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RECRUITMENT STRATEGIES FOR PREVENTIVE TRIALS. THE MAPT STUDY (MULTIDOMAIN ALZHEIMER PREVENTIVE TRIAL)

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Abstract: 1680 participants were randomized over the recruitment period in MAPT study. A total of 1290 participants were recruited in the 7 University Hospital centers, and 390 participants in the 6 memory clinics around Toulouse Gerontopole / Alzheimer Disease research clinical center. The first randomization was on May 30, 2008, and the targeted number of randomized participants was reached on February 24, 2011; 2595 subjects were finally screened, of which 1680 fulfilled the eligibility criteria which represents 64.8%. Approximately, one quarter of screened people refused to participate after the detailed presentation of the study and 4.3% were still interested in participating but missed for unknown reasons the baseline visit even after repeated contacts. Of the 1810 subjects who signed the consent for participating to the study at the baseline visit, 130 (7.1%) were excluded because one of the eligibility criteria was not satisfied. Interestingly, the higher percentage of randomizations compared to screened participants is the personal contact source; almost 85 % of screened participants entered in the study. In an equivalent way, Medias and conferences are efficient recruiting sources to enrol volunteers in the study. Unexpectedly, only about 60% of screened participants from the hospital and GP sources were randomized and 33.2% from health care services. Almost a quarter of the randomized participants come from the hospital outpatients clinics and approximately 20% from public conferences. A total of 1128 contacts yielded to 556 screened volunteers and 345 randomized participants in the coordinating center of Toulouse. Thus, 30 % of contacts were recruited.

Key words: Prevention trial, Alzheimer's disease, recruitment strategies, multidomain intervention, elderly.

Introduction

Prevention strategies for Alzheimer's disease (AD) are urgently needed due to its high and rising prevalence (1). Because of the multifactorial nature of AD, it now seems pertinent to propose a « multi-domain » intervention, combining interventions that target several physio-pathological pathways leading to the onset of the disease, in order to examine their potential synergistic action in reducing the risk. The Multidomain Alzheimer disease Preventive Trial (MAPT) is a three-year prospective study of frail older adults randomized to treatment (omega-3 and /or multi-domain intervention) or placebo. The proposed multidomain intervention consists of collective training sessions in the following three areas: nutrition, physical activity, cognitive training and preventive consultations (to control risk factors). The primary objective of the study is to determine the effect of treatment with omega-3 and/or multi-domain intervention on slopes of cognitive decline. The main outcome measure is the change in cognitive function at 3 years determined by the Grober and Buschke Test (a memory-recall test of 16 words). The design and rationale of the study have already described (2, 3).

After including the 1680 frail participants, the study group was well aware about the recruitment challenges particularly difficult and time-consuming in this population. Recruitment is defined as reaching out and interacting with individuals who will participate in research studies. Health studies recruitment is a combination of health science communications, marketing, and public relations (4). It is known that recruiting older adults in clinical trials is a real challenge and needs to develop specific strategies (5-7). In this paper, the different strategies for recruiting frail elderly people in MAPT study were described.

Methods

Study design

MAPT is a multicentre, randomized, placebo controlled study, using a 4-group design including 3 treatment groups (omega 3 alone, multi-domain intervention alone, omega 3 plus multi-domain intervention at n=420 each) and a placebo group

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(n=420). Visits are scheduled every 6 months to assess physical condition, diseases and corresponding treatments, adherence to and tolerance of omega 3 treatment, adherence to multi-domain intervention, and to deliver the supplement. Cognitive and functional assessments are conducted at baseline, six months, and annually at 1, 2 and 3 years by independent research staff blinded to intervention. All the assessments are performed by hospital practitioner memory experts. The protocol is registered on a public-access clinical trial database (www.clinicaltrials.gov). In addition, three neuroimaging ancillary studies were proposed to MAPT participants: (i) the MRI-MAPT study will explore the effects of interventions on cerebral atrophy (total brain and hippocampal volumes); (ii) the FDG-Pet study will explore the effects of multi-domain intervention on cerebral metabolism (only in Toulouse center) and (iii) the AV45-PET study will evaluate brain amyloid deposits.

Participants

The recruitment goal for the MAPT trial was to enrol 1680 frail elderly people, aged 70 years and over, living independently in good functional and cognitive status. Definition of frailty is to date not consensual but we used three clinical components to identify frail persons based on epidemiological evidence: memory complaint to their primary care physician, limitation in one instrumental activity of daily living (ability to use the telephone, shop, prepare meals, do housekeeping, do one's laundry, use transportation, follow a medication schedule and manage money) (IADL) and slow walking speed (speed lower than 0.8 m/s which means more than 5 seconds to walk 4 meters). Participants were excluded from the study when presenting dementia (DSMIV criteria), Mini Mental State Examination (MMSE) score lower than 24 over 30, subjects who had incapacities for basic activities of daily living (ADL score lower than 6 over6), and those who were severely depressed (Geriatric Depression Scale (GDS) score over 15) and, other disorders that could interfere with the interpretation of the study (like visual or hearing impairments). The inclusion period lasted 33 months. The MAPT study was conducted in 7 University Hospital centers (UH) (Toulouse, Bordeaux, Montpellier, Limoges, Dijon, Lyon and Nice) and 6 General Hospitals (GH) (Castres, Foix, Tarbes, Lavaur, Montauban, and Monaco). The study is coordinated from the hospital reference centre in Toulouse.

Recruitment Strategies

The coordinating center developed different strategies for recruiting and all communication materials were validated by the Advisory Committee for the protection of Persons. Each field center was charged with developing recruiting plans to best suit local needs. The first evident recruiting source was the hospital outpatient consultations and the memory clinic. So, a simplified brochure and panels for volunteer were elaborated, with the possibility to be customized by each center. Moreover, a volunteer call was published online on both intranet and internet sites of the hospitals. All the physicians involved in outpatient consultations were specifically informed and trained on inclusion and exclusion criteria of the MAPT study. Study procedures were repeated on a regularly basis all along the study. Other health services from the participating hospitals were contacted in order to inform about the study protocol and specific actions were undertaken when interest in participating was evoked.

It was crucial to involve general practitioners (GP) in the recruiting strategies due to the fact that the MAPT target population mainly consults their GP (8). Thus, information meetings were organised with the local GPs placing brochures and fliers in their office. Moreover recruitment letters and panels were also sent to a large number of GPs, including listings of specific GPs networks.

We contacted numerous health care services (thermal spa, care service associations, prevention centers) which are in charge of older adults with difficulties in activities of daily living. The study procedures were presented locally at each organization with the possibility of placing brochures and areas frequented by older adults and mailing the recruitment letter to their health care users.

Presentations (and diffusion of brochures) were performed in different senior centers and at organizations that provide social and leisure services for older adults. In association with the local retirement funds, we organized conferences on prevention of cognitive decline, dependency or frailty. Retirement funds only invited to conference local age-eligible members. It was the occasion to present the research on Alzheimer's disease and the interest to participate in a clinical trial. All the volunteers from the conference willing to participate were contacted by phone in order to inform about enrolment procedures. When complying with inclusion criteria, a baseline visit was proposed.

An institutional press release was performed at the beginning of the study. Each recruiting center received a press file for the Medias to be adapted and used locally during newspaper, radio and television interventions.

Finally, the MAPT participant newsletter was used to enhance recruitment by a "name of Friend" approach. The MAPT participants could be helpful recruiters through word-of-mouth endorsements by identifying age-eligible acquaintances. These potential participants were contacted by the recruiting centers and screened following the standardized procedures.

Participant Screening

According to the recruitment source, interested volunteers were either directly interviewed, either contacted by phone to start the staged screening process. The first stage screening questionnaire was designed to identify eligible participants. Major eligibility criteria were checked on a self-reported basis (spontaneous memory complaint, difficulties in instrumental activities and impairments in mobility disabilities). The second stage was to present the study in detail. At this stage, after presenting the study the volunteer was asked if he was still

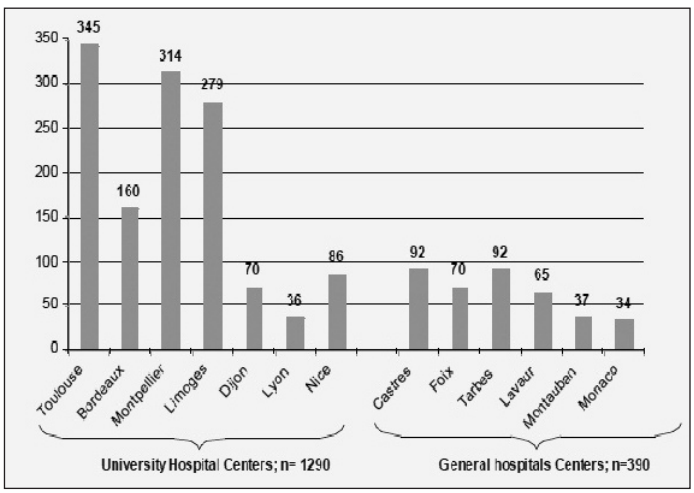
willing to participate. In the case that the volunteer was interested in participating to the study, we checked major exclusion criteria (under omega-3 treatment; severe pathologies) then proposed an appointment for a baseline visit with a study physician (stage 3). Finally, baseline visit assured randomization or screen failure based on the specific trial inclusion and exclusion criteria. For all volunteers, we asked basic demographic information and how the volunteer learned of the study in order to identify the source recruitment.

Results

Recruitment objectives

1680 participants were randomized over the recruitment period. Figure 1 represents the total number of randomizations by recruiting centers. A total of 1290 participants were recruited in the 7 University Hospital centers, and 390 participants in the 6 General Hospital centers. As shown in Figure 2, the first randomization was on May 30, 2008, and the targeted number of randomized participants was reached on February 24, 2011. From an initial stage of pre-screening using the different recruitment strategies, a total of 2595 subjects were finally screened, of which 1680 fulfilled the eligibility criteria which represents 64.8% (Figure 3). Approximately, one quarter of screened people refused to participate after the detailed presentation of the study and 4.3% were still interested in participating but missed for unknown reasons the baseline visit even after repeated contacts. Of the 1809 subjects who signed the consent for participating to the study at the baseline visit, 130 (7.1%) were excluded because one of the eligibility criteria was not satisfied.

Figure 1
Number of randomized participants in each recruiting center



Efficacy of Recruitment sources

Table 1 shows the percentage of randomized/screened participants by recruiting source. Interestingly, the higher percentage of randomizations compared to screened participants is the personal contact source; almost 85 % of screened participants entered in the study. In an equivalent way, Medias and conferences are efficient recruiting sources to enrol volunteers in the study. Unexpectedly, only about 60% of screened participants from the hospital and GP sources were randomized and 33.2% from health care services.

Figure 2
Cumulative number of randomizations

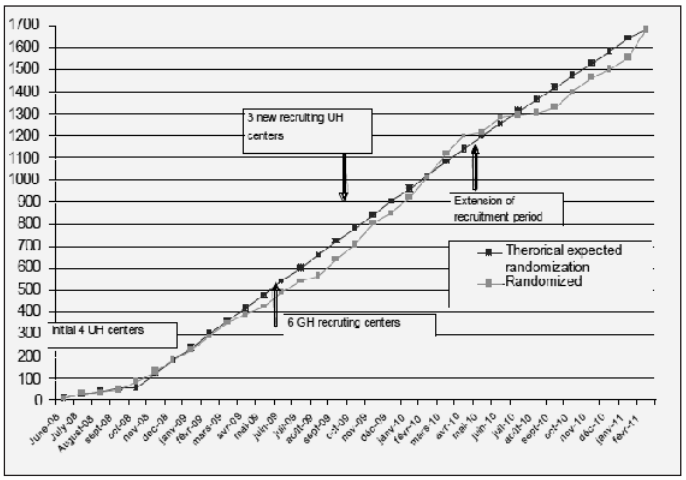


Figure 3
Flow-chart of screened participants

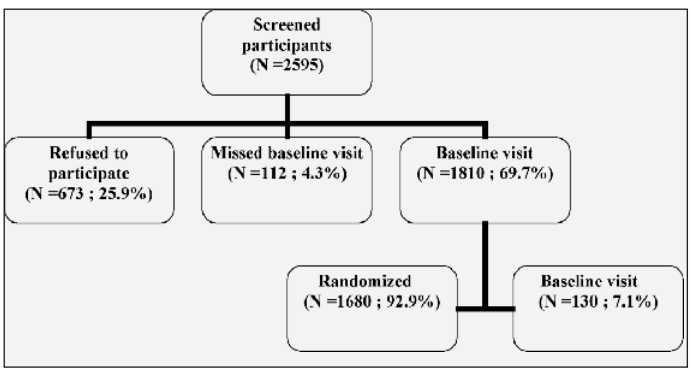


Table 1
Percentage of randomized participants by recruiting source

Recruiting source	Randomized /screened 1680/ 2595	% of randomized 64.8%
Hospital outpatients clinics	414/ 717	57.7
General Practitioners	42/ 75	56.0
Health Care services	66/199	33.2
Senior organizations	101/168	60.1
Conferences	312/ 476	65.5
Medias	611/795	76.9
Personal contact	127 / 151	84.1
Unknown	7/14	50.0

Table 2 showed that the principal source for recruiting in MAPT study was Medias. Almost a quarter of the randomized

participants come from the hospital and approximately 20% from conferences. The recruiting profile between the HU and the CG centers was similar.

Table 2
Origins of the 1680 participants in MAPT study

Recruiting source	1290 randomized older adults in Hospital University Centers	390 randomized older adults in General Hospital Centers	Overall 1680 randomized older adults
Hospital outpatients clinics	315 (24.4%)	99 (25.4%)	414 (24.6%)
General Practitioners	37 (2.9%)	5 (1.3%)	42 (2.5%)
Care services	64 (5%)	2 (0.5%)	66 (3.9%)
Senior organizations	86 (6.7%)	15 (3.8%)	101 (6.0%)
Conferences	203 (15.7%)	109 (27.9%)	312 (18.6%)
Medias	492 (38.1%)	119 (30.5%)	611 (36.4%)
Personal contact	86 (6.7%)	41 (10.5%)	127 (7.5%)
Unknown	7 (0.5%)	0	7 (0.4%)

Data from Toulouse: A total of 1128 contacts yielded to 556 screened volunteers and 345 randomized participants in the coordinating center of Toulouse. Thus, 30 % of contacts were recruited. This result is in accordance with the analysis performed by Mc Murdo et al. (6) indicating that the number needed to be screened to recruit one older participant is around 3:1.

Preliminary results on drop-outs

The MAPT study began 3 years ago, and the number of drop-outs in February 2012 was 300; about 17.8%. All participants should have to complete the one-year visit at the end of April 2012. At this time, there were 1643 participants with at least 1 year of follow-up. Among these 1643 participants, the drop-out rate during the first year was 13.0 % (213/1643). There is a significant difference between the percentage of drop-outs in UH and GH, with drop-out levels higher in the UH (Table 3). These preliminary results might indicate that performing single research protocols in smaller recruiting centers could improve adherence compared to recruiting in large research centers with many ongoing protocols.

Table 3
Preliminary results on drop-out rate in 1643 participants with at least 12 months of follow-up

	Hospital University centers	General Hospitals centers	
Randomized	1281	362	
drop-outs	178	35	
% (IC 95%)	13.9 (12-15.8)	9.7 (6.7-12.7)	P=0.034*

* Chi-squared statistics

Recruitment in neuroimaging ancillary studies (Table 4)

MRI-MAPT ancillary study

The MRI-MAPT study was conducted in the 7 University Hospital centers (Toulouse, Bordeaux, Montpellier, Limoges, Dijon, Lyon and Nice) and 2 General Hospitals (Foix, Tarbes). The first inclusion was on January 8, 2010, and the targeted number of 500 participants was reached on August 31, 2011.Currently, 504 participants have undergone baseline MRI. A final MRI at the end of the study (3 years) will be performed.

Table 4
Number of participants in MAPT neuroimaging studies

		MAPT-MRI	FDG-PET	AV45-PET
	Toulouse	67	68	146
	Bordeaux	54	NP	3
	Montpellier	167	NP	40
	Limoges	57	NP	2
	Dijon	55	NP	NP
	Lyon	27	NP	NP
UH	Nice	46	NP	10
	Castres	NP	NP	
	Foix	7	NP	
	Tarbes	24	NP	
	Lavaur	NP	NP	
	Montauban	NP	NP	
GH	Monaco	NP	NP	NP
	Total	**504**	**68**	**201**

NP= Not Participating

FDG-PET ancillary study

The first inclusion was on June 8, 2009, and the targeted number of 68 participants was reached on February 9, 2011. All FDG-PET scans were performed at baseline and at 6 months. A final FDG-PET scan at the end of the first year of the study will be performed.

AV45-PET ancillary study

The first inclusion was on July 12, 2010, and the enrolment is still in progress. At this time, 201 PET-scans were performed during the two first years of the study.

Conclusion

For MAPT study, the 13 centers recruited 1680 frail elderly people aged 70 years and over in a relative short inclusion period. To include frail older adults in RCTs is challenging but different recruitment strategies have shown their efficacy. In between these strategies, Medias and personal contacts seemed most efficient when screening frail older adults. Medias and the recruiting centers were the most frequent source of finally enrolling older adults in the MAPT study.

Retention in the study is the new challenge once the population was included. Although the recruiting profile between the HU and the CG centers was similar, adherence seems to be better in CG.

The expected number of participants in the different ancillary studies was easily reached due to the fact that the target population for these studies was already available in the main MAPT study.

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References

1. Alzheimer's disease International. ADI Publication. World Alzheimer's Report 2009.
2. Gillette-Guyonnet S, Andrieu S, Dantoine T, Dartigues JF, Touchon J, Vellas B; MAPT Study Group. Commentary on "a roadmap for the prevention of dementia II. Leon Thal Symposium 2008." The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. Alzheimers Dement. 2009 ; 5, 2:114-21.
3. Andrieu S, Aboderin I, Baeyens JP, Beard J, Benetos A, Berrut G, Brainin M, Cha HB, Chen LK, Du P, Forette B, Forette F, Franco A, Fratiglioni L, Gillette-Guyonnet S, Gold G, Gomez F, Guimaraes R, Gustafson D, Khachaturian A, Luchsinger J, Mangialasche F, Mathiex-Fortunet H, Michel JP, Richard E, Schneider LS, Solomon A, Vellas B.IAGG workshop: health promotion program on prevention of late onset dementia. J Nutr Health Aging. 2011;15(7):562-75.
4. Bonk J, A road map for the recruitment and retention of older adult participants for longitudinal studies. Journal of the American Geriatrics Society 2010
5. Witham M and McMurdo M. How to Get Older People Included in Clinical Studies. Drugs Aging 2007: 24 : 187-196.
6. McMurdo ME, Roberts H, Parker S, Wyatt N, May H, Goodman C, Jackson S, Gladman J, O'Mahony S, Ali K, Dickinson E, Edison P, Dyer C; on behalf of the Age and Ageing Specialty Group, NIHR, Comprehensive Clinical Research Network. Improving recruitment of older people to research through good practice. Age and ageing 2011; 0 : 1-7
7. Mody L, Miller DK, McGloin JM, Freeman M, Marcantonio ER, Magaziner J, Studenski S. Recruitment and retention of older adults in aging research. J Am Geriatr Soc. 2008 ;56(12):2340-8.
8. Oustric, S. Rouge-Bugat, M-E. Vellas, B. Primary Care Practitioners on the front line of Alzheimer's Disease Care. J Am Med Dir Assoc. 2011 Oct;12: 545-546.