Multi-arm trials with repurposed drugs in progressive MS

Jeremy Chataway-UK MS Society

Queen Square MS Centre
University College London
National Hospital for Neurology and Neurosurgery, London

SP/PPMS is untreatable

£c3bn/year/UK alone

Trials take too long (phase II) from start….

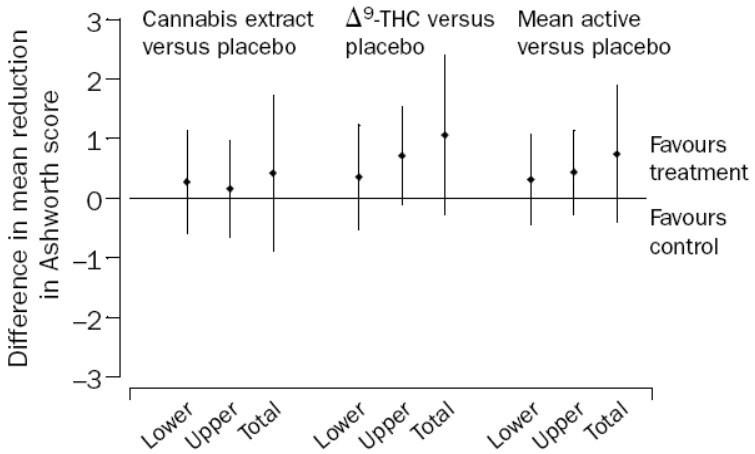
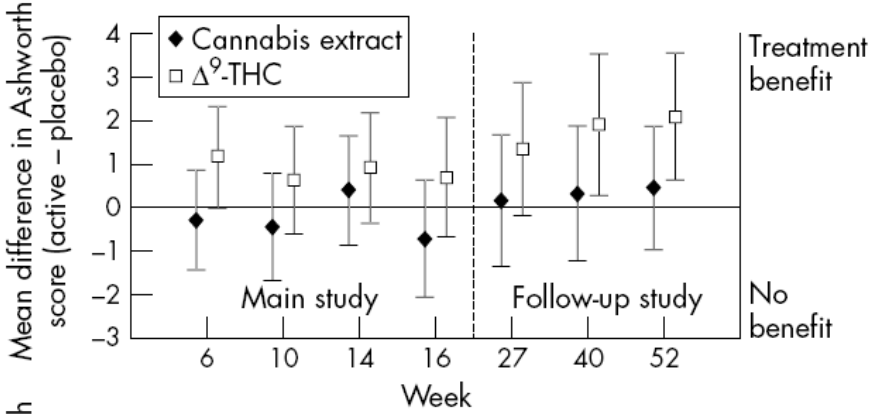
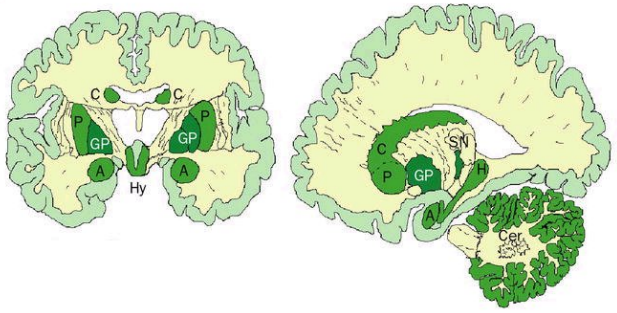


Figure 2: **Changes in Ashworth scores from baseline to 13 weeks' follow-up, adjusted for ambulatory status and centre effects**
Estimates (95% CI) shown for lower-body, upper-body, and total scores



12 month follow-up (80%)

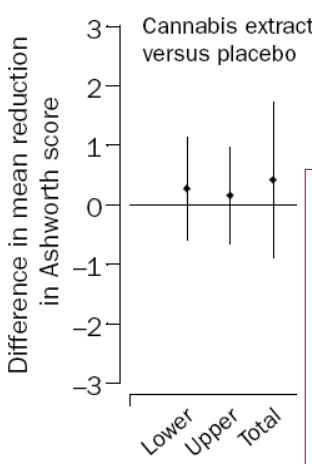
N=657 CAMS

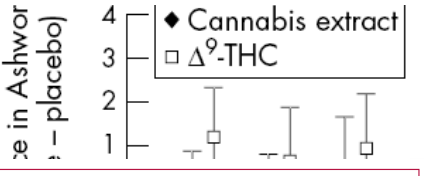


Zajicek Lancet 2003; JNNP 2005

Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial

John Zajicek, Susan Ball, David Wright, Jane Vickery, Andrew Nunn, David Miller, Mayam Gomez Cano, David McManus, Sharukh Mallik, Jeremy Hobart, on behalf of the CUPID investigator group





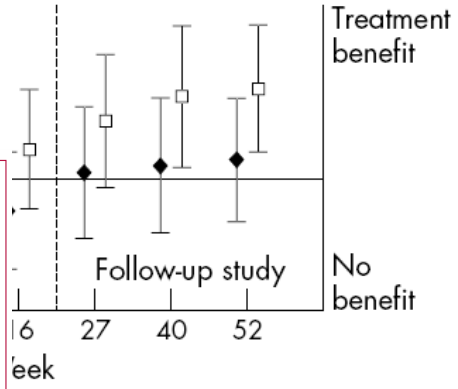
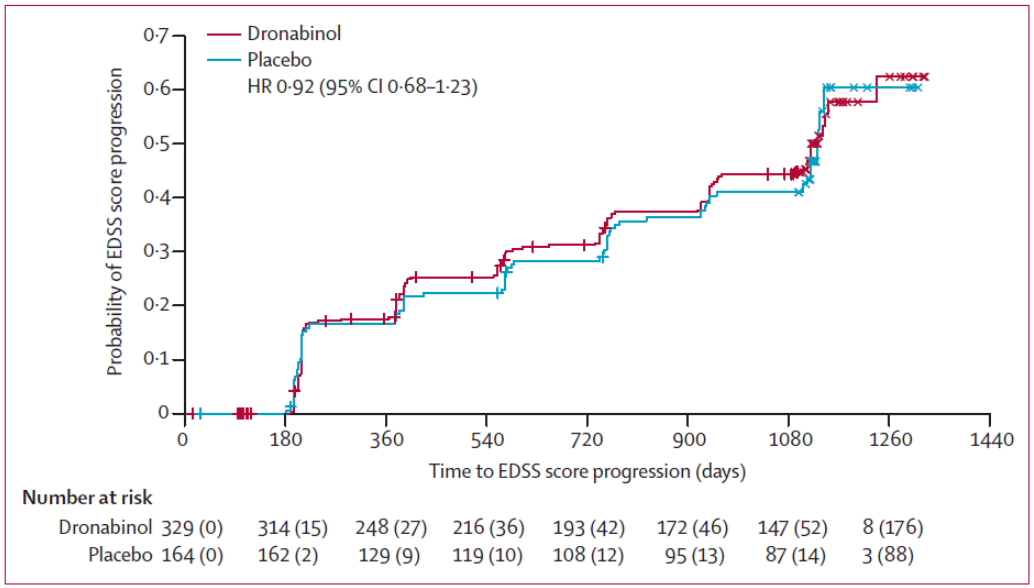
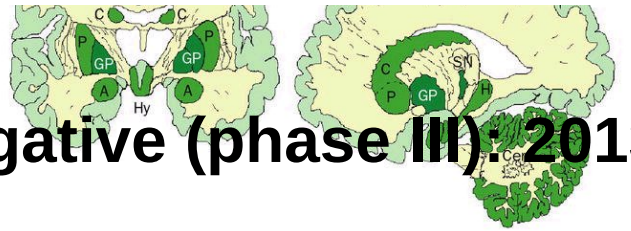


Figure 2: **Changes in Ash**
13 weeks' follow-up, adj
centre effects
Estimates (95% CI) shown fo



llow-up (80%)



To finish….

And can turn out negative (phase III): 2013

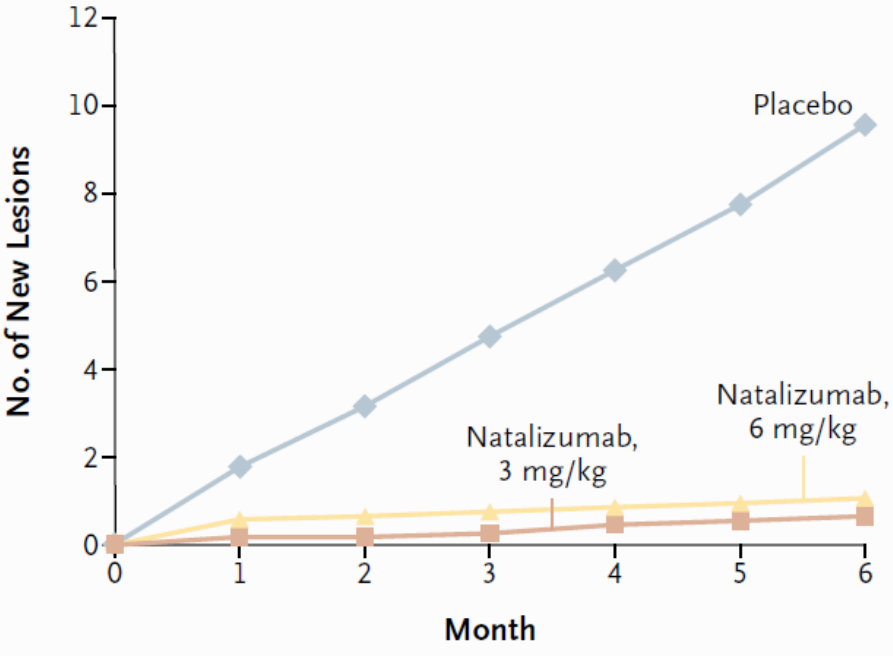
Published Online
July 13, 2013
http://dx.doi.org/10.1016/
S1474-4422(13)70159-5

Repeatedly (n~5000)

Table 2 A: Trials in MS								
Trial	**N**	**Follow Up in Yrs**	**Entry EDSS**	**Active Treatment**	**Primary outcome measure**	**Primary Result**	**Comments**	**Publication Yr & Ref**
Cyclosporine-MSSG	547	1.5	3.0-7.0	Cyclosporine	Time to confirmed EDSS worsening	-ve	Two other co-primary endpoints were also used: time to wheelchair bound (+ve); activites of daily living (-ve)	**1990**
CCMSSG	168	2 (mean)	4.0-6.5	Cyclo-phosphamide or plasma exchange	Comparison of rates of EDSS worsening	-ve		**1991**
EUSPMS	718	3	3.0-6.5	Betaseron 8MU/alternate days vs placebo	Time to confirmed EDSS worsening	-/+ve	Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)	**1998**
SPECTRIMS	618	3	3.0-6.5	Rebif (22 or 44mcg 3/week)	Time to confirmed EDSS worsening	-ve		**2001**
IMPACT	436	2	3.5-6.5	Avonex (60mcg/week)	MSFC	-/+ve	Positive outcome on MSFC (upper limb but not walking component), but not EDSS	**2002**
MIMS	188	2	3.0.-6.0	Mitoxantrone 5 or 12 mg/m2 every 3 months	Composite measure (EDSS/ ambulation index/relapses)	-/+ve	50% of cohort RRMS; 5 domain outcome measure not validated; cardiotoxicity/leukaemia risk	**2002**
NASG	939	3	3.0-6.5	Betaseron 8MU or 5MU/m2 alternate days	Time to confirmed EDSS worsening	-ve		**2004**
ESIMS	318	2	3.0-6.5	Immunoglobulin 1g/kg/month (27 months)	Time to confirmed EDSS worsening	-ve		**2004**
MAESTRO	612	2	3.0-6.5	MBP8298	Time to confirmed EDSS worsening	-ve		**2011**

Table 2 B: Current UK Trials in SPMS						
Trial	**N**	**Follow up Yrs**	**Entry EDSS**	**Active Treatment**	Primary outcome measure	**Reporting Date**
CUPID (Phase III)	493	3	4.0-6.5	Tetra-hydrocannabinol	Time to confirmed EDSS worsening; MSIS29 mean change	**2012**
MS-STAT (Phase IIb)	140	2	4.0-6.5	Simvastatin	MRI brain atrophy	**2012**

We need this in SP/PPMS



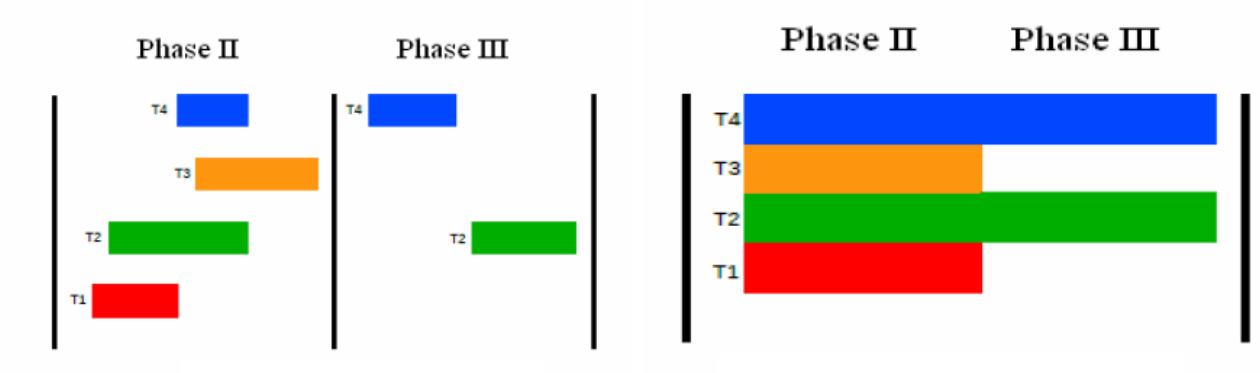
No. with Data							
Placebo	71	68	66	65	66	62	64
Natalizumab, 3 mg/kg	68	66	66	67	65	66	66
Natalizumab, 6 mg/kg	74	73	70	67	68	66	66

Figure 1. Cumulative Mean Number of New Gadolinium-Enhancing Lesions on MRI in Each Group during Treatment.

Need to move on from classical design and apply these concepts

Multi-arm Multi-stage (MAMS)

- The traditional approach is to test each one by one in separate controlled clinical trials.
- An alternative is one trial in which several novel treatments are compared. Advantages:
  - Efficient and cheaper, since a shared control group is used.
  - More treatments can be tested with a limited set of patients.
  - More popular with patients as a greater chance of being allocated to a new treatment.



(a) Traditional (b) MAMS

Advantages of MAMS trials

MRC Clinical Trials Unit

1. Fewer patients	Randomised from the start
2. Less overall time	Concurrent assessment of agents (not sequential assessment) No delay between phase II and III Fewer applic^{n}s: finance, approvals
3. Increased flexibility	Adapts to intermediate results Focus on more promising arms
4. Reduced costs	Limited resources for trials Must use fairly and efficiently Provide value

Multi-arm (Multi-stage) STAMPEDE

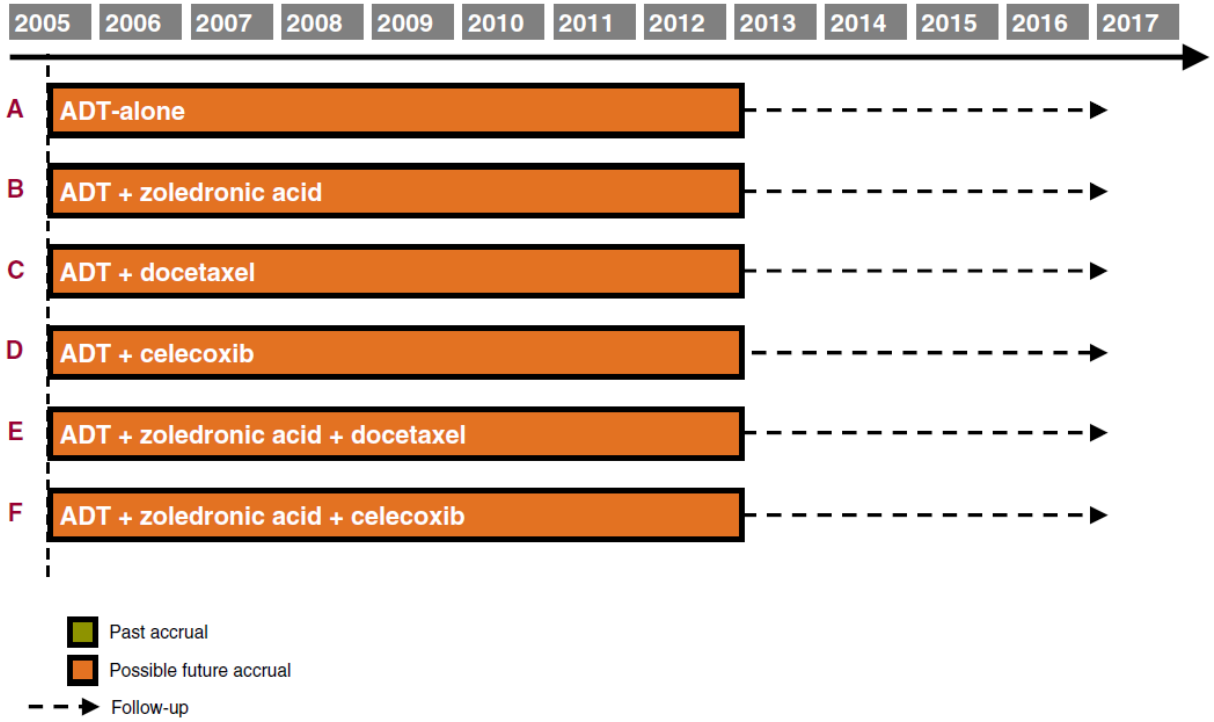


Figure 1 Trial arms open to allocation and further timelines at start of trial.

Dropping and adding

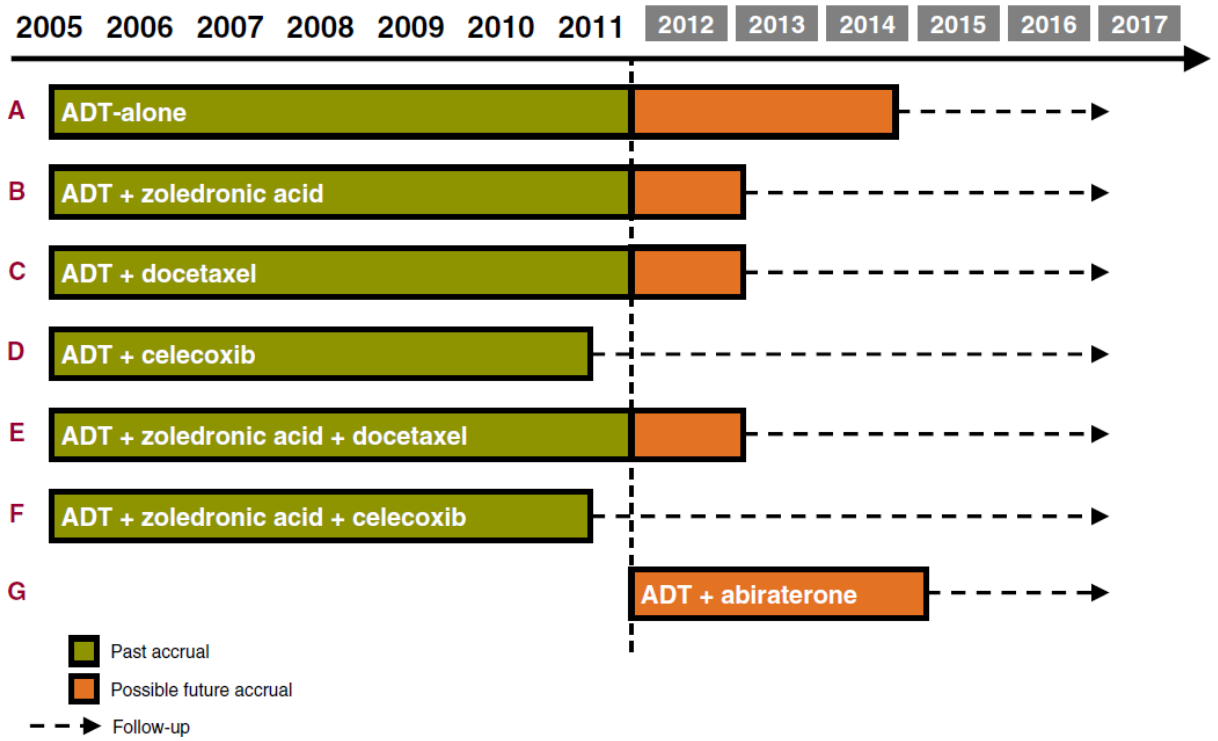


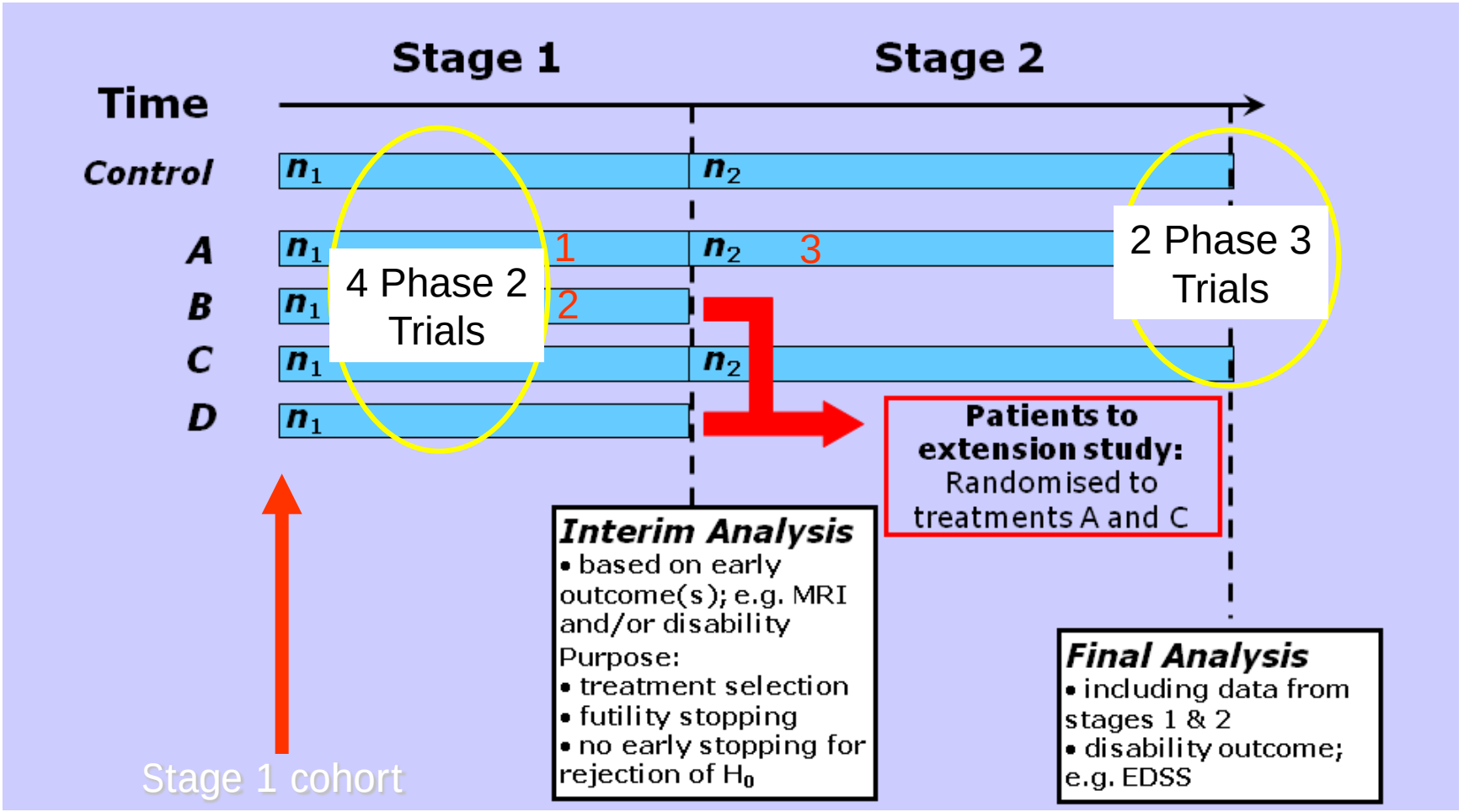
Figure 5 Trial arms open to allocat ion and fur ther t imelines as of Nov 2011.

Adaptive trial designs

- Adaptive randomization design
- Group sequential design
- Flexible sample size re-estimation design
- Drop-the-losers (play-the-winner) design
- Adaptive dose finding design
- Biomarker-adaptive design
- Adaptive treatment-switching design
- Adaptive-hypotheses design
- Seamless adaptive trial design
- Multiple adaptive design

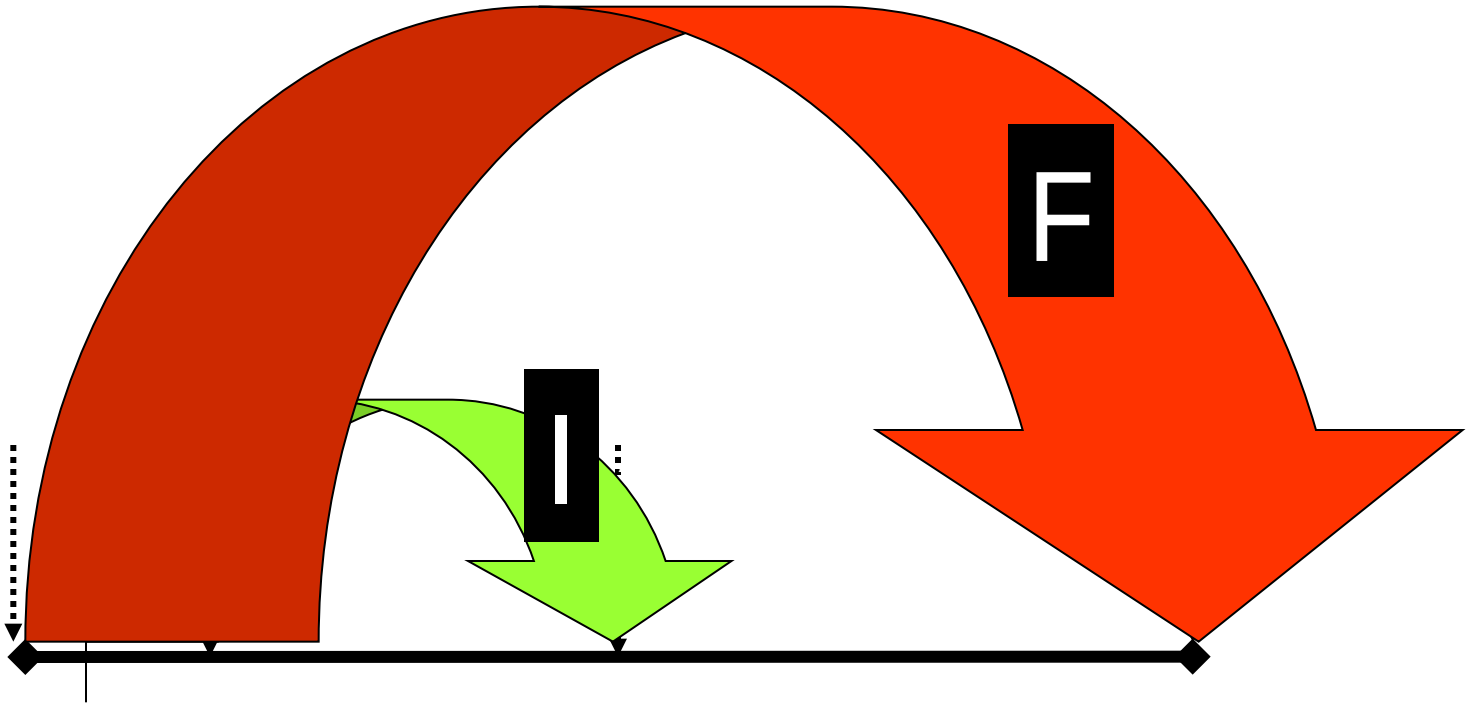
MS Trial Design

e.g. Design for 4 test treatments and 1 control (placebo)



Chataway J et al: A novel adaptive design strategy increases the efficiency of clinical trials in secondary progressive multiple sclerosis. *Multiple Sclerosis* 2011; 17: 81-8

Linkage



Multiple Sclerosis Society

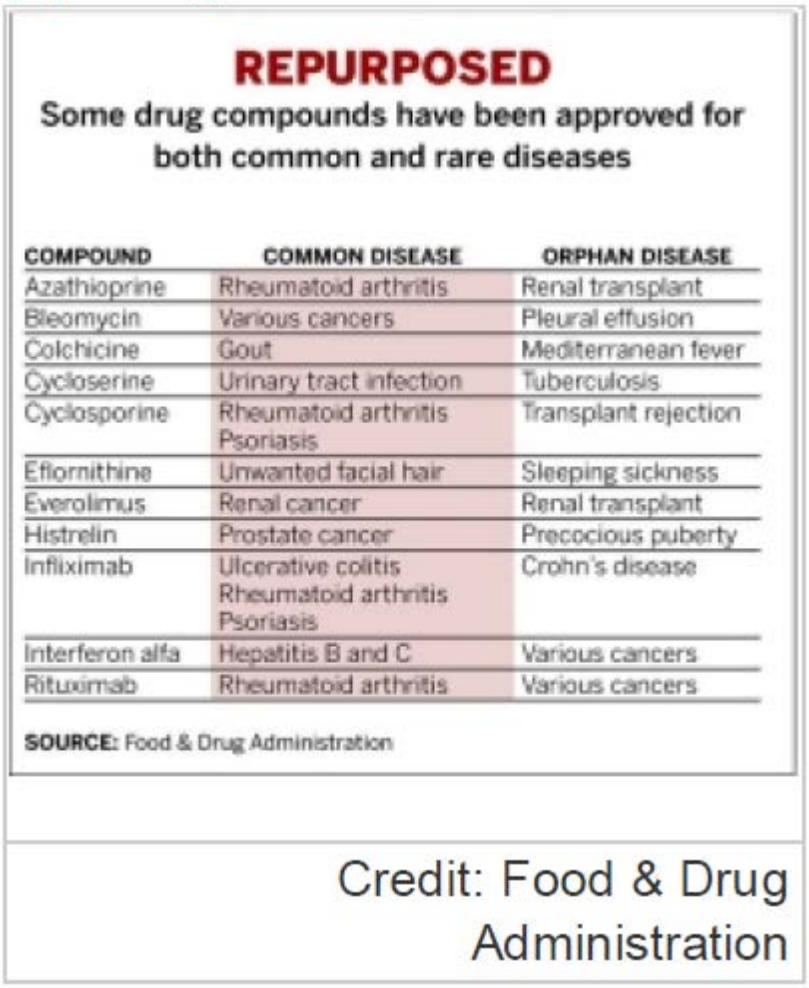
Crucial data

Embracing Repurposing

Advantages

- Drug known in detail eg AE
- Better phase II [25% vs 10%] and phase III success [65% vs 50%] than new molecular entities
- Cost

Examples



REPURPOSED

Some drug compounds have been approved for both common and rare diseases

COMPOUND	COMMON DISEASE	ORPHAN DISEASE
Azathioprine	Rheumatoid arthritis	Renal transplant
Bleomycin	Various cancers	Pleural effusion
Colchicine	Gout	Mediterranean fever
Cycloserine	Urinary tract infection	Tuberculosis
Cyclosporine	Rheumatoid arthritis Psoriasis	Transplant rejection
Eflornithine	Unwanted facial hair	Sleeping sickness
Everolimus	Renal cancer	Renal transplant
Histrelin	Prostate cancer	Precocious puberty
Infliximab	Ulcerative colitis Rheumatoid arthritis Psoriasis	Crohn's disease
Interferon alfa	Hepatitis B and C	Various cancers
Rituximab	Rheumatoid arthritis	Various cancers

SOURCE: Food & Drug Administration

Credit: Food & Drug Administration

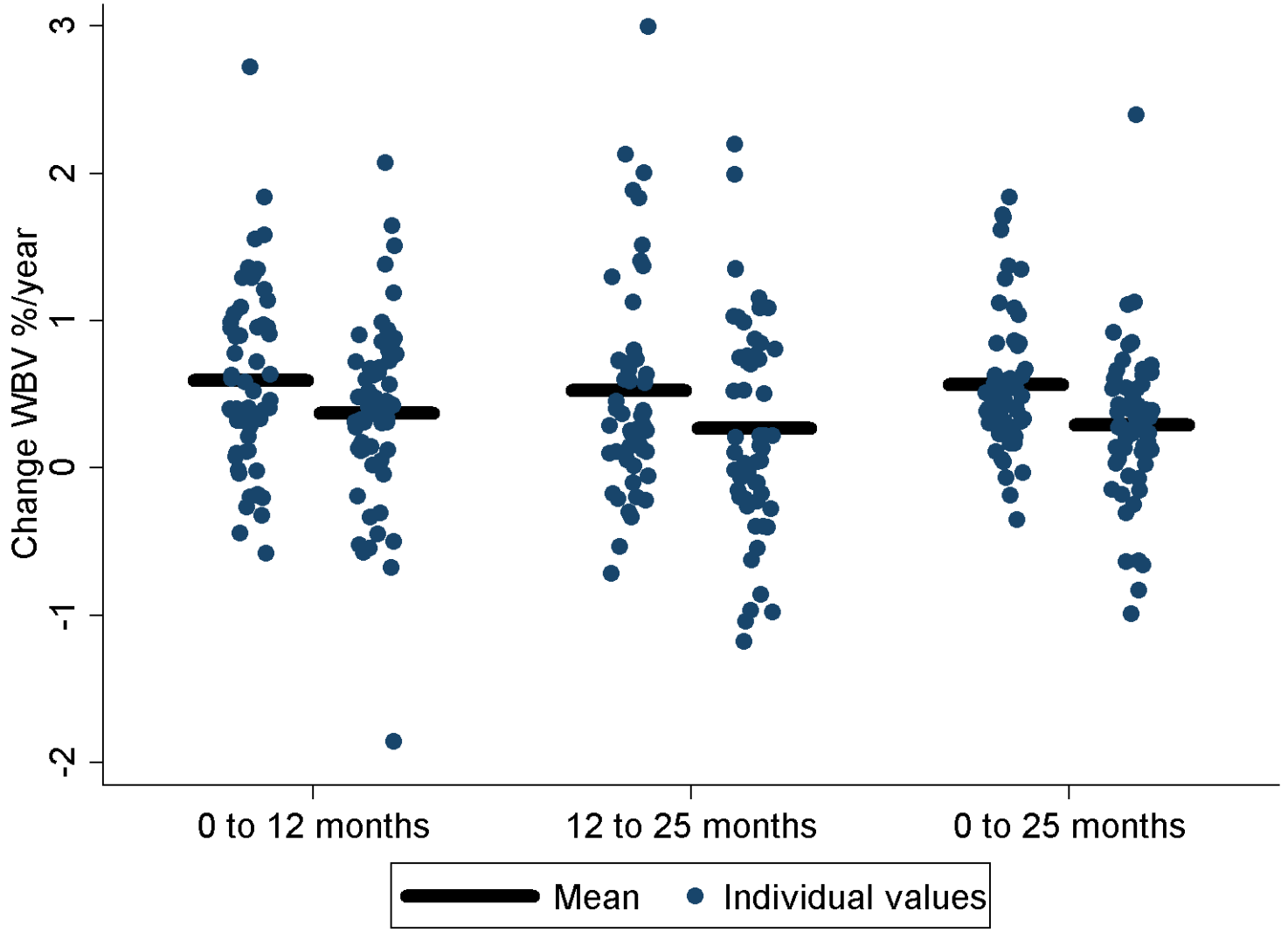
Worked example in MS (phase II)
MS-STAT trial
High dose (80mg) simvastatin

	Mean (SD) placebo	**Mean (SD) simvastatin**	**Difference in means (95% CI)***	**p-value**
Change WBV (%/year)	0.589 (0.528)	0.298 (0.562)	-0.254 (-0.423 to -0.085)	0.003
Number patients evaluated	64	66		

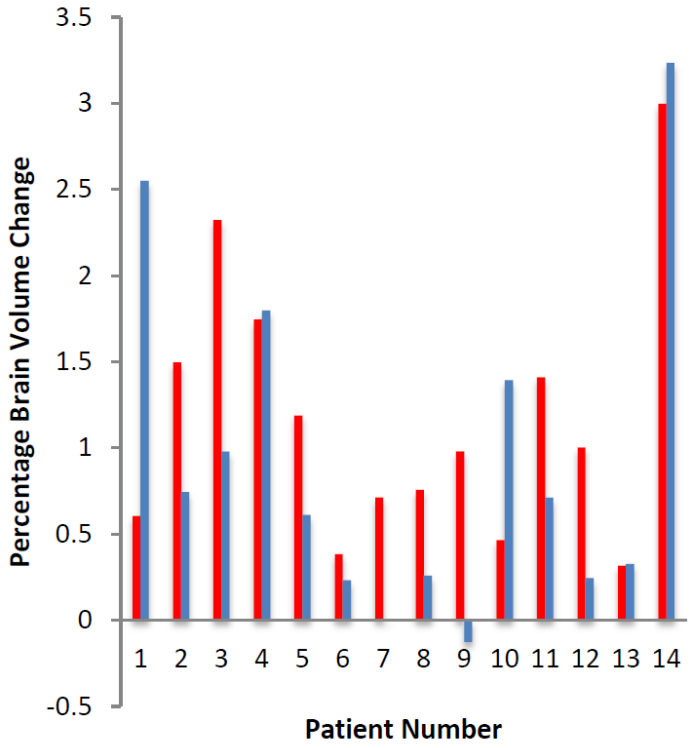
*Adjusting for minimisation variables and MRI site

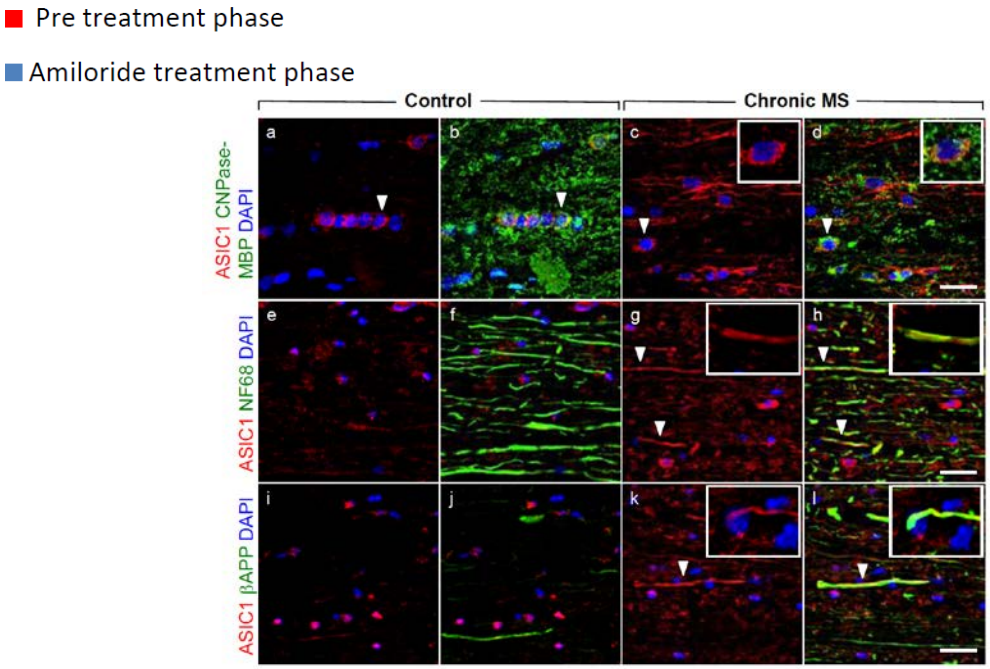
Chataway et al ECTRIMS 2012; AAN 2013

Change whole brain volume (%/yr)



Another example: Amiloride





Multiple Sclerosis Secondary Progressive Multiple Arm Randomised Trial

Bringing multi-arm/repurposing together

UCL

THE UNIVERSITY OF EDINBURGH

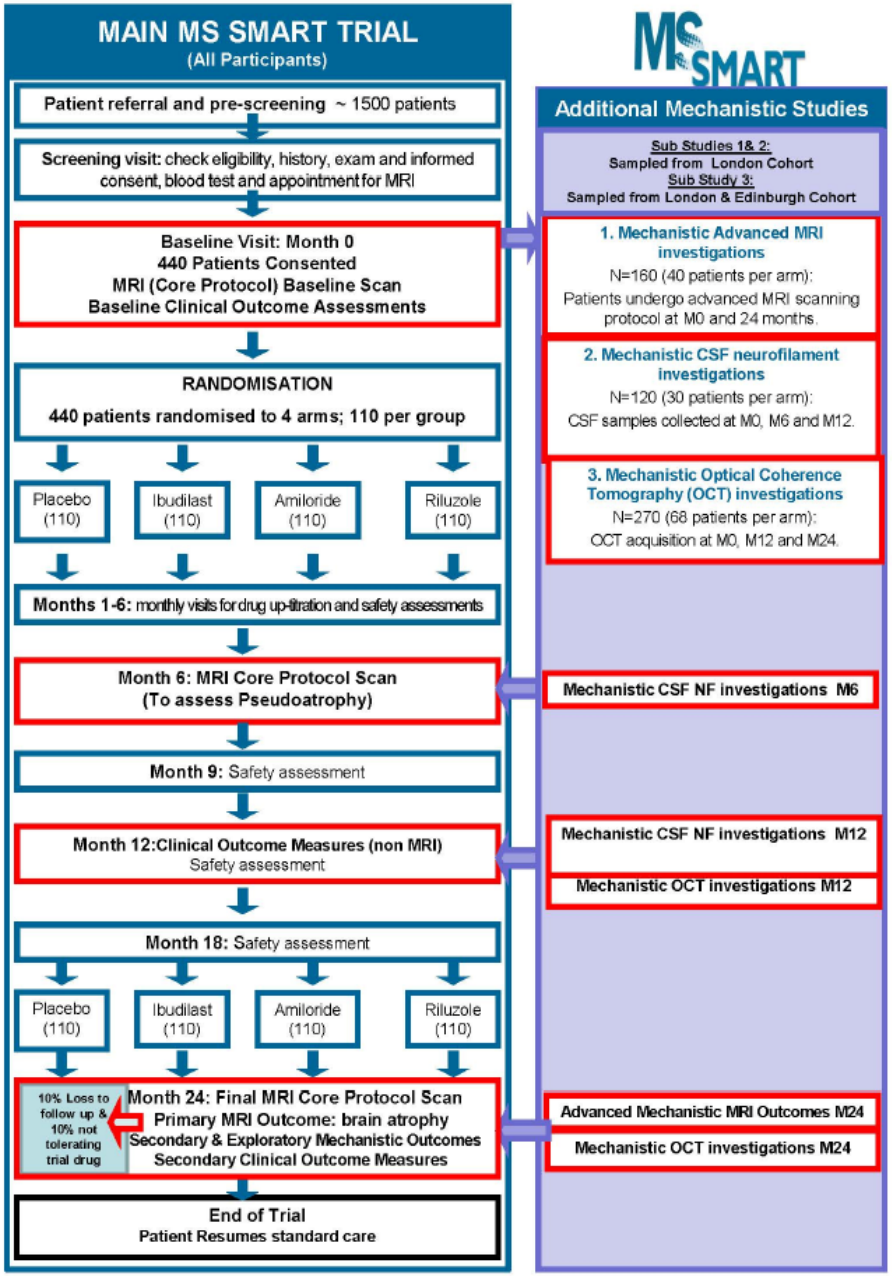
ECTU
Edinburgh Clinical Trials Unit

MS
Multiple Sclerosis Society

MRC Medical Research Council

NHS
National Institute for Health Research

440 patients
UK
SPMS



Conclusions

- Multi-arm trials are efficient and *possible*
- Seamless adaptation to phase III even better
- 40% reduction in PBVC *might* be the threshold
- Re-purposing is a valid and complementary approach
- However the move from +ve phase II to phase III is onorous

Thank you