	Early HD (N=123)			Controls (N=123)		
	N	%		N	%	
Gender (% female)	123	67 (54.5)		123	68 (55.3)	
Stage (% Stage II at baseline)	123	46 (37.4)			-	
Site						
Leiden		30 (24.4)			30 (24.4)	
London		30 (24.4)			30 (24.4)	
Paris		30 (24.4)			30 (24.4)	
Vancouver	123	33 (26.8)		123	33 (26.8)	
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)
Age (years)	123	48.8 (9.9)	49.9 (22.8-64.1)	123	46.1 (10.3)	45.6 (23.0-65.7)
CAG repeat length	123	43.7 (3.0)	43 (39-59)		-	-
Disease Burden score*	123	376.6 (73.3)	382.2 (156.2-566.5)		-	-
Education Score	123	3.7 (1.3)	4 (1-6)	123	4.0 (1.3)	4 (1-6)
Baseline TMS	123	23.7 (10.8)	23 (5-52)	123	1.5 (1.7)	1 (0-7)
Baseline TFC	123	10.9 (2)	11 (7-13)	123	13 (0.1)	13 (12-13)
Baseline SDMT	123	33.6 (10.2)	34 (12-64)	123	52.1 (9.5)	54 (30-78)
Baseline speeded tapping IOI SD** (sec)	109	0.123 (0.077)	0.100 (0.022-0.359)	114	0.031 (0.015)	0.027 (0.011-0.084)
Baseline Brain Volume (mL)	104	1055.0 (108.4)	1053.1 (801.2-1340.6)	111	1183.7 (122.3)	1177.0 (938.1-1541.8)
Baseline Caudate Volume (mL)	104	5.0 (1.0)	4.9 (3.0-8.1)	111	8.0 (1.1)	7.9 (5.5-12.0)

*Computed as age in years multiplied by (CAG-35.5)[25] **Inter-onset interval standard deviation for the non-dominant hand

Table 1: Demographic and other baseline data on Early-HD participants and Controls in the TRACK-HD study. All participants have measurements for all the non-imaging variables other than speeded tapping (where 14/123 early HD subjects and 9/123 controls have missing data). Nineteen early HD patients and 12 controls are missing baseline imaging data.

Design optimization for clinical trials in early stage manifest Huntington's disease

			Sample Size Requirements (95% Confidence Interval) according to design and outcome variable									
				Speeded Tapping			Brain Atrophy			Caudate Atrophy		
			SDMT	IOI SD	TMS	TFC						
							mL	%base	%ICV	mL	%base	%ICV
Controls (n)			*116*	*114*	-	-	*104*	*104*	*104*	*102*	*102*	*102*
Early HD (n)			*116*	*109*	*116*	*116*	*99*	*99*	*99*	*99*	*99*	*99*
Design												
Follow-up	Interim visits	Treatment effect										
1 year	None	20% 40%	1503 (1022, 2381) 376 (256, 596)	3181 (1867, 6997) 796 (467, 1750)	3248 (2191, 5306) 812 (548, 1327)	2925 (2108, 4794) 732 (527, 1199)	676 (484, 1067) 169 (121, 267)	622 (447, 973) 156 (112, 244)	636 (454, 1001) 159 (114, 251)	495 (371, 786) 124 (93, 197)	367 (292, 579) 92 (73, 145)	484 (363, 777) 121 (91, 195)
	Six monthly	20% 40%	1502 (1022, 2380) 376 (256, 595)	3177 (1866, 6983) 795 (467, 1746)	3240 (2187, 5297) 810 (547, 1325)	2919 (2099, 4782) 730 (525, 1196)	676 (488, 1071) 169 (122, 268)	621 (447, 965) 156 (112, 242)	636 (455, 1009) 159 (114, 253)	491 (376, 765) 123 (94, 192)	366 (296, 550) 92 (74, 138)	482 (365, 763) 121 (92, 191)
2 years	None	20% 40%	482 (321, 803) 121 (81, 201)	969 (563, 2184) 243 (141, 546)	1075 (771, 1803) 269 (193, 451)	1087 (785, 1763) 272 (197, 441)	305 (222, 467) 77 (56, 117)	295 (219, 438) 74 (55, 110)	289 (211, 435) 73 (53, 109)	191 (141, 336) 48 (36, 84)	165 (130, 280) 42 (33, 70)	197 (145, 358) 50 (37, 90)
	Annual	20% 40%	482 (321, 803) 121 (81, 201)	969 (563, 2184) 243 (141, 546)	1073 (771, 1796) 269 (193, 449)	1084 (783, 1762) 271 (196, 441)	305 (223, 470) 77 (56, 118)	295 (220, 444) 74 (55, 111)	289 (212, 444) 73 (53, 111)	190 (141, 343) 48 (36, 86)	164 (131, 279) 41 (33, 70)	197 (145, 360) 50 (37, 90)
	Six monthly	20% 40%	412 (272, 700) 103 (68, 175)	824 (479, 1882) 206 (120, 471)	940 (675, 1598) 235 (169, 400)	972 (701, 1561) 243 (176, 391)	280 (205, 433) 70 (52, 109)	273 (205, 412) 69 (52, 103)	266 (195, 416) 67 (49, 104)	167 (120, 316) 42 (30, 79)	149 (117, 269) 38 (30, 68)	176 (127, 331) 44 (32, 83)
3 years	None	20% 40%	288 (184, 523) 72 (46, 131)	552 (312, 1319) 138 (78, 330)	677 (469, 1190) 170 (118, 298)	751 (532, 1217) 188 (133, 305)	237 (166, 381) 60 (42, 96)	235 (169, 360) 59 (43, 90)	225 (158, 355) 57 (40, 89)	135 (92, 271) 34 (23, 68)	127 (95, 220) 32 (24, 55)	144 (98, 284) 36 (25, 71)
	Annual	20% 40%	272 (171, 501) 68 (43, 126)	518 (293, 1261) 130 (74, 316)	647 (441, 1113) 162 (111, 279)	726 (510, 1177) 182 (128, 295)	231 (161, 372) 58 (41, 93)	230 (166, 354) 58 (42, 89)	220 (154, 351) 55 (39, 88)	129 (86, 266) 33 (22, 67)	124 (92, 246) 31 (23, 62)	139 (94, 282) 35 (24, 71)
	Six monthly	20% 40%	230 (141, 443) 58 (36, 111)	430 (238, 1152) 108 (60, 288)	571 (374, 1015) 143 (94, 254)	663 (461, 1074) 166 (116, 269)	216 (148, 354) 54 (37, 89)	217 (154, 341) 55 (39, 86)	207 (143, 336) 52 (36, 84)	117 (74, 248) 30 (19, 62)	115 (83, 206) 29 (21, 52)	128 (84, 268) 32 (21, 67)
Successful bootstraps (n)			*1995*	*1992*	*2000*	*2000*	*1988*	*1993*	*1996*	*1996*	*1996*	*1991*

Table 2: Predicted sample sizes for simple trial designs.

Predicted sample sizes per arm for clinical trials with various outcome variables, assuming the treatment reduces the mean rate of change by 20% and 40% (TMS and TFC), and mean excess slope (relative to mean in controls) by 20% and 40% (all other outcomes). Sample sizes assume stratified randomisation by (and adjustment for) site only, no dropouts, 90% statistical power and (two-tailed) 5% statistical significance. Bias corrected and accelerated 95% bootstrap confidence limits for sample sizes calculated from 2000 bootstrap samples.

Designs including stratified randomisation and covariate adjustment	Effect	Sample Size Requirements (95% Confidence Interval) according to design and outcome variable									
		SDMT	Speeded Tapping IOI SD	TMS	TFC	Brain Atrophy			Caudate Atrophy		
						mL	%base	%ICV	mL	%base	%ICV
A. Two year trial with 6 monthly interim visits, stratified randomisation by, and adjustment for, site alone	20% 40%	412 (272, 700) 103 (68, 175)	824 (479, 1882) 206 (120, 471)	940 (675, 1598) 235 (169, 400)	972 (701, 1561) 243 (176, 391)	280 (205, 433) 70 (52, 109)	273 (205, 412) 69 (52, 103)	266 (195, 416) 67 (49, 104)	167 (120, 316) 42 (30, 79)	149 (117, 269) 38 (30, 68)	176 (127, 331) 44 (32, 83)
B. Design A further stratified and adjusted for age, CAG, disease burden and stage (clinical) or baseline (imaging),	20% 40%	378 (256, 660) 95 (64, 165)	733 (434, 1740) 184 (109, 435)	817 (601, 1384) 205 (151, 346)	947 (680, 1592) 237 (170, 398)	270 (206, 449) 68 (52, 113)	245 (193, 408) 62 (49, 102)	247 (189, 415) 62 (48, 104)	130 (98, 234) 33 (25, 59)	87 (73, 125) 22 (19, 32)	139 (104, 236) 35 (26, 59)
C. Design B with allowance for dropouts. Clinical outcomes: 5% in year 1 and 5% in year 2; imaging outcomes: 15% in year 1 and 10% in year 2. No allowance for intermittent missing values	20% 40%	410 (277, 712) 103 (70, 178)	795 (472, 1891) 199 (118, 473)	884 (651, 1499) 221 (163, 375)	1021 (735, 1715) 256 (184, 429)	327 (251, 530) 82 (63, 133)	296 (235, 493) 74 (59, 124)	299 (230, 487) 75 (58, 122)	160 (121, 285) 40 (31, 72)	107 (90, 154) 27 (23, 39)	170 (127, 289) 43 (32, 73)
Enriched Designs											
D. Design B with restriction to subjects with CAG > 43 (median)	20% 40%	299 (192, 791) 75 (48, 198)	565 (304, 1705) 142 (76, 427)	477 (381, 805) 120 (96, 202)	778 (472, 2473) 195 (118, 619)	221 (138, 507) 56 (35, 127)	199 (122, 407) 50 (31, 102)	199 (118, 435) 50 (30, 109)	46 (40, 64) 12 (10, 16)	39 (35, 56) 10 (9, 14)	47 (39, 69) 12 (10, 18)
E. Design B with restriction to subjects with burden > 382.2 (median).	20% 40%	231 (169, 391) 58 (43, 98)	400 (253, 860) 100 (64, 215)	502 (375, 1073) 126 (94, 269)	522 (319, 1207) 131 (80, 302)	144 (108, 273) 36 (27, 69)	135 (104, 242) 34 (26, 61)	136 (102, 257) 34 (26, 65)	72 (59, 113) 18 (15, 29)	60 (52, 84) 15 (13, 21)	78 (62, 128) 20 (16, 32)
F. Design B with restriction to HD2 subjects (clinical) or those with baseline<74.4%TIV (whole brain) or baseline<0.356%TIV (caudate) (median value restriction)	20% 40%	248 (173, 490) 62 (44, 123)	342 (220, 676) 86 (55, 169)	919 (549, 3161) 230 (138, 791)	1340 (683, 5429) 335 (171, 1358)	226 (175, 396) 57 (44, 99)	199 (152, 355) 50 (38, 89)	210 (159, 389) 53 (40, 98)	90 (75, 145) 23 (19, 37)	70 (61, 95) 18 (16, 24)	93 (75, 147) 24 (19, 37)

Table 3: Predicted sample sizes for clinical trials with design modifications.

Predicted sample sizes per arm for two year clinical trials with six-monthly interim visits and various outcome variables, assuming the treatment reduces the mean rate of change by 20% and 40% (TMS and TFC), and mean excess slope (relative to mean in controls) by 20% and 40% (all other outcomes). Bias corrected and accelerated 95% bootstrap confidence limits for sample sizes calculated from 2000 bootstrap samples. The variables considered here (site, age, CAG repeat length, disease burden, stage and baseline volume) were all pre-specified. Others such as gender were also considered, but were found not to have statistically significant effects on mean rates of change.