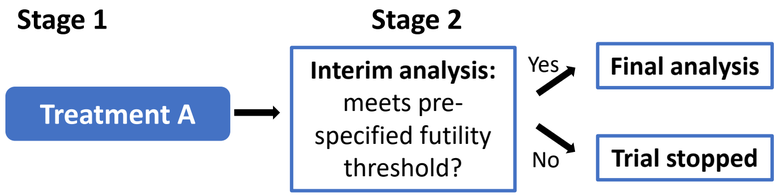
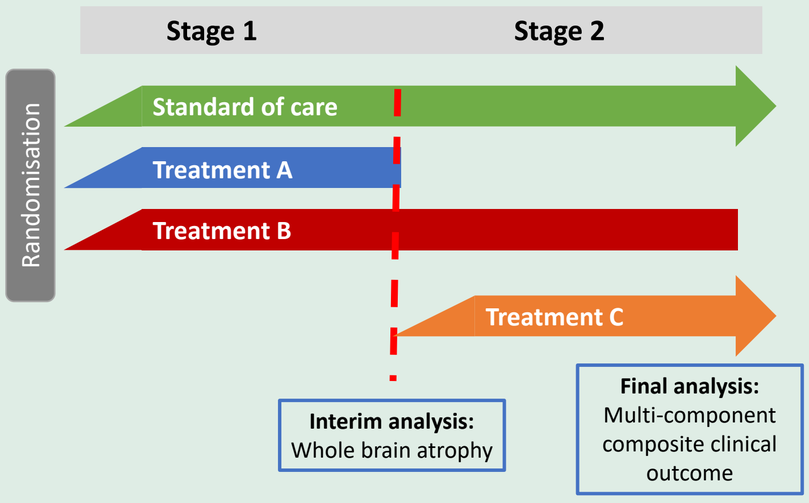
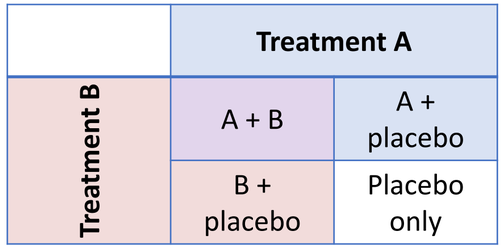
Figure 1

Trial design	Details and Example	Advantages	Disadvantages

A. Simon two-stage futility
 
	• Efficiently screens treatments using an initial futility study
	• Further development stops for futility but cannot stop for overwhelming efficacy
	• Domperidone [NCT02308137] – a 1-year, open-label, phase 2, single-arm futility trial in SPMS
	  • Null hypothesis: 40% of participants would have worsening of T25FW at 12 months
	  • Outcome: did not reject futility in reducing disability progression
	• Similar design is tested hydroxychloroquine [NCT02913157] and rejected futility (Table 1).
		• Highly efficient –follows fewer participants for a shorter duration than standard designs
		• Provides definitive go/no-go decisions
		• All participants receive active treatment
			• Screening study only - does not make definitive conclusions about efficacy or futility
			• Dependent on historical controls
			• Particularly dependent on full ascertainment

B. Multi-arm multi-stage (MAMS) 	• Two or more experimental arms compared to standard of care arm in two or more stages • This is a multi-arm phase 3 trial with an interim analysis (there can be more than one) • Interim analysis of data from stage 1 (analogous to phase 2b) is used to determine if an arm ultimately proceeds to the end of stage 2. Recruitment continues until that decision • Additional arms may be added over time (treatment C) • OCTOPUS [ISRCTN14048364] • Treatment(s) that slow brain atrophy at 18 months (Stage 1) will continue to Stage 2, where outcome is time to six-month CDP based on composite clinical score (EDSS and/or Timed 25-Foot Walk and/or 9-Hole Peg Test) • Trial size about two-thirds the size of separate two-arm phase 2 and 3 trials and take about half the time	• Fewer total participants • Shorter total trial • Reduced set up time • Adaptive elements and new interventions can be introduced over time • Higher proportion receiving active treatment	• More complex set up and operation • Relies upon validated interim outcome measure

C. Factorial
 
	• Two-by-two (or more) factorial trial
	• Compares three treatments: Treatment A, Treatment B, and Both
	• Assesses for synergy in treatments
	• CogEx [NCT03679468]
	  • Active interventions are aerobic exercise (EX) and cognitive rehabilitation (CR)
	  • Primary outcome is improvement in processing speed (SDMT)
		• Allows simultaneous evaluation of two treatments
		• Can evaluate each treatment individually and in combination
		• Higher proportion receiving active treatment
			• Complex analysis
			• Larger sample size required if there is an interaction between two interventions

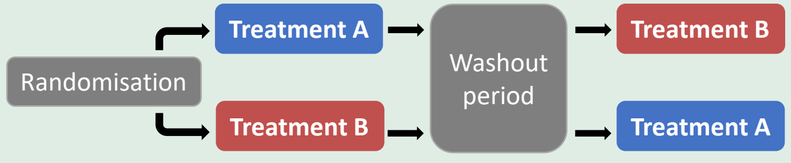
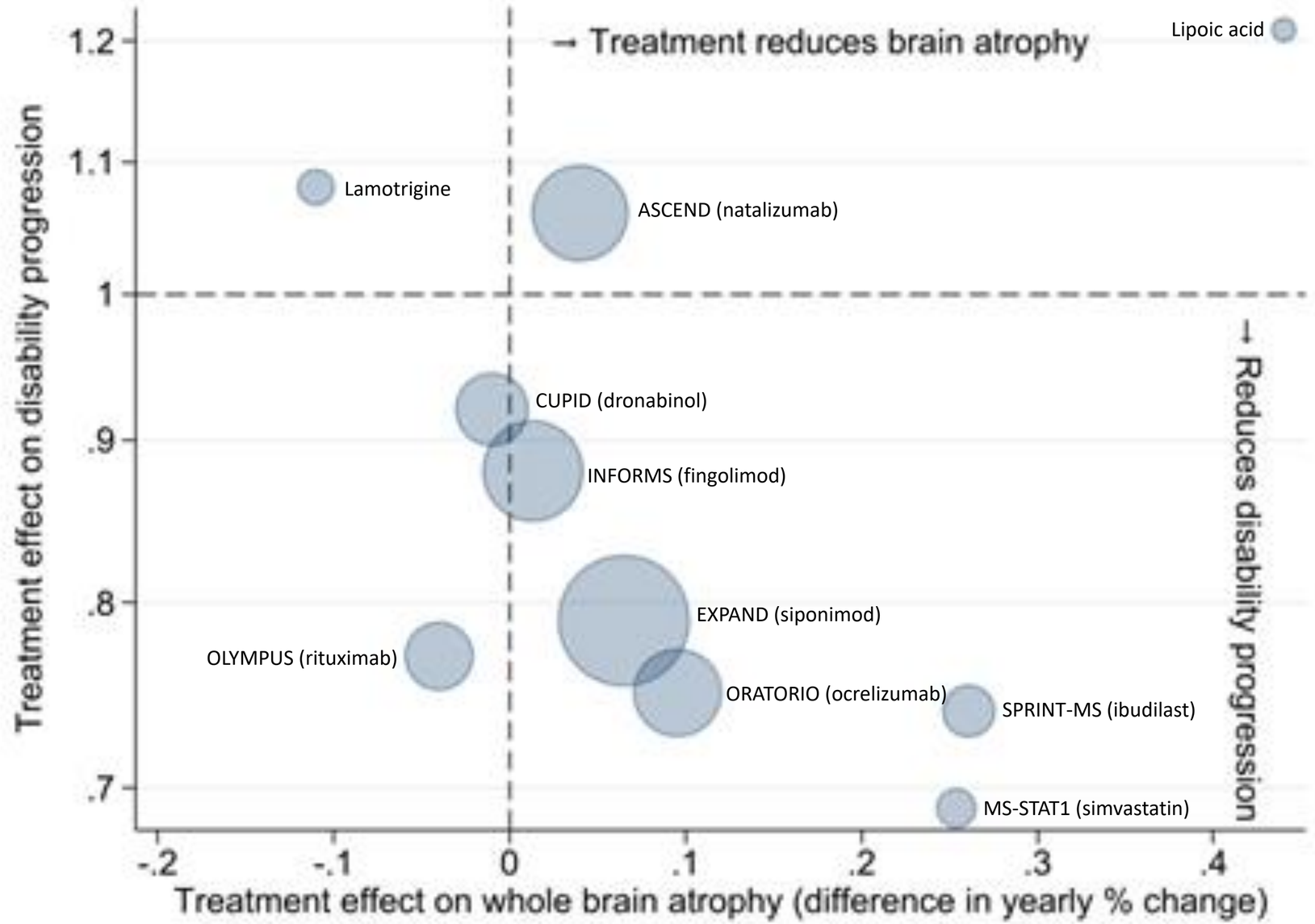
D. Crossover 	• Two (or more) treatments are given to the same subjects but at different times. • ReBUILD [NCT02040298] - a phase 2 trial of clemastine vs placebo in chronic demyelinating optic neuropathy • Primary outcome: multi-focal visual evoked potentials	• Fewer total participants • Each participant acts as own control • All participants receive active treatment	• Carryover effects may require washout period

Figure 2


→ Treatment reduces brain atrophy
→ Reduces disability progression
Treatment effect on disability progression
Treatment effect on whole brain atrophy (difference in yearly % change)
1.2
1.1
1
.9
.8
.7
-.2
-.1
0
.1
.2
.3
.4
Lipoic acid
Lamotrigine
ASCEND (natalizumab)
CUPID (dronabinol)
INFORMS (fingolimod)
EXPAND (siponimod)
OLYMPUS (rituximab)
ORATORIO (ocrelizumab)
SPRINT-MS (ibudilast)
MS-STAT1 (simvastatin)