evidence Based Medicine

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EBM Assessment Tools

- Systematic Reviews
- Meta-analyses
- Relative Risk
- Number needed to treat (NNT)
- Number needed to harm (NNH)

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Outcome Assessment

Relative Risk

$$RRisk = \frac{\text{Risk of illness (exposed or treated)}}{\text{Risk of illness (unexposed or untreated)}}$$

$$RRate = \frac{\text{Rate of illness (exposed or treated)}}{\text{Rate of illness (unexposed or untreated)}}$$

$$ROdds = \frac{\text{Odds of illness (exposed or treated)}}{\text{Odds of illness (unexposed or untreated)}}$$

Outcome Assessment

NNT / NNH

$$\frac{1}{\text{NNT}} = \frac{1}{\text{Risk controls – Risk treated}}$$

$$= \frac{1}{\text{ARR}}$$

$$\frac{1}{\text{NNH}} = \frac{1}{\text{Events / Patient}}$$

$$= \frac{\text{Patients / Event}}{}$$

Prospective Randomized Trial

Randomization

Sampling

Entire Population

Sample Population

Outcome Assessment

$$RR = \frac{(1/6)}{(4/6)} = 0.25$$

$$ARR = \frac{(4/6) - (1/6)}{0.5} = 0.5; \ NNT = 2$$
There are three kinds of lies: lies, damned lies, and statistics.

Benjamin Disraeli
1804-1881

- Type I error rate ($\alpha$) represents probability of incorrectly rejecting the null hypothesis (H0)
  ($\alpha<5\%$ is generally considered significant)
- $p=0.05$ corresponds to a minimum $\alpha$ error (posterior probability) of either 13% (2-sided test) or 21% (1-sided test)
- For minimum $\alpha$ error (posterior) to be 5%, it requires either $p=0.01$ (2-sided test) or $p=0.005$ (1-sided test)
- As a result, observations with $p$-values between 0.01 and 0.05 should be considered marginal
Statistical Concepts
Effect Size and Significance

- Both the magnitude of the clinical effect (the effect size) and the statistical significance provide important complimentary information regarding the quality of the evidence.
- The effect size relates to the clinical importance of the observation.
- The statistical significance relates to the believability of the observation.
- Marginally significant findings of clinical importance and significant findings of marginal importance should both be regarded as equivocal.


Statistical Concepts
Bias

“ It ain’t so much the things we don’t know that gets us into trouble. It’s the things we know that ain’t so.”

Artemus Ward
Clinical Trial Errors
Common Sources

1. Post hoc (unplanned) analyses
   - Identification of subgroups
   - Failure to use *a priori* statistical analysis plan
   - Failure to make appropriate statistical adjustments
   - Failure to recognize implicit comparisons

2. Post hoc data manipulation
   - Exclusion of data
   - Recoding of data
   - Alteration of *a priori* assumptions

3. Inadvertent Sample Bias
   - Use of non-simultaneous comparisons
   - Failure to recognize important covariates

4. Analysis Bias

5. Bias in Systematic Reviews

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Statistical Concepts - Bias
Subgroup Analyses
Sub-Group Analysis

Mean = 4.6 Relapses ± 2.1; [n = 1000]

Sub-Group Analysis

Mean Sub-Group 1 = 4.1 Relapses ± 2.0 [n=500]
Mean Sub-Group 2 = 5.1 Relapses ± 2.3 [n=500]

\[ t = 7.2; \quad p < 10^{-11} \]

IV Atenolol in Myocardial Infarction
Randomized trial of 16,027 Patients

<table>
<thead>
<tr>
<th>Astrological Birth Sign</th>
<th>Reduction in Odds of Death</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire Group</td>
<td>-15% ± 7</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Scorpio</td>
<td>-48% ± 23</td>
<td>p&lt;0.04</td>
</tr>
<tr>
<td>All Others</td>
<td>-12% ± 8</td>
<td>ns</td>
</tr>
</tbody>
</table>

Bonferroni Adjustment (13 independent comparisons):
\[ \alpha = \frac{0.05}{12} = 0.004 \]

Effect of IFNβ on Brain Atrophy
MSCRG Trial

<table>
<thead>
<tr>
<th></th>
<th>IFNβ-1α (n=68)</th>
<th>Placebo (n=72)</th>
<th>p</th>
<th>55% reduction in brain atrophy Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>-0.763</td>
<td>-0.699</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>-0.333</td>
<td>-0.521</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Bonferroni Adjustment (2 independent comparisons):
α = (0.05)/2 = 0.025

MSCRG Trial
Sub-Group Bias

Relapse Rate, Avonex Arm
- 2 Year Completers (57%)
- 2 Year Non-completers (43%)

1 Year Data
- 29%

2 Year Data
- 32%

Statistical Concepts - Bias
Post-Hoc Adjustments
### Post Hoc Analysis Bias

<table>
<thead>
<tr>
<th>Height of Group I</th>
<th>Height of Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>5.2 *</td>
<td>5.8</td>
</tr>
<tr>
<td>5.2</td>
<td>6.3</td>
</tr>
<tr>
<td>5.5</td>
<td>6.1</td>
</tr>
<tr>
<td>5.3</td>
<td>5.9</td>
</tr>
<tr>
<td>6.0</td>
<td>5.2</td>
</tr>
<tr>
<td>5.1</td>
<td>5.8</td>
</tr>
<tr>
<td>5.3</td>
<td>6.4</td>
</tr>
<tr>
<td>5.6</td>
<td>5.1 *</td>
</tr>
<tr>
<td>5.7</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Mean Height: 5.5

Mean Height: 5.9

Significance of difference in mean height between groups:

\[ t = 2.1; \ p < 0.06 \]

* If these subjects are excluded from analysis (i.e., 10% excluded):
  \[ t = 3.7; \ p < 0.005 \]

* If these subjects are recoded as being in the opposite group (i.e., 10% recoded):
  \[ t = 4.9; \ p < 0.0005 \]

### Design and Methods

ONTT

1. **Primary Outcomes**
   1. Visual field
   2. Contrast sensitivity

2. **Secondary Outcomes**
   1. Visual acuity
   2. Color vision

### Results of the ONTT (1992)

**Primary Outcomes:** (6-month recovery)

1. Visual field: IVMP = placebo (p=0.054)
2. Contrast sensitivity: IVMP > placebo (p=0.049)

**Secondary Outcomes:** (6-month recovery)

1. Visual acuity: IVMP = placebo (p=0.764)
2. Color vision: IVMP = placebo (p=0.055)

IVMP=Intravenous methylprednisone.
Results of the ONTT
(1992)

Exploratory Outcomes (Two Years):
1. Rate of Recurrent ON:
   - Oral Prednisone > Placebo;
     RR = 1.79;  p = 0.02
   - IVMP = Placebo;
     RR = 0.81;  ns

2. Rate of CDMS:
   - Oral Prednisone = Placebo;
     RR = 1.17;  ns
   - IVMP = Placebo;
     RR = 0.65;  ns (CI = 0.37-1.17)


Recoding of Data
ONTT

Patients underwent a masked re-coding for both baseline and F/U status between 1992 and 1993

Baseline Status
a. 4 patients were changed from non-MS to CDMS.
b. 5 patients were changed from CPMS to CDMS.

Follow-up Status
a. 8 patients were changed from CDMS to non-CDMS because diagnosis had been made only on the basis of fellow-eye optic neuritis.
b. 4 patients were changed from CDMS to non-CDMS because criteria were not met.
c. 1 patient was changed from non-CDMS to CDMS because criteria were met.

New Data from Second Study
a. 12 patients were excluded because of CPMS at baseline with new CDMS at F/U

As a result of these changes we would expect:
a. $83^* - 4 - 5 - 8 - 4 + 1 - 12 = 51$ patients with CDMS in 1992 using 1993 criteria

$^*$ number of pts with new CDMS in the 1992 (50 identified in 1993)


Exclusion and Inclusion Criteria
ONTT (1993)

Patients Excluded from ONTT (1993)
- 35 patients with Clinically Definite MS
- 30 patients with Clinically Probable MS
- 2 patients with compressive optic neuropathy

Patients Excluded from ONTT (1993)
- 17 patients with prior fellow-eye optic neuritis
- 79/89 patients with prior neurological symptoms described as "consistent with MS"
- 150 patients with grade 2-4 MRI scans
d. 2 patients with optic neuritis secondary to connective tissue disease
- 3 patients with ischemic optic neuropathy

Baseline Poser Category

Patients Included in ONTT (1993)
- CDMS A1 or CPMS C1
- CDMS A1 or CPMS C1 / C2
- CDMS A2 or CPMS C3
- non-MS
- non-MS

Statistical Concepts - Bias
Non-Simultaneous Comparisons

Non-Concurrent Control Group
Treatment v. Baseline Design

- MRI Scans
- Clinical Evaluation

Vollmer et al., Lancet 2004;363:1607

Annual Attack Rate
Placebo Group

- Avonex
- Betaferon
- Copaxone
- Rebif
- Tysabri

p < 0.0001  p < 0.0001  p < 0.002  p < 0.0001
Statistical Concepts - Bias
Long-Term Data

Long-Term (6 yr) Follow-up GA Trial
Outcome during Double Blind Phase

- Elected to Continue on GA (n = 208)
- Elected not to Continue (n = 43)

Disability Progression

\( p < 0.001 \)

Annual Attack Rate

\( p < 0.001 \)

The Extended GA Study
Clinical Outcome, 10 years

- 108 patients (43%) on continuous GA therapy
  (Range: 7.9 - 11.9 yrs)
  - 8% with EDSS \( \geq 6.0 \)
  - GA Start EDSS = 2.56
  - 10 yr EDSS = 3.06
- 50 patients who dropped out but returned for LTFU
  - 50% with EDSS \( \geq 6.0 \)
  - GA Start EDSS = 2.98
  - 10 yr EDSS = 5.22 \( (p < 0.0001) \)
### Outcome in 6 yr GA Study
**Comparison to Natural History**

<table>
<thead>
<tr>
<th></th>
<th>GA Extended, 6 yr</th>
<th>London, Ontario†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unchanged</td>
<td>69%</td>
<td>23%</td>
</tr>
<tr>
<td>Worse (Δ EDSS ≥ 1)</td>
<td>31%</td>
<td>77%</td>
</tr>
</tbody>
</table>

* 47% (EDSS ≤ 2); 41% (EDSS = 2-4); 12% (EDSS = 4-5)
† 42% (EDSS ≤ 3); 9% (EDSS = 4-5); 49% (EDSS > 5)


### Outcome in 10 yr GA Study
**Comparison to Natural History**

<table>
<thead>
<tr>
<th></th>
<th>GA Extended Mean EDSS = 2.6*</th>
<th>Rochester, MN EDSS &lt; 3.0†</th>
<th>Rochester, MN EDSS ≤ 5.0†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing GA / Stable</td>
<td>43%</td>
<td>68%</td>
<td>62%</td>
</tr>
<tr>
<td>Dropped out / Worse</td>
<td>57%</td>
<td>32%</td>
<td>38%</td>
</tr>
</tbody>
</table>

* 47% (EDSS ≤ 2); 41% (EDSS = 2-4); 12% (EDSS = 4-5)
† 41% (EDSS < 3); 29% (EDSS = 3-5); 39% (EDSS > 5)


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**Evidence Based Medicine**
**Assessing the Data**
EBM
Structure of an Assessment

- Defining the problem:
  - formulating the clinical question

- Assembling evidence:
  - literature search; defining inclusion/exclusion criteria

- Classifying and interpreting/evidence:
  - different classification schemes exist but all are quite similar

- Translating evidence into recommendations

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>Class of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Control Group</td>
<td>●</td>
</tr>
<tr>
<td>Representative Population</td>
<td>●</td>
</tr>
<tr>
<td>Assessment Independent of R{x}</td>
<td>●</td>
</tr>
<tr>
<td>Blinded Outcome Assessment</td>
<td>●</td>
</tr>
<tr>
<td>Prospective Design</td>
<td>●</td>
</tr>
<tr>
<td>Randomized *</td>
<td>●</td>
</tr>
</tbody>
</table>

* Also meets standards of:
  - Primary outcomes defined;
  - Exclusion/inclusion criteria defined;
  - Dropout rate low and accounted for;
  - Baseline characteristics detailed and substantially equivalent.

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Level of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 Consistent Class I Studies</td>
<td>A</td>
</tr>
<tr>
<td>≥ 1 Convincing* Class I Study</td>
<td>●</td>
</tr>
<tr>
<td>≥ 2 Consistent Class II Studies</td>
<td></td>
</tr>
<tr>
<td>≥ 1 Convincing* Class II Study</td>
<td></td>
</tr>
<tr>
<td>≥ 2 Consistent Class III Studies</td>
<td></td>
</tr>
</tbody>
</table>

* = Lower limit of the 95% CI for Odds Ratio ≥ 2.0

A = Established as effective, ineffective, or harmful
B = Probably effective, ineffective, or harmful
C = Possibly effective, ineffective or harmful
U = Data inadequate or conflicting

### Classifying the Evidence

**MS Clinical Trials**

#### Interferon-β Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Size</th>
<th>Control</th>
<th>Randomized</th>
<th>Prospective</th>
<th>Blinded</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betaseron, RRMS</td>
<td>372</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
<tr>
<td>Avonex, RRMS</td>
<td>301</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
<tr>
<td>Rebif, RRMS</td>
<td>560</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
<tr>
<td>Betaseron, SPMS (E)</td>
<td>718</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
<tr>
<td>Betaseron, SPMS (NA)</td>
<td>939</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
<tr>
<td>Avonex, SPMS</td>
<td>436</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
<tr>
<td>Rebif, SPMS</td>
<td>506</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
</tbody>
</table>

#### Glatiramer Acetate Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Size</th>
<th>Control</th>
<th>Randomized</th>
<th>Prospective</th>
<th>Blinded</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copaxone, RRMS</td>
<td>251</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
</tr>
<tr>
<td>Copaxone, RRMS (9 mo)</td>
<td>249</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>I</td>
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<tr>
<td>Copaxone, Extended</td>
<td>152</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>?III</td>
</tr>
<tr>
<td>Copaxone, Comparative</td>
<td>156</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>?III</td>
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</tbody>
</table>

Natalizumab Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Size</th>
<th>Control Group</th>
<th>Randomized</th>
<th>Prospective</th>
<th>Blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II, RRMS</td>
<td>213</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>● I</td>
</tr>
<tr>
<td>AFFIRM, RRMS</td>
<td>942</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>● I</td>
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<tr>
<td>SENTINEL, RRMS</td>
<td>1171</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>● I</td>
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</tbody>
</table>


Analyzing the Evidence

MS Clinical Trials

Interferon-β Trials

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Betaseron, RRMS</td>
<td>●</td>
<td>●</td>
<td>ns</td>
<td>●</td>
</tr>
<tr>
<td>Avonex, RRMS</td>
<td>●</td>
<td>●</td>
<td>ns</td>
<td>●</td>
</tr>
<tr>
<td>Rebif, RRMS</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Betaseron, SPMS (E)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Betaseron, SPMS (NA)</td>
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<td>●</td>
<td>ns</td>
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<td>Avonex, SPMS</td>
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<td>●</td>
<td>ns</td>
<td>●</td>
</tr>
<tr>
<td>Rebif, SPMS</td>
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<td>ns</td>
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</table>

### Glatiramer Acetate Trials

**MS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Clinical Activity</th>
<th>MRI Activity</th>
<th>Clinical Severity</th>
<th>MRI Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copaxone, RRMS</td>
<td>•</td>
<td></td>
<td>•</td>
<td>ns</td>
</tr>
<tr>
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<td>•</td>
<td>•</td>
<td>•</td>
<td>ns •</td>
</tr>
<tr>
<td>Copaxone, Extended</td>
<td>•</td>
<td>?</td>
<td>•</td>
<td>?</td>
</tr>
<tr>
<td>Copaxone, Comparative</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- • Significantly Improved (p<0.01)
- • Marginally Improved (P=0.01-0.05)
- ns not improved


### Natalizumab Trials

**MS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Clinical Activity</th>
<th>Clinical Severity</th>
<th>MRI Severity</th>
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<tbody>
<tr>
<td>Phase II, RRMS</td>
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<td>• •</td>
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<td>• •</td>
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<tr>
<td>SENTINEL, RRMS</td>
<td>• •</td>
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<td>• •</td>
</tr>
</tbody>
</table>


### Current and Emerging Therapies in MS

**Douglas S. Goodin**
The Need for Head-to-Head Trials

Relative Efficacy (RR)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relapse Rate (%)</th>
<th>Progression-free (%)</th>
<th>New T2 Lesions (%)</th>
<th>Gd+ Lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1a 30 µg qw</td>
<td>-16%</td>
<td>-34%</td>
<td>-24%</td>
<td>-64%</td>
</tr>
<tr>
<td>IFNβ-1b 250 µg qod</td>
<td>+42%</td>
<td>+96%</td>
<td>+96%</td>
<td>+57%</td>
</tr>
<tr>
<td>IFNβ-1a 44 µg tiw</td>
<td>-37%</td>
<td>-96%</td>
<td>-30%</td>
<td>-42%</td>
</tr>
<tr>
<td>GA 20 mg qd</td>
<td>-38%</td>
<td>-92%</td>
<td>-70%</td>
<td>-43%</td>
</tr>
<tr>
<td>NTZ 300 mg qm</td>
<td>-48%</td>
<td>-98%</td>
<td>-33%</td>
<td>-60%</td>
</tr>
</tbody>
</table>

Relapse rate (annualized)

Relapse-Free (2 years)

New T2 Lesions

Gd+ Lesions

BOD

-6%  -17%  -15%  -8%  -18%

The Need for Head-to-Head Trials

Absolute Efficacy (NNT / NNH)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relapse Rate (%)</th>
<th>Progression-free (%)</th>
<th>New T2 Lesions (%)</th>
<th>Gd+ Lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNβ-1a 30 µg qw</td>
<td>7.3</td>
<td>2.9</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>IFNβ-1b 250 µg qod</td>
<td>8.6</td>
<td>6.8</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>IFNβ-1a 44 µg tiw</td>
<td>8.6</td>
<td>13.5</td>
<td>10.4</td>
<td>8.6</td>
</tr>
<tr>
<td>GA 20 mg qd</td>
<td>13.3</td>
<td>0.34</td>
<td>0.3</td>
<td>0.17</td>
</tr>
<tr>
<td>NTZ 300 mg qm</td>
<td>13.6</td>
<td>2.15</td>
<td>0.15</td>
<td>0.89</td>
</tr>
</tbody>
</table>

All Drop Out

-33  14  27  21  42

The REGARD Trial

Time to First Relapse (1st endpoint)

Hazard ratio (95% CI):

\[ 0.943 (0.74, 1.21) \]

\[ p = 0.643 \]
The BEYOND Trial
Relapse Risk (1st endpoint)

Primary Analysis

Sensitivity Analysis
(no major protocol violations, 100% of doses, post-hoc)

IFNβ-1b
500 μg vs. 250 μg

P-value (one-sided)
P = 0.16
P = 0.73
P = 0.43

Betaseron
250 μg vs. GA
IFNβ-1b
500 μg vs. GA

P = 0.29

The BEYOND Trial
Relapse Risk (1st endpoint)

AFFIRM, BEYOND, and REGARD Trials
Relapse Rates (Before and After Rx)

Annual Attack Rate

Year Prior to Rx
After Rx

AFFIRM
BEYOND
REGARD

Event Rates in MS Clinical Trials
Summary of the “On-Drug” Experience

By Date of Study End
One clear advantage of the NNT approach is that it lends itself, naturally, to cost-benefit analyses which can be useful in setting societal priorities.

However, cost-benefit should not be confused with efficacy.

The combined use of the NNT and NNH approach also seems to lend themselves to assessment risk-benefit but, here, looks can be deceiving.

Both are outcome-dependent. So is RR, but more transparently.

RR exaggerates small absolute differences. For example, changing a persons risk from 0.1% to 2% represents an absolute change of only 1.9% but a 20-fold increase in relative risk.

When comparing efficacy, neither approach is preferred. Both methods provide complimentary views of the data. If they don’t agree, all bets are off.

“Researchers have already cast much darkness on the subject, and if they continue their investigations we shall soon know nothing at all about it.”

Mark Twain