

Outline Trials Application

1. TITLE OF THE TRIAL

E3.1 Early detection of patients with mild cognitive impairment and dementia in primary care

2. PRINCIPAL / COORDINATING INVESTIGATORS

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3. INNOVATION AND RELEVANCE OF THE TRIAL**3.1. Medical problem**

Due to the increasing helplessness of the patients, dementias pose a huge problem both medically and socially. The disease is manifested mainly at an advanced age: while dementias play only a minor role below the age of 60 with a prevalence rate of less than 0.1 per cent, their prevalence increases to 1 per cent in patients aged 60-69, and to 20 per cent in patients aged 80 (Eccles et al., 1998)¹.

The onset of some subtypes of dementia, especially Alzheimer's dementia, is insidious. There is a continuum between normality and early symptoms, transitional states are very frequent. Therefore an early and correct diagnosis of dementia in clinical practice is complicated and often results in a late diagnosis at a progressed state of the disease, at which patients don't have the ability to make plans for their future any more. In addition the following aspects complicate the establishment of an early and correct diagnosis and should be addressed by research:

- To some extent, cognitive symptoms, which do not fulfil the criteria for dementia can at least hint at dementia. These symptoms are combined in the term Mild Cognitive Impairment (MCI). But there are considerable discrepancies concerning the definition of this syndrome.
- The sensitivity of the common screening instruments for detecting MCI is also limited.
- Little is known about the transition of mild cognitive impairment to dementia in the general population.

3.2. Hypothesis

The aims of this project can be summarized in four subject areas, that all aim at improving early diagnosis:

- Identification of risk factors for the development of dementia and mild cognitive impairment through examination of patients on the basis of the known risk factors in the general population.
- Evaluation of neuropsychological test methods with regard to their association with the risk of developing dementia. Also, identification of (definitive) early symptoms of dementia using these test methods.

¹ Eccles M, Clarke J, Livingstone M, Freemantle N, Mason J (1998) North of England evidence based guidelines development project: guideline for the primary care management of dementia. Br Med J 317: 802-808.

- Quantification of the risk of developing dementia for given patterns of risk factors and early symptoms, and development of early diagnosis instruments for routine use in general practice.
- Description of the progress of mild cognitive impairment under current treatment conditions.

3.3. Novel aspect

The novel aspect of the proposed trial is, that patients are recruited in primary care and therefore represent the general population and that patients are followed up for nearly 3 years, what is in comparison to other studies a long time.

3.4. Evidence

Evidence for the need to perform this trial has been gained by a thorough literature review including the following subjects:

- epidemiology in the general population and at general practice level
- risk factors for the development of dementia
- diagnostic criteria and concepts of MCI
- neuropsychological methods of assessing the risk of developing dementia.

Sample of important literature:

- Almkvist O, Winblad B (1999) Early diagnosis of Alzheimer dementia based on clinical and biological factors. *Eur Arch Psychiatry Clin Neurosci* 249, Suppl 3: 3-9.
- Heun R, Papassotiropoulos A, Jessen F (1998) The validity of psychometric instruments for detection of dementia in the elderly general population. *Int J Geriatr Psychiatry* 13: 368-380.
- Rubin EH, Storandt M, Miller JP et al. (1998) A prospective study of cognitive function and onset of dementia in cognitively healthy elders. *Arch Neurol* 55: 395-401.
- Small BJ, Fratiglioni L, Viitanen M et al. (2000) The course of cognitive impairment in preclinical Alzheimer disease. *Arch Neurol* 57: 839-844.
- Tierney MC, Szalai JP, Snow WG et al. (1996) Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. *Neurology* 46: 661-665.

3.5. Results

The results of the trial will allow the development of a prognostic instrument for early diagnosis of dementia in a general practice setting.

4. DESIGN OF THE TRIAL

4.1. Trial design

The project of E3.1 is a prospective longitudinal study, which is conducted simultaneously in 6 study centres (Bonn, Düsseldorf, Hamburg, Leipzig, Mannheim and Munich) using the same methodology. Patients were recruited in 20 cooperating general practices in each of the six study centres. The recruitment procedure was as follows: the general practitioner draws up a list of all patients aged 75-89, patients who meet the exclusion criteria are left out, and then, depending on the number left, 40-60 patients following a fixed pattern are selected (e.g. every second or third patient). These patients receive a brief written information about the project and are invited to the general practice for more details. If they agree to take part in the study, they are registered and undergo a comprehensive interview – and a blood sample for E3.2 is taken.

Two follow-up interviews are planned for each patient: the first 18 months after the primary examination and the second 12 months after the first follow-up.

In the study module, which in its core consists of psychometric tests, the primary examination and the follow-ups are nearly identical. The follow-ups differ from the primary examination in two aspects. If a patient develops dementia, a relative is interviewed additionally during the follow-up, because his/her evaluation is

taken into account in the diagnosis according to SIDAM. Furthermore, some instruments are left out during the follow-ups, such as the social questionnaire.

4.2. Trial interventions

The project of E 3.1 is a prospective longitudinal study without any intervention that would intend a change in the patients or general practitioners' activities.

4.3. Inclusion / exclusion criteria

Inclusion criteria: All patients aged 75-89 who follow the written invitation should be included in the study, when they agree.

Exclusion criteria:

- Patients, who are visited only on house-calls or in nursing homes.
- Severely ill patients, whose life expectancy does not exceed 3 months.
- Patients without sufficient knowledge of German.
- Patients with uncompensated, distinct hearing impairment or blindness.
- Patients incapable of giving their consent.
- Patients who are not regular patients of the respective practice.
- Other reasons (only in exceptional cases). Please explain.

4.4. Duration

Time schedule for E3.1: Early detection of patients with mild cognitive impairment and dementia in primary care

Study centres	1. Funding period (11/02-10/04)			2. Funding period (11/04-5/07)	
Bonn Düsseldorf Hamburg Leipzig Mannheim Munich	Preparation	recruitment of patients by general practitioners, first examination by members of the study team	Follow-up I (18 months)	Follow-up II (17 months)	
		taking a blood sample for genetic analysis (sub-project E.3.2.)			
time period	11 - 12/02	1/03 - 7/04	8/04 - 10/04	11/04-01/06	02/06 - 03/07

4.5. Outcome measures

- Risk factors for the development of dementia and MCI.
- Neuropsychological scales of potential relevance to the risk of MCI/AD.
- Changes in cognitive ability criteria between the first examination and follow-up 1 and 2.
- Odds ratios as basic measures of association of the identified risk indicators and early symptoms with the risk of developing dementia.

4.6. Methods against bias

In order to prevent bias during the recruitment procedure the general practitioner was asked to draw up a list of all patients aged 75-89, then patients who met the exclusion criteria were left out, and then, depending on

the number left, 40-60 patients following a fixed pattern were selected and were written an invitation letter to participate in the study (e.g. every second or third patient).

4.7. Power calculations

As this study follows an explorative approach power calculations are not possible.

4.8. Numbers of participants

Aim of the first study period was to include and examine 3.000 participants. Each center therefore had to recruit 500 participants within 18 months corresponding to 28 included and examined patients per month. Taking into account the organisational work (contact and instruction of 20 GPs per center, preparation of documentation materials for each GP practice, selection of participants, arrange appointments with patients, visiting them at home for examination etc.) the planned number of participants could only be achieved with a full time employee.

Final numbers of included and examined participants: Hamburg 607, Bonn 524, Mannheim 581, Düsseldorf 585, Leipzig 531 and Munich 502. Sum for the six centers: **3.330**.

Handling of drop-outs: For patients who are alive at the date for a follow-up investigation but cannot be examined for follow-up in person, the health status is documented using information from relatives and/or the GP of the patient. We expect that in the majority of such cases the data obtained in this way will allow the clinical investigator to determine whether or not a conversion to dementia did occur. In contrast, patients who die in the interval between two consecutive examination dates will be treated as contributing no information on the conversion rate for the respective interval. In view of the comparatively high mortality in the target population of patients aged ≥ 75 , this implies that the estimates of the conversion rates will have to be based on samples of markedly reduced size (as compared to the numbers of patients initially enrolled).

4.9. Trial sites

Six study centres are participating: Hamburg, Bonn, Mannheim, Düsseldorf, Leipzig and Munich.

4.10. Analyses

- Exploratory analyses regarding the relevance of examined variables for conversion to MCI and dementia
- Forward and backward logistic regression analyses to obtain predictive models containing all relevant risk factors and odds ratios considering conversion to MCI and dementia

5. ETHICAL CONSIDERATIONS

5.1. Risks for participants

No risk for participants is assumed. Potential irritations of patients by the test procedure were to be collected by their GPs, who were asked to forward information about irritations to the study centers. No irritations were reported by now.

6. TRIAL MANAGEMENT AND EXPERTISE

Persons responsible for design, management, and analysis of the trial

#	Name	Affiliation	Responsibility / Role	Signature
1	Prof. Dr. W. Maier	Uni Bonn	Principal investigator	
2	Prof. Dr. H. van den Bussche	Uni Hamburg	Principal Investigator	

3 Prof. Dr. S. Wellek

ZI Mannheim

Biostatistics

6.1. Trials expertise

The group of principal investigators and co-investigators (names underlined) have gained good experience in performance of trials on the subject of dementia.

- Burkart M, Heun R, Maier W et al. (1998) Demenzscreening im klinischen Alltag. Eine vergleichende Analyse von NMSE, SIDAM und ADAS. Nervenarzt 69: 983-990
- Cooper B, Bickel H, Schaufele M (1996) Early development and progression of dementing illness in the elderly: a general-practice based study. Psychol Med. 26: 411-419.
- Matschinger H, Schork A, Riedel-Heller SG et al. (2000) On the application of the CES-D with the elderly: Dimensional structure and artefacts resulting from oppositely worded items. Int J Meth Psychiatr Res 9: 119-209.
- Riedel-Heller SG, Busse A, Angermeyer MC (2000) Are cognitively impaired individuals adequately represented in community surveys? Recruitment challenges and strategies to facilitate participation in community surveys of older adults. A review. Eur J Epidemiol 16: 827-835.
- Sandholzer H, Breull A, Fischer GC (1999) Früherkennung und Frühbehandlung von kognitiven Funktionseinbußen: eine Studie über eine geriatrische Vorsorgeuntersuchung im unausgelesenen Patientengut der Allgemeinpraxis. Z Gerontol Geriat 32: 172-178.

6.2. Trial-supporting facilities

IT-support was provided by the Central Information Office in Göttingen and will in future be provided by Mrs. Birgitt Wiese, Hannover. As the data transfer from the laptops to the central databank in Göttingen is still too slow and disturbs the testing procedures to a high degree, all future examinations will be performed on a paper and pencil basis. The measures for quality assurance are described in the "Monitoring-Protocol", established in August 2003.

7. FINANCIAL SUMMARY

7.1. Estimation of research costs for the second funding period (11/04-05/07), reduced inclusion according to the results of the midterm evaluation

Personnel

- For each center 1 BAT IIa for follow-up examinations for 14 months (11/04-12/05) and 0,8 BAT IIa for 15 months: for six centers a total of 735.948 € (Position 812).
- For five centers student personnel for 11 h a month for 31 months (11/04-05/07, 9,- € per hour): for five centers a total of 15.345 (Position 820).
- For the center in Hamburg: 0,5 BAT IIa for coordinating activities for 31 months (11/04-05/07): 73.304 € (Position 812).

Total personal costs: 824.597 Euro (recommended 825.000 Euro)

Consumables

- Compensation for the GPs for each follow up (per patient 15 Euro): total costs for six centers 90.000 €
- Compensation for the local coordinators in Bonn, Mannheim, Leipzig and Munich (11.540 for the second funding period each): total costs 46.160 €
- Travelling expenses for the coordinators and the project leaders: 7.000 €
- Office equipment (paper for the interviews etc.): 4.000 €
- 2 meetings with participating GPs in each center (40 € per GP, 20 GPs per center): 9.600 €

Total consumables: 156.760 Euro (recommended 156.760 Euro).

7.2. Co-financing

Co-financing is not yet established.