Outcomes (? stating the obvious)

1) **Long term** outcomes (LTOs) account for main social, medical & economic impact of MS, exponentially w T
2) SP - main determinant LTO, progressive cane, bed, dead
3) Development of SP matters most to patients, families, 3rd party payers - predictable, irreversible
4) SP Rx Studies negative, 0 focus on SP devel In RR trials
5) Relapse/MRI reduction - many Rx - none convincingly influence LTO, lengthen T to SP, nor SP probability
6) Relapses not suitable outcomes if LTO is target and short term “disability” measures relapses not disability
7) Nat Hist data on early relapses operate via SP so this is what should be measured if you insist on relapses
“It is important to measure what matters most, not make what can most easily be measured matter.”

Very apropos of MS clinical trials as this epitomises much of the last 25 years

So let’s go back 25 years
Table 1. Measures of response to experimental therapy

<table>
<thead>
<tr>
<th>Outcome measure (ranked)</th>
<th>Responses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probably significant n (%)</td>
<td>Most convincing n (%)</td>
</tr>
<tr>
<td>Change EDSS ≥ 1.0 on 2 consecutive exams</td>
<td>29 (47)</td>
<td>19 (30)</td>
</tr>
<tr>
<td>Change ambulation index ≥ 2 steps on 2 consecutive exams</td>
<td>21 (34)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Change mean EDSS between treatment groups</td>
<td>34 (55)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Change mean ambulation index between groups</td>
<td>36 (58)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Number MRI events</td>
<td>27 (44)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Opinion blinded MD</td>
<td>29 (47)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Change mean quantitative neurologic exam between groups</td>
<td>25 (40)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Estimated probability of no worsening</td>
<td>25 (40)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Number of treatment failures per group</td>
<td>26 (42)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Time to treatment failure</td>
<td>24 (39)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Relapse frequency</td>
<td>24 (39)</td>
<td>8 (13)</td>
</tr>
</tbody>
</table>
London Ont. Natural History Study

1023 pts followed yearly (806 RR rest PP)

Population-based sample

“Full” ascertainment

concomitant prev. study Middlesex Cty core subcohort (n=300)

Stable population

little outmigration,

NH 1-10, Weinshenker et, Cottrell et, Kremenchutzky et, Scalfari et

i saw 20-30 MS patients for almost 25y to collect plus many colleagues
Reanalysis 28,000 patient-yrs.

shortest followup in the sample was 16 years
and the only nat hist study giving an accounting of loss/retention

95% followup  806 RR

97% diagn. accuracy
clin criteria preMR no treatable missed

> 40% dead , > 40% Dss 6+

>75% of lifetime,  >90% ambulatory course

Focus – preSP i.e. from onset
Predictive effect of latency to progression

Duration of RR phase = latency of SP

- Short (continuous line) = 1-5 years
- Int. (dashed line) = 6-12 years
- Long (dotted line) ≥ 13 years

Survival analysis from disease onset

Time to DSS 6

- (RR ≥13 yrs) = 23.2 years
- (RR 6-12 yrs) = 12.6 years
- (RR 1-5 yrs) = 7.6 years

Huge effect

Time to DSS 8

- (RR ≥13 yrs) = 33.9 years
- (RR 6-12 yrs) = 22.2 years
- (RR 1-5 yrs) = 17.5 years

Huge effect
Relapses and progression
DSS 6, 8, 10 i.e. cane, bed, and dead (no sissy outcomes)

**Site of first attack?** cf. compartmentalisation theory Lassmann

- Recovery from first attack complete vs. partial
- Polysymptomatic/disseminated onset vs. unifocal
- PPMS primary progressive disease +/- relapses?

**Age onset progressive course** (none vs one vs many preceding)

- PPMS/SAPMS/SPMS - survival (none vs one vs many)
- Progression and relapses? y1-y2 vs. y3-SP vs all

**Suppression of relapses and progression** LTF data

**Suppression of MRI and progression** LTF data

SAP is single attack followed by progression
Site of first attack ~ irrelevant for long term outcomes

No significant difference among common sites (there might be for low levels but certainly not for 6,8,10)

Brain stem only marginally worse p<0.02 not sig after bonferroni

better and motor cord worse? No

Preferential progress site of initial attacks? No

So much for onset-specific compartmentalisation predicting progression to begin and be worse at sites of previous attacks
Relapses and progression
DSS 6,8,10 i.e. cane, bed, and dead (no sissy outcomes here)

Site of first attack?

Recovery from first attack
Polysymptomatic/disseminated onset vs. unifocal
PPMS primary progressive disease +/- relapses?
Age onset progressive course (none vs one vs many)
PPMS/SAPMS/SPMS - survival (none vs one vs many)
Progression and total relapses? y1-y2 vs. y3-SP
Suppression of relapses and progression? LTF data
Suppression of mri and progression? LTF data

SAP is single attack followed by progression
Complete recovery vs. partial vs. none

No difference - lack of recovery not an intrinsic feature of individual disease
(determined by random factors, evident to experienced clinicians following individual patients and in studies of CIS)
Relapses and progression
DSS 6,8,10 i.e. cane, bed, and dead

- Site of first attack? cf. compartmentalisation theory Lassmann
- Recovery from first attack complete vs. partial
- Polysymptomatic/disseminated onset vs. unifocal
  - PPMS primary progressive disease +/- relapses?
  - Age onset progressive course (none vs one vs many)
  - PPMS/SAPMS/SPMS - survival (none vs one vs many)
- Progression and total relapses? y1-y2 vs. y3-SP
- Suppression of relapses and progression? LTF data
- Suppression of mri and progression? LTF data

SAP is single attack followed by progression.
Polysymptomatic vs. unifocal onset
~Severe vs. mild onset

**No difference** in T to 6, 8, or 10
Relapses and progression
DSS 6,8,10 i.e. cane, bed, and dead

Site of first attack?
Recovery from first attack
Polysymptomatic/disseminated onset vs. unifocal

**PPMS primary progressive disease +/- relapses?**
Age onset progressive course (none vs one vs many)
PPMS/SAPMS/SPMS - survival (none vs one vs many)

Progression and total relapses? y1-y2 vs. y3-SP
Suppression of relapses and progression? LTF data
Suppression of MRI and progression? LTF data

SAP is single attack followed by progression
PPMS with relapses (28%) = PPMS without for times to DSS 6, 8, 10
Survival distribution of PP MS with (PR) & without (‘pure’ PP) superimposed relapses

Time to **DSS8**

No diff in curves to DSS8, no LT rationale for RP MS favoured by Lublin respondents

Kremenchutzky et al, Brain

1999
Relapses and progression
DSS 6, 8, 10 i.e. cane, bed, and dead

Site of first attack?
Recovery from first attack
Polysymptomatic/disseminated onset vs. unifocal
PPMS primary progressive disease +/- relapses?

Age onset progressive course (none vs one vs many attacks)
PPMS/SAPMS/SPMS - survival (none vs one vs many attacks)

Progression and total relapses? y1-y2 vs. y3-SP
Suppression of relapses and progression? LTF data
Suppression of MRI and progression? LTF data

SAP is single attack followed by progression
Do relapses shorten SP latency? main outcome determinant

Mean ages of onset of progressive deficit (DSS≤2)

<table>
<thead>
<tr>
<th>Progressive MS types</th>
<th>Onset progression</th>
<th>Mean (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N = 759</td>
<td></td>
</tr>
<tr>
<td>SPMS - all</td>
<td>N=270</td>
<td>39.4</td>
</tr>
<tr>
<td>SPMS (-SAP)</td>
<td>N=130</td>
<td>39.2</td>
</tr>
<tr>
<td>*SAPMS</td>
<td>N=140</td>
<td>40.9</td>
</tr>
<tr>
<td>PPMS</td>
<td>N=219</td>
<td>38.6</td>
</tr>
</tbody>
</table>

Many relapses preSP vs. none? - onset not sooner but slightly later

NO INDICATION THAT RELAPSES INFLUENCE AGE OF ONSET OF SP

* includes second series of SAPMS
Causality Predictions (widely believed)
(if relapses and late disability were causally related)

Relapse freq influences onset age of SP
as main outcome determinant dwarfing all others
No, none vs. many - sl. earlier onset PP vs SP 38y
SP40y ↑Total attacks relate to worse outcome
No , (actually y3+ assoc. (trials) with better outcome)
Attacks during pivotal trials more
NB No they aren’t, they are clearly less important and no rationale for suppressing them as a primary target
Poss. rationale for v. early attacks
Effect of latency to progression on **SP course itself**

- Little effect on times to DSS6 or 8 from **SP onset** (most SP onset at DSS3)

**Duration of RR phase**
- Short (continuous line) = 1-5 years
- Int. (dashed line) = 6-12 years
- Long (dotted line) ≥ 13 years

Survival analysis from **onset of secondary progression**

- **P = 0.05**
  - Time to DSS 6 (RR ≥13 yrs) = 6.0 years
  - (RR 6-12 yrs) = 4.7 years
  - (RR 1-5 yrs) = 4.8 years

- **p = 0.06**
  - Time to DSS 8 (RR ≥ 13 yrs) = 16.7 years
  - (RR 6-12 yrs) = 13.7 years
  - (RR 1-5 yrs) = 14.4 years

Little effect
Relapses and progression
DSS 6,8,10 i.e. cane, bed, and dead

Site of first attack?
Recovery from first attack
Polysymptomatic/disseminated onset vs. unifocal
PPMS primary progressive disease +/- relapses?
Age onset progressive course

**PPMS/SAPMS/SPMS - survival** (none vs one vs many) 6,8,10
Progression and total relapses? y1-y2 vs. y3-SP
Suppression of relapses and progression? LTF data
Suppression of mri and progression? LTF data

SAP is single attack followed by progression
Time to DSS 6/8/10 - years from onset of progressive MS

DSS10 dead
DSS8 bed
DSS6 cane

% of patients

PP-MS dss2
SP-MS dss2
SAP-MS dss2

yrs
Relapses and progression
DSS 6,8,10 i.e. cane, bed, and dead

Site of first attack?
Recovery from first attack
Polysymptomatic/disseminated onset vs. unifocal
PPMS primary progressive disease +/- relapses?
Age onset progressive course
PPMS/SAPMS/SPMS - survival

**Progression and total relapses?** (y1-y2 vs. y3-SP)
Suppression of relapses and progression LTF data
Suppression of mri and progression LTF data

SAP is single attack followed by progression
Total Relapses during RR phase

<table>
<thead>
<tr>
<th>Num of relapses</th>
<th>HR (p = 0.76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>0.97</td>
</tr>
<tr>
<td>5</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Time to DSS 6

- 1-2 relapses = 15.0 years
- 3-4 relapses = 15.8 years
- ≥ 5 relapses = 15.6 years

Can’t assume relapse suppr. will make diff for T to 6, but this is what has been assumed!

HR = Hazard ratio

Relapses → ? Causal or concomitant? → Late outcome
Relapses Y3 - onset SP assoc. with **better** outcome

**These** are the relapses enumerated in most trials

Scalfari et al. 2010

This is a slightly bigger effect than y1y2 associating with more rapid disability
Early relapses (Y1+Y2) show meaningful association

Time to DSS 6

1 relapse = 22.7 years
2 relapses = 18.7 years
≥ 3 relapses = 15.1 years

<table>
<thead>
<tr>
<th>Num of relapses</th>
<th>HR (p &lt; 0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.23</td>
</tr>
<tr>
<td>2</td>
<td>1.51</td>
</tr>
<tr>
<td>3</td>
<td>1.85</td>
</tr>
<tr>
<td>4</td>
<td>2.27</td>
</tr>
<tr>
<td>5</td>
<td>2.79</td>
</tr>
</tbody>
</table>

Time to SP

1 relapse = 19.9 years
2 relapses = 16.7 years
≥ 3 relapses = 15.1 years

<table>
<thead>
<tr>
<th>Num of relapses</th>
<th>HR (p &lt; 0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.25</td>
</tr>
<tr>
<td>2</td>
<td>1.56</td>
</tr>
<tr>
<td>3</td>
<td>1.94</td>
</tr>
<tr>
<td>4</td>
<td>2.42</td>
</tr>
<tr>
<td>5</td>
<td>3.02</td>
</tr>
</tbody>
</table>
Early relapse association via?

extremes approach - frequent y1y2 relapsers

• 1) relapses leave successive cumulative unremitting disability at relapse time?
   Answer: it does to a degree in minority so 1/5 get to DSS3 via relapse and stay there but no impact on 6,8,10 for total relapse frequency

• 2) increased probability of progression?
   Answer: marginally

   3) shortened latency to SP?
   Answer: yes big effect, nearly all of it, so freq early relapse hasten SP onset

• 4) faster slope of worsening?
   Answer: slight
Relapses and progression
DSS 6,8,10 i.e. cane, bed, and dead

Site of first attack?
Recovery from first attack
Polysymptomatic/disseminated onset vs. unifocal
PPMS primary progressive disease +/- relapses?
Age onset progressive course
PPMS/SAPMS/SPMS - survival
Progression and total relapses? (y1-y2 vs. y3-SP)

Suppression of relapses and progression - LTF data
Suppression of mri and progression - LTF data
Univariate regressions of relationship between 2-year outcome measured in the original IFNβ-1b study and the 16-year outcome for physical and cognitive abilities *

<table>
<thead>
<tr>
<th>Baseline Variables</th>
<th>Physical Outcome (logistic regression)</th>
<th>Cognitive Outcome (linear regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>p-value**</td>
</tr>
<tr>
<td>Baseline EDSS</td>
<td>0.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MSSS at Trial Onset</td>
<td>0.07</td>
<td>0.0004</td>
</tr>
<tr>
<td>Baseline MRI T2 BOD (mm²)</td>
<td>0.07</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of MS (y)</td>
<td>0.05</td>
<td>0.003</td>
</tr>
<tr>
<td>3rd Ventricular Width (mm)</td>
<td>0.04</td>
<td>0.011</td>
</tr>
<tr>
<td>Age at Trial-start</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>Age at MS-onset</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>Annual relapse rate prior to Trial (2y)</td>
<td>0.00</td>
<td>ns</td>
</tr>
<tr>
<td>Pre-Morbid IQ</td>
<td>0.00</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td>0.00</td>
<td>ns</td>
</tr>
</tbody>
</table>

Rsq is percent of variance explained by factor
<table>
<thead>
<tr>
<th><strong>On-Study</strong> Variables</th>
<th>physical</th>
<th>cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual relapse rate But these are treatment resistant relapses ? sig</td>
<td>0.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDSS change from baseline shows little meaning for the trial defns of disability</td>
<td>0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Categorical EDSS change (≥1 point)</td>
<td>0.06</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Confirmed 1-point EDSS progression</strong> The trial outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change, 3rd Ventricular Width (mm)</td>
<td>0.00</td>
<td>ns</td>
</tr>
<tr>
<td>Treatment Group during RCT</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>Total IFNβ-1b Exposure (y) (on LTF)</td>
<td>0.00</td>
<td>ns</td>
</tr>
<tr>
<td>Number of New T2 Lesions</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>NAbs (≥ 20 NU/ml)</td>
<td>0.00</td>
<td>ns</td>
</tr>
<tr>
<td>Change, MRI T2 BOD (mm²)</td>
<td>0.00</td>
<td>ns</td>
</tr>
</tbody>
</table>

Rsq - % of variance explained by factor, 1 result near sig for cognitive 3rd ventric. Width, 2 for physical
What to do?
All suggested to P. Leber FDA in 1993, they asked for 4) but did not enforce

- 1) Stop marketers from misleading patients & families that RR drugs prevent disability*
- 2) For trials to be ethical, outcomes must be validated, primary data with the investigators
- 3) Aim for LTOs and the most accessible is SP development, and would take less than 5y
- 4) Any lesser outcome should require obligatory LTF, drug licence pulled for non-compliance

*or tell patients that" disability" does not mean what they think it means
Many contributors

• Especially colleagues in London Ontario for the nat hist studies, recent relapse analyses Antonio Scalfari
• LTF studies made possible by Bayer esp V Knappertz
• Sylvia Lawry Centre esp. Martin Daumer
• Let the wild rumpus start
  Maurice Sendak

finis