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## **Challenges to recruitment of participants with MCI in a multicentric neuropsychological study**

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## Abstract

**Background:** Data on recruitment of Mild Cognitive Impairment (MCI) samples are seldom reported and this issue can be an important source of research waste.

**Aims:** To describe the recruitment challenges and reasons for non-eligibility faced during a bi-centres clinical study assessing the predictive value of a neuropsychological battery of the progression to dementia.

**Methods:** Potential MCI participants were identified from databases of the two memory clinics based in Milan (Italy) and invited to the screening assessment.

**Results:** About 50% of the cases initially identified were ineligible according to inclusion/exclusion criteria and the two sites took 22 months to recruit the planned 150 people. The main reason for non-eligibility were the MMSE score (41%), age (14%), presence of cerebrovascular disorders (9%), perceptual deficits (6%), neurological (6%) or psychiatric (4%) comorbidities and low education (5%).

**Discussion/ Conclusion.** Awareness of the reasons for exclusion and of the time needed to recruit the planned sample would provide hints for the planning of future studies on MCI.

**Keywords:** MCI; recruitment; eligibility; clinical research; neuropsychology

## **Introduction**

Difficulty in participant recruitment is a significant barrier to clinical research progress and many trials struggle to complete enrolment in a timely frame despite substantial effort.

In Alzheimer's disease (AD) studies only a selection of patients are eligible according to recruiting criteria and it was estimated that approximately only 20%-25% of people with AD are enrolled in clinical trials [1,2]. Participants are more likely to be eligible and to agree to participate in non-pharmacological studies compared with clinical drug trials [3,1]. One major focus of research on AD is on diagnosis and treatment in prodromal stages such as Mild Cognitive Impairment (MCI), a condition which, depending on various neurobiological and psychological factors, carries a high risk of developing dementia.

Data on recruitment of MCI samples are seldom reported, especially for non-interventional studies. The lack of a consistent and established diagnostic procedures and methods for identifying participants with MCI is challenging and raises questions regarding the nature of the sample selected: study comparisons may prove difficult and recruited participants may not adequately represent the greater population [4,5].

This report describes the recruitment challenges and reasons for non-eligibility of people with MCI faced during a multicentric study (study n. PE-2013-02356465 funded by The Italian Ministry of Health) that might provide strategies to overcome barriers for recruitment in future clinical studies.

## **Study Context Procedure and Participants**

PE-2013-02356465 is a multicentric clinical study assessing the predictive value of a neuropsychological memory battery of the progression to AD dementia in at-risk participants presenting with MCI. According to power calculation, to meet the aims of the study the final MCI sample size required should be 150 participants. Potential participants (age 60–85 years, education >5 years) were identified from the clinical MCI database of the two memory clinics involved in the recruitment (Site 1- Sacco Hospital, and Site 2- San Raffaele Hospital) and were invited to the screening assessment.

The recruitment and selection procedures were the same across sites and had been approved by the two local ethics committees (Reference number: 2017/ST/241). MCI was diagnosed as: (a) abnormal cognitive function adjusted for age and education level, (b) self- or informant- reported cognitive complaints, and (c) normal activities of daily living [6]. Patients were screened at the study sites to determine if they met all the following criteria: patient or informant reporting a cognitive problem, Mini-mental State Examination (MMSE) score  $\geq 24$ ; CDR score  $= 0.5$ . Cognitive impairment was documented with at least one

neuropsychological test showing a performance below or equal to 1.5 standard deviations compared to norms [7,8].

Potential participants were excluded if they had: major cerebrovascular disorder (Hachinski Ischemic Scale >4); visuo-perceptual impairment, neurological and/or psychiatric comorbidities. Eligible patients undertook a neurological screening visit and a follow-up assessment in which a battery of pen-and-paper and computerized neuropsychological tests was administered. This battery included MMSE, Clock Drawing Test, Trail Making Test A&B, Attentional Matrices, Token Test, Phonemic verbal fluency, Paired associates learning. The experimental tests were also administered in the same session. A clinical interview for the assessment of symptoms of depression, functional status and subjective cognitive decline concluded the formal assessment. The duration of the entire assessment was about two hours for each participant. Within the two follow-up assessments (after one and two years), all participants were given the same full baseline battery; diagnosis was reviewed by the same clinical and research team.

To harmonize assessment and data entry procedures all neuropsychologists involved in the study received a 1-week training conducted by Site-1 researchers.

Clarification of the subtypes of MCI was needed since the amnesic form of MCI has a higher likelihood of progressing to AD; for the target study, we included both amnesic (single or multiple domain) and non-amnesic (single or multiple domain) MCI participants. Differences of demographic and cognitive characteristics of patients enrolled and recruitment ratios between centres were tested by means of t-tests (for continuous variables) and Chi-square tests (for dichotomous or categorical variables).

### **Data report**

The two sites took 22 months to recruit the planned 150 people with MCI. Site 1 started the recruitment phase ten months earlier than site 2, on January 2018, and reached the expected target of 75/150 participants on March 2019 (15 months). Site 2 took longer to set-up the study and receive the approval from the local ethics committee, starting effective recruitment on November 2018, and finished the recruitment phase 5% short of the recruitment target on November 2019 (12 months).

A significant difference in the number of non-eligible cases was found between the two recruitment centres, with more non-eligible cases in Site 2 (Chi-square tests;  $p < 0.05$ ). No difference was found between sites in the recruited/screened ratio and refusal to participate rate.

Site 1 recruited older participants with lower MMSE scores (T- tests;  $p < 0.05$ ) (see Table 1).

----- Insert Table 1 about here -----

About 50% of the cases initially identified resulted eligible according to inclusion/exclusion criteria. The main reason for ineligibility was a MMSE score <24 (41%) followed by age outwith the set boundaries (>85 or <60 years old) (14%), concurrent cerebrovascular disorders (9%), visuo-perceptual deficits (6%), other neurological (6%) or psychiatric (4%) comorbidities or low education (5%). A total of 16% refused to participate to the study (see Figure 1). Such refusals were due to lack of interest in the study (6%), difficulties with transportation (6%) or unwillingness to undergo a long cognitive assessment (4%).

----- Insert Figure 1 about here -----

The MCI final sample was showing deficits mainly affecting the amnestic domain (single 36%, multiple 53%) while the non-amnestic group was relatively smaller (single 6%, multiple 5%).

## **Discussion**

Recruitment is one of the most challenging aspect of a clinical study but often it is not adequately detailed. The two main goals of the recruitment phase are to enrol a sample representing the target population and to engage sufficient participants to meet the power requirements of the study [9]. Problems with recruitment can disrupt the timetable of a research project and reduce the ability of the study to answer the initial research question, ultimately resulting in research waste with the study curtailed and the outcome unpublished. Trial enrolment may not represent the target disease-suffering population, and this may result in trial findings that are not readily generalizable. Successful clinical study recruitment shows a balance between rapidly achieving full enrolment and ensuring an appropriate study sample.

The main recruitment challenge met in our study was that the pool of eligible MCI participants according to our inclusion and exclusion criteria was limited to about half of the cases initially identified. Consequently, the time needed to complete the enrolment was much longer than expected (22 instead of 12 months), due to the need to recruit further participants in the memory clinics. Even if both recruitment sites were based in the same city, a mild difference between sites for number of non-eligible participants, age and MMSE score emerged, possibly reflecting different social characteristic of the respective urban areas. Knowledge of the reasons for exclusion and of the time needed to achieve the planned sample size may provide some hints for the planning of future studies on MCI. To improve the

enrolment process we suggest demarcating the exclusion criteria as much as the specific research question permits.

In particular, for our study the set MMSE score became a major reason for exclusion. According to most studies (see [4] for a review) and to our previous research on the same target population [10] we selected a cut-off score of  $\geq 24$ , but the choice of other cut-off scores, such as  $\geq 23$  or a score adjusted for age/education [4], might have increased chances of inclusion, with little detriment to the research question. A possible reason for this high rate of participant with  $MMSE < 24$  can be due to the enrolment in a memory clinic setting in which the study was conducted. Older people may access a memory clinic when cognitive deficit is already relevant. Possible alternative recruitment settings such as older adults leisure centres can be an option for future studies.

The second reason for exclusion was age outwith the set boundaries. MCI patients are older adults, hence likely to suffer from comorbidities that exclude participation, which is another relevant issue to be considered for future studies. This was another cause of high attrition.

Even if the number of non-eligible patients was higher, the number of participants who refused to participate was lower than those highlighted in previous reports of pharmacological trials (e.g., [11]). Refusal to participate to a clinical study depends on the perceived costs and benefits of the study by the participants and family members. The low refusal-to-participate rate could be explained by the non-interventional nature of our study (no risk of harm or to be included in a placebo arm), the rather innovative diagnostic neuropsychological battery which may have been of interest, and the scheduled clinical monitoring for two years, which may have offered some solace to the patients and their relatives. However, the cognitive battery used in the target study required between 1.5 to 2 hours to be completed and could have caused some level of frustration and distress. In people with MCI aware of their impairment, the reminder of their cognitive struggles can be overwhelming and may ultimately result in unwillingness to participate. Similarly, witnessing the difficulties encountered by the participants could be unacceptable to some relatives. Performing visits at home or offering travel costs refunding may increase the willingness of patients and families to participate, though it was not feasible for this study.

In conclusion, our findings emphasise the need to harmonise the procedures of identification, recruitment and selection of participants in clinical studies, hopefully through evidence-based methodological guidelines. Systematic reports of the recruitment phase in studies submitted for publication can guide the interpretation of consequent research findings.

**Figure Caption**

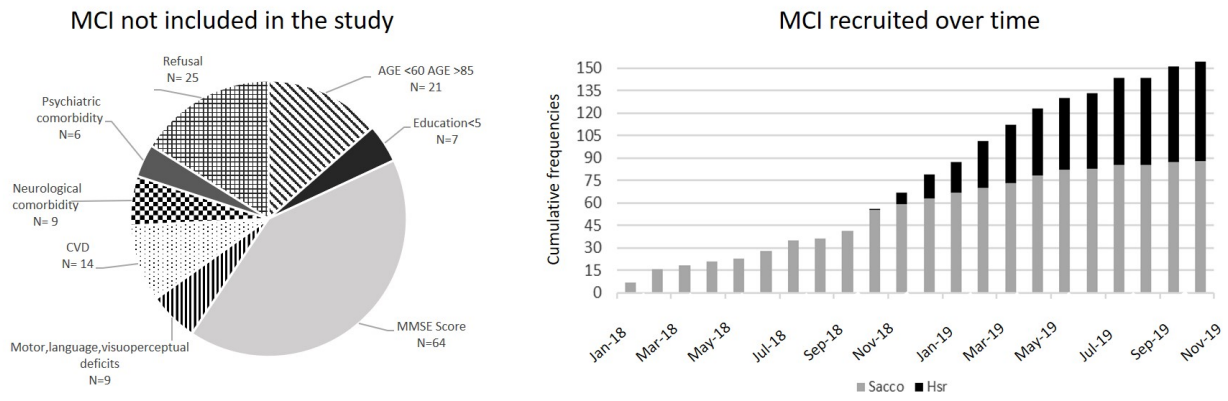


Figure 1. Reasons for non-eligibility and time needed for the recruitment of the final sample



Table 1. Demographic and cognitive measures in each recruitment MCI group at baseline.

Variable	Site 1	Site 2	Group Differences (t-test/Chi-square)
Recruited /Screened : ratio (%)	88/167 (52.7)	67/142 (47.2)	p=0.627
Non-eligible: N (%)	59 (35)	70 (49)	p =0.046*
Refusal to participate: N(%)	20 (12)	5 (4)	P=0.089
Gender, % women	40	50	p=0.364
Age (years): mean (SD)	76.2 (5.3)	73.5 (5.8)	p=0.003*
Education (years): mean (SD)	10.0 (4.0)	10.5 (4.2)	p=0.451
MMSE: mean (SD)	26.0 (1.5)	26.7 (1.9)	p=0.011*

SD: standard deviation; \* indicates p<0.05

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**Declarations****Compliance with ethical standards:**

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study was conducted in accordance with the ethical principles of the Helsinki declaration.

Informed consent: Informed consent from all participants was obtained.

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**Authors' contributions**

SP and SDS contributed to the study conception and design. Material preparation, data collection and analysis were performed by MB, SP and FA. The first draft of the manuscript was written by MB and SP. MP and SDS revised critically the manuscript. All authors read and approved the final manuscript.