The external validity of the multi-arm multi-stage OCTOPUS trial in progressive MS: recruitment phase

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Background

- External validity is a key issue for trials.
- OCTOPUS is a multi-arm multi-stage (MAMS) trial in progressive MS (pMS).
- The UK MS Register (UKMSR) collects patient reported outcomes (PROs) on areas such as disability or quality of life, and hosts a platform for UKMSR and non-UKMSR participants to register interest in OCTOPUS.
- This provides an opportunity to compare characteristics and disease progression of those who do and do not randomise into OCTOPUS.

Aim

Compare characteristics of those on the UKMSR randomised to OCTOPUS, those eligible at online questionnaire completion but not randomised and those potentially eligible on the UKMSR who did not express interest.

Method

- Progressive people with MS (pwMS) on the UKMSR were invited to complete an OCTOPUS online eligibility questionnaire.
- We classified pwMS who opted in and potentially eligible as Group 1(G1). Sites select people from G1 to undergo telephone and in person pre-screening and randomisation (Group 2(G2)). Group 3(G3) are UKMSR pwMS who fulfil age criteria but did not register interest.
- We compared demographics, UKMSR engagement, and prior disability worsening between groups. Prior engagement with UKMSR PROs was defined as 'Good' when >50% PROs were completed during the first 2 years of participation. Disability worsening was defined using the Multiple Sclerosis Impact Scale physical sub-score (MSIS-29-phys), a PRO assessing the physical impact of MS.

	G1	G2	G3
n	1136	118	4227
Age (mean (SD))	55.63 (8.43)	57.33 (8.57)	59.58 (7.73)
DiagnosisAge (mean (SD))	41.69 (10.45)	42.64 (11.43)	40.30 (10.13)
OnsetAge (mean (SD))	35.95 (10.60)	36.25 (11.17)	34.65 (10.65)
TimeToDiagnosis (median [IQR])	3.00 [1.00, 7.00]	3.00 [1.00, 7.00]	2.00 [1.00, 7.00]
Gender = FEMALE/MALE (%)	723/411 (63.8/36.2)	79/37 (68.1/31.9)	2880/1347 (68.1/31.9)
Employment (%)			
Other	187 (16.5)	18 (15.5)	636 (16.0)
Permanently sick/disabled	338 (29.8)	32 (27.6)	1657 (41.7)
Regular Paid Employment	317 (27.9)	28 (24.1)	596 (15.0)
Retired	294 (25.9)	38 (32.8)	1085 (27.3)
time_on_register (mean (SD))	5.04 (4.00)	5.39 (4.04)	7.86 (4.03)
total_core_PROs (mean (SD))	10.53 (11.07)	11.21 (12.30)	5.33 (9.08)
MSISPhys_3years_prior_to_trial (median [IQR])	56.67 [36.67, 70.84]	53.33 [38.33, 68.33]	NA [NA, NA]
MSISPhys_at_trial_reg (median [IQR])	60.00 [45.00, 75.00]	58.33 [43.33, 71.67]	NA [NA, NA]
MSISPhys_at_UKMSRreg (median [IQR])	NA [NA, NA]	NA [NA, NA]	63.33 [46.67, 78.33]

Table 1: Demographic and clinical characteristics of G1, G2 and G3. MSIS-29-phys is provided 3 years prior to trial and at trial registration for those who registered interest, and at time of UKMSR registration for those who did not.

Results

- By March 2024, 170 people were randomised in OCTOPUS -118 (69.4%) were registered on the UKMSR (G2). In the UKMSR, a further 5363 had pMS and fulfilled OCTOPUS age criteria, of whom 1136 had expressed an interest (G1), and 4227 had not (G3) (table 1).
- Rates of good engagement with UKMSR were highest for G2 (79.7%) and G1 (73.4%) and lowest in G3 (55.3%).
- Group 1&2 were younger than G3 (mean 57 years vs 56 vs 60) and less likely to be permanently sick (self-defined) (29.8% vs. 27.6% vs. 41.7%, p<.001), see figure 1a.
- Disability accrual was faster in G3 vs G1 or 2 during the 3 years prior to study initiation (G3 n=1373; Groups 1&2 n=371; median time to disability worsening 1.01 years v 1.46 years, p<.001), see figure 1b.

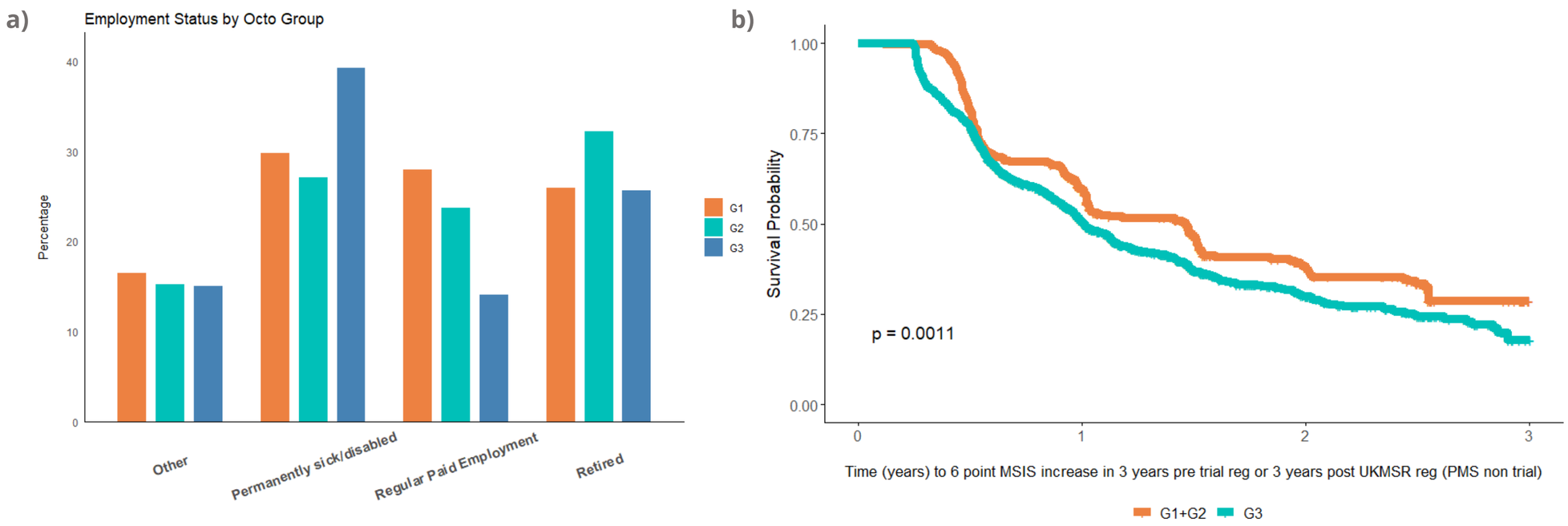

Figure 1: a) Percentage of G1, G2 and G3 in each employment category, showing higher % of G3 are permanently sick disabled and lower % are in regular paid employment. b) Survival curve showing faster time to disability worsening in G3 compared to G1+G2

Conclusions

~70% of OCTOPUS participants take part in the UKMSR PROs enabling benchmarking of trial recruitment. Many participants in the UKMSR have not expressed an interest in taking part in OCTOPUS despite being potentially eligible yet seem to represent a more severely affected population.

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