

Efficacy of an Active Geriatric Evaluation for geriatric syndromes (AGE tool) to prevent functional decline in elderly patients in family medicine: a pragmatic cluster randomized trial

Clinical Study Protocol

AGE3 (Active Geriatric Evaluation program, 3rd phase)

| | |
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| Study Type: | Clinical trial of a clinical intervention (without Investigational Medicinal Product (IMP) and without Medical Device (MD)) |
| Study Categorisation: | Risk category according to LHR A |
| Study Registration: | ClinicalTrials.gov NCT02618291 CER-VD 2016-00422 Registration number (from FOPH portal) eventually other registries and numbers if applicable: NCT02618291 |
| Study Identifier: | SNF Grant 32003B_159863/1 |
| Sponsor: | Swiss National Fund, Biology and Medicine Division, Wildhainweg 3, 3001 Bern, tel: 031 308 22 22 |
| Principal Investigator: | Prof Nicolas Senn University Institute of Family Medicine, Department of ambulatory care and community medicine (DACCM, Policlinique Médicale Universitaire), University of Lausanne, rue du Bugnon 44, 1011 Lausanne, Email : Nicolas.senn@hospvd.ch, Phone: +41 21 314 04 06; Mobile phone +41 79 556 07 48 |
| Investigational Intervention: | Active Geriatric Evaluation (AGE) tool for geriatric syndromes |
| Protocol Version and Date: | Version 9, 19.12.2018 |

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STUDY SYNOPSIS

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| Sponsor / Investigator | Sponsor: Swiss national Fund Promoter-Investigator: Dr Nicolas Senn University Institute of Family Medicine, Department of ambulatory care and community medicine (DACCM, Policlinique Médicale Universitaire) |
| Study Title: | Efficacy of an Active Geriatric Evaluation for geriatric syndromes (AGE tool) to prevent functional decline in elderly patients in family medicine: a pragmatic cluster randomized trial |
| Short Title / Study ID: | AGE3 |
| Protocol Version and Date: | Protocol version 9, 19/12/2018 |
| Trial registration: | Clinicaltrials.gov Identifier: NCT02618291 |
| Study category and Rationale | <p>Category A: the intervention under study has only limited risks and is associated with minimal constraints.</p> <p>The assessment component of the tool ("Brief Assessment Tool" or BAT) has been developed following a comprehensive literature search and has been validated against a standard geriatric consultation. The proposed management strategies are based on the current evidence and best geriatric practices.</p> <p>The study participants will be submitted to an annual phone interview to assess their functional status (study outcome). If they receive the intervention, their physician will conduct the BAT once per year (twice in total), which will add an extra-20 minutes to the medical consultation. These can be considered as minimal constraints.</p> |
| Clinical Phase: | Not relevant |

Background and Rationale:

According to demographic projections, a significant increase in the proportion of the elderly population is anticipated worldwide. This aging of the population will lead to an increase in the prevalence of chronic diseases and functional impairment, and will result in a growing use of the health care system for which western societies are largely unprepared. In that regards, family practitioners (FP) are in the front line of this huge epidemiological challenge.

Current perspectives in the management of elderly persons consider that it is more important to reduce morbidity and improve the quality of life rather than increasing life expectancy. Therefore, interventions should be tailored to prevent functional decline and improve quality of life. If chronic diseases are often well defined, it is less the case of *geriatric syndromes*, which are multifactorial clinical conditions that share common features such as older age. Tinetti and colleagues proposed the following definition: "*Geriatric syndromes are multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render [an older] person vulnerable to situational challenges*».(1)

Numerous screening tests for specific geriatric syndromes have been developed, but few were specifically designed for a comprehensive geriatric assessment in primary care and even those suffer some limitations. In order to develop an instrument better suited for the screening and management of geriatric syndromes by FP's, the Active Geriatric Evaluation program (AGE) was launched in 2011 by the investigators of the present study. It consists in 4 steps: 1) a literature review to identify suitable screening tools for geriatric syndromes and design a Brief Assessment Tool (BAT), development of a theoretical framework and construction of the management tool for FP's; 2) Validation of the geriatric consultation as a gold standard for assessing geriatric syndromes (study named **AGE 1**); 3) a prospective study to assess the performances (sensitivity, specificity,...) of the BAT (study named **AGE 2**); and 4) assessment of the efficacy and efficiency of the AGE tool implemented in family practice (**AGE 3**: present proposal). The BAT was developed for the screening of eight geriatric syndromes in primary care. But because screening for geriatric syndromes might provide by itself only a limited impact on functional decline, it was further integrated to a global tool that includes also diagnostic complementary investigations and management strategies (AGE tool).

The AGE tool is a tool which is designed to be performed by independent FPs. It was developed step by step and the screening instrument (BAT) that composes the core of the tool proved to perform well in excluding geriatric syndromes. However, the efficacy of the global tool aiming to preventing functional decline has not yet been tested in family practice.

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| Objective(s): | <p>The primary objectives of this project are to determine whether the AGE tool used in family medicine:</p> <ol style="list-style-type: none"> 1. reduces the functional decline of elderly patients. <p>The secondary objectives of this project are to determine if the AGE tool used in family medicine:</p> <ol style="list-style-type: none"> 2. improves the quality of life of elderly patients. 3. reduces the incidence of hospital admissions 4. reduces the incidence of institutionalizations 5. reduces the incidence of emergency visits 6. impacts on the number of FP outpatient visits 7. improves the processes of care (diagnoses and management) of elderly patients 8. is acceptable and feasible for patients and family practitioners 9. is cost-effective |
| Outcome(s): | <p>Primary outcome measures</p> <ol style="list-style-type: none"> 1. Instrumental activities of daily living (ADL) score 2. Activities of daily living (ADL) score <p>Secondary outcome measures</p> <ol style="list-style-type: none"> 3. Health related quality of life (WHOQOL-OLD) score 4. Incidence of hospital admissions 5. Incidence of institutionalization 6. Incidence of emergency visits 7. Incidence of outpatient visits 8. Process outcome measures: number of geriatric syndromes identified / confirmed, managements strategies adopted (medication adaptation, referral to specialty care, supportive measures,...). 9. Qualitative assessment of acceptability and feasibility, as well as of perceptions of autonomy for elderly patients and family physicians 10. Costing of FP costs, estimation of costs induced by management differences, differences in prescriptions, and health care utilization |
| Study design: | <p>Controlled, open label, cluster-randomized trial. The unit of randomization will be a family practitioner (FP).</p> |

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| <p>Inclusion / Exclusion criteria:</p> | <p>Study population</p> <p>The AGE tool is designed to be used by FP in routine setting to prevent as early as possible the functional decline of community elderly people. Therefore the intervention will be performed with any patients aged 75 years or older being follow-up in a FP practice.</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. <i>The participating FP should fulfill the following criteria:</i> <ul style="list-style-type: none"> • Working as family practitioner (≥ 20 hours per week) • Family medicine being their main activity • Working in the french-speaking part of Switzerland • Willing to recruit twelve patients into the study 2. <i>The patients should fulfill the following criteria:</i> <ul style="list-style-type: none"> • Aged 75 years or more • Consider the enrolling physician as his/her reference FP • Able to understand French • Living at home (not in institutions) • Visited his/her FP at least twice during the past year • Giving signed informed consent (or, in the absence of discerning capacity, giving assent in the presence of a surrogate signing the consent form) <p>Exclusion criteria</p> <ol style="list-style-type: none"> 1. <i>For FP's</i> <ul style="list-style-type: none"> • Having participated in the AGE2 study • If another FP from the same practice is already participating to the study • Planning to handover the practice within the next 2 years • Holding a subspecialty title in geriatrics ("formation approfondie en gériatrie") 2. <i>For patients</i> <ul style="list-style-type: none"> • Having had a geriatric or specialized memory consultation in the past 3 months • Planning to leave the study area or to change of FP in the next 2 years |
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Measurements and procedures:

Recruitment of FP's

Study information, sent by email and/or post, will be targeted to the FPs most likely to participate: the contact list of the University Institute of Family Medicine, cantonal FP professional association (MFVaud), and physicians known to the investigators for their interest in participating in research. Information about the study will be given during medical association meetings and continuous training sessions ("cercle de qualité"). Posters will be depicted at the Policlinique Médicale Universitaire and CHUV, at locations attended by FPs for continuous training. Information about the study will also be made available on the website of the Policlinique Médicale Universitaire.

Enrolment of patients

All participating FP's will be responsible to recruit 10 patients, independently of the study arm and before randomisation. FPs will be given a unique ID consecutively at the time of the previsit by the study staff.

Randomization of FP's

Randomisation using uneven block size will be made by an independent statistician and allocation be consigned in sealed envelopes numbered consecutively.

FP allocation to intervention or usual care group will occur after patient recruitment, during monthly training sessions organised at the Policlinique Médicale Universitaire. During each training session, the FP will open the envelope corresponding to his preassigned unique ID.

Baseline assessment of patients and follow-up

Baseline assessment is performed by the FP at the next patient visit, planned within 3 months after screening.

Within two weeks of enrollment of the patient visit, a study staff will contact all consented patients by phone and will administer a baseline questionnaire to collect basic socio-demographic data and administer a baseline ADL IADL and WHOQOL-OLD questionnaires.

Thereafter, each patient will be contacted by phone once a year by the research assistant to repeat these questionnaires.

Another study staff will visit each participating physician annually and extract from the medical records the information concerning hospitalization, emergency visit and institutionalization, and assess the **process outcomes** that are related to the use of the AGE tool.

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| <p>Study Product / Intervention:</p> | <p>FP allocated to the intervention arm will perform the AGE tool once a year for a total of 2 years with the patients included. The AGE tool should be performed within the framework developed for the AGE program which is displayed in the figure 3.</p> <div data-bbox="523 344 1056 909" style="border: 1px solid black; padding: 10px; margin: 10px auto; width: fit-content;"> <pre> graph TD A[Functional ability evaluation: (I)AVQ / 4 items] --> B[Geriatric syndromes screening with BAT] B --> C[Complementary investigations] C --> D[Specific management attitudes for identified geriatric syndromes] D --> E[Plan of care that takes into consideration: Non-geriatric problems (internal medicine) Polypharmacy Social context Overall prognosis Patient's preferences] </pre> </div> <p>The brief assessment tool (BAT) will be used to screen patients for the following syndromes:</p> <ul style="list-style-type: none"> - Cognitive impairment - Mood disorder - Gait and balance impairment - Visual impairment - Hearing impairment - Urinary incontinence - Malnutrition - Osteoporosis <p>Once the presence of one or more geriatric syndromes is suspected using the BAT, a management strategy is proposed. It is divided in two distinct steps: 1) perform additional tests to confirm or exclude the diagnosis and 2) to propose specific management attitudes. All proposed attitudes are based on literature review and geriatrician expertise.</p> |
| <p>Control Intervention (if applicable):</p> | <p>This arm called “usual care” will serve as control group. In this arm, FP’s will be responsible to recruit 10 patients each. No specific intervention will be provided to these patients, except what FP’s usually do. In that regards, it is possible that some FP’s might use structured interventions similar to the AGE tool. This will be neither encouraged nor discouraged. This might be the case if two FP’s are belonging to the two different arms and know each other’s or participate to quality groups. This will be reported in the study records. Patients of this arm will also have the same follow-up as described above.</p> |
| <p>Number of Participants with Rationale:</p> | <p>Initial sample size of 66 FPs and 792 patients was revised after reviewing initial assumptions. Revised sample size of</p> <p>40 FP’s (20 per arm) and 400 patients was estimated to have sufficient power (>90%) to to show a difference in the proportion of patients that lose at least one IADL (incident disability), i.e. patients, of 15% after 2 years.</p> |
| <p>Study Duration:</p> | <p>3 years and 9 months</p> |

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| Study Schedule: | May 2016 to February 2020 |
| Investigator(s): | <p>Prof Nicolas Senn, MD PhD</p> <p>Dr Yolanda Müller Chabloz, MD MIH, specialist in prevention and public health</p> <p>Dr Isabella Locatelli, PhD, statistician</p> <p>Prof Jacques Cornuz, MD MHS, Director</p> <p>Department of community medicine and ambulatory care (DACCM)</p> <p>Rte du Bugnon 44; 1011 Lausanne</p> <p>PD Dr Stéphanie Monod, MD, Geriatrician</p> <p>Head of Public Health Office, Canton de Vaud & CHUV; BAP, Casernes 2, 1014 Lausanne</p> |
| Study Centre(s): | University Institute of Family Medicine, Department of ambulatory care and community medicine (DACCM, "Policlinique Médicale Universitaire"), University of Lausanne |
| Statistical Considerations: | <p>This is a superiority trial aiming at showing a difference in functional status assessed by the IADL between elderly patients followed by a family practitioner using the comprehensive assessment and management tool and elderly patients followed in usual care. The test of the null hypothesis will be two-sided and use a level of significance of 0.05.</p> <p>In order to estimate the sample size needed for our purposes, we assumed that 10% of patients would lose independence in at least one activities (IADL) in the intervention group, compared with 25% in the control group. A mixed effect logistic model was adopted in order to describe data, with a doctor-related random effect. With these parameters, cluster data were generated with n FP's per group and m patients per FP ($n = 5, 10, \dots, 55, 60$; $m = 5, 10, \dots, 25, 30$). For each combination of n and m, 10'000 datasets were generated and the power was empirically calculated as the percentage of datasets on which a significant ($\alpha=0.05$) difference between the two arms was obtained via the logistic mixed effect model, for different levels of ICC. In the absence of available data of intracluster coefficient (ICC) for such a type of interventions, and with an ICC of 0 at baseline, we expect only a cluster effect in half of the participants after 2 years (intervention arm), which we postulated to be 0.10 considering the standardized nature of the intervention.</p> <p>This approach allows choosing the best cluster combination that includes also feasibility considerations. For example to achieve a power of 90%, 8 patients per FP are sufficient if we have 20 FP's per arm, based on an ICC is 0.10. Taking into account the loss to follow-up estimated at 15%, we increased the number of patients per FP to $8/(1-0.15)=10$, corresponding to a total of 40 FP's and 400 patients, corresponding to a final sample size of 40 FPs for a total of 400 patients..</p> |
| GCP Statement: | This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements. |

STUDY SUMMARY IN LOCAL LANGUAGE

Le vieillissement de la population et l'augmentation de la prévalence des maladies chroniques et de la dépendance fonctionnelle représentent un défi majeur de santé publique. Une prise en charge optimale des pathologies liées à l'âge est donc nécessaire. En effet, une identification précoce des syndromes gériatriques contribue à diminuer le déclin fonctionnel, le risque d'institutionnalisation et améliore la qualité de vie des patients. Les médecins de famille sont, dans ce contexte, des acteurs essentiels dans la prise en charge des patients âgés.

Or, le diagnostic précoce ainsi que la prise en charge des syndromes gériatriques restent encore déficitaires en médecine de famille. Les outils de diagnostic précoce des syndromes gériatriques sont le plus souvent mal adaptés aux besoins du médecin généraliste. Il apparaît dès lors essentiel de développer un outil performant, adapté à la médecine de famille, qui permette une optimisation du diagnostic précoce des syndromes gériatriques.

Le projet **AGE**, fruit d'une étroite collaboration entre médecins gériatres et médecins de famille, a pour objectif de répondre à ce besoin. Ce projet a permis de développer et de valider un outil (Evaluation Gériatrique Brève (EGB)) pour le diagnostic précoce des syndromes gériatriques en médecine de premier recours.

La troisième partie du projet AGE (étude AGE3) vise maintenant à tester au travers d'un essai randomisé, l'effectivité de l'Evaluation Gériatrique Brève (EGB) assortie de recommandations de prise en charge sur la prévention du déclin fonctionnel des personnes âgées en médecine de famille.

Le projet AGE a donc pour objectif de répondre aux besoins des médecins praticiens de disposer d'un outil de dépistage des syndromes gériatriques approprié à leur pratique. A terme, il devrait permettre d'améliorer la prise en charge des personnes âgées vivant dans la communauté.

ABBREVIATIONS

Provide a list of abbreviations used on the protocol – to be completed

| | |
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| AE | Adverse Event |
| AGE | Active Geriatric Evaluation |
| BAT | Brief Assessment Tool |
| CA | Competent Authority (e.g. Swissmedic) |
| CEC | Competent Ethics Committee |
| CHUV | Centre Hospitalier Universitaire Vaudois |
| CMS | Centre Médico-Social |
| CRC | Centre de Recherche Clinique |
| CRF | Case Report Form |
| ClinO | Ordinance on Clinical Trials in Human Research (<i>in German: KlinV, in French: Oclin</i>) |
| eCRF | Electronic Case Report Form |
| CTCAE | Common terminology criteria for adverse events |
| DSUR | Development safety update report |
| FP | Family Practitioner |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| Ho | Null hypothesis |
| H1 | Alternative hypothesis |
| HRA | Federal Act on Research involving Human Beings |
| IIT | Investigator-initiated Trial |
| ISO | International Organisation for Standardisation |
| ITT | Intention to treat |
| LPT _h | Loi sur les produits thérapeutiques |
| LRH | Loi fédérale relative à la recherche sur l'être humain |
| MA | Medical Assistant |
| Oclin | Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (<i>in German : KlinV, in English : ClinO</i>) |
| PI | Principal Investigator |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |

STUDY SCHEDULE

| | Study Periods | Filled by | Pre study | Screening | Intervention Period | | | | | | Follow-up | | | Unplanned |
|-------------------------------|---|-----------|------------|-----------------------|---------------------|--------------|-----------------|---------------------|--------------------|---------------------|-------------------|-------------------|-------------------|--------------------------------------|
| Visit type | Patient visits to FP | | | Screening | Inclusion visit | | | 1-year visit | | | 2-years visit | | | Extra-visits |
| | Phone interviews with patient | | | | | Phone 0 | | | Phone 1 | | | Phone 2 | | |
| | Study staff visits to FP (without patient) | | FP visit 0 | | | | FP visit 1 | | | FP visit 2 | | | Closure visit | |
| | Time (hour, day, week) | | | minus 1 day to 6 mths | 0 | 0 to 14 days | 1 day to 3 mths | 1 year (+/- 3 mths) | 1 year (+/- 1 mth) | 1 year (+/- 3 mths) | 2 years (+3 mths) | 2 years (+3 mths) | 2 years (+3 mths) | Any visit between D0 and final visit |
| Specific forms | Physicians form (CRF 1) | FP | x | | | | | | | | | | | |
| | Patient Information and Informed Consent | FP | | x | | | | | | | | | | |
| | Screening log | FP | | x | | | | | | | | | | |
| | Screening (CRF 2) | FP | | x | | | | | | | | | | |
| | Contact details (CRF 0) | FP | | x | | | | | | | | | | |
| | Inclusion (CRF 3) | FP | | | x | | | | | | | | | |
| | If intervention arm: BAT (CRF 4) | FP | | | x | | | x | | | x (both arms) | | | |
| | Primary Variables (phone interview): IADL, ADL, WHOQOL-OLD (CRF 5) | SA2 | | | | x | | | x | | | x | | |
| | Cormorbidities (CRF 6) | SA1 | | | | | x | | | | | | x | |
| | Secondary Variables (from FP records): hospital admissions, institutionalizations, emergency visits, number of falls, outpatient visits (CRF 6) | SA1 | | | | | x | | | x | | | x | |
| | Process evaluation (CRF 6) | SA1 | | | | | x | | | x | | | x | |
| | Plan of care (CRF 10) | FP | | | | | | | | | | | | |
| | Visit date (CRF 7) | FP | | | | | | x | | | x | | | x |
| | Current medication (CRF 12) | FP | | | x | | | x | | | x | | | x |
| | Adverse Events (CRF 11) | FP | | | x | | | x | | | x | | | x |
| Check contact details (CRF 6) | SA1 | | | | | x | | | | x | | | | |
| End of follow-up (CRF 8) | FP | | | | | | | | | x | | | | |

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor-Investigator

Prof Nicolas Senn, MD PhD, Primary Care Physician, director of the university institute of family medicine

University Institute of Family Medicine, Department of ambulatory care and community medicine (DACCM, Policlinique Médicale Universitaire), University of Lausanne, rue du Bugnon 44, 1011 Lausanne, Email : nicolas.senn@hospvd.ch

1.2 Principal Investigator(s)

Co- investigator and study coordinator:

Dr Yolanda Müller Chabloz, MD MIH, public health specialist, University Institute of Family Medicine, Department of ambulatory care and community medicine (DACCM, Policlinique Médicale Universitaire), University of Lausanne, rue du Bugnon 44, 1011 Lausanne, Email : Yolanda.mueller@hospvd.ch

Co-investigators

PD Dr Stéfanie Monod, MD, Geriatrician

Head of Public Health Office, Canton de Vaud & CHUV, department of Geriatrics, Rte du Bugnon 44, 1011 Lausanne, Email : Stefanie.Monod-Zorzi@chuv.ch

Dr Isabella Locatelli, PhD, Statistician

Department of ambulatory care and community medicine (DACCM), University of Lausanne, 10, route de la Corniche, CH - 1010 Lausanne

Email: isabela.locatelli@hospvd.ch

Prof Jacques Cornuz, MD MHS

Director, Department of community medicine and ambulatory care (DACCM)

Rue du Bugnon 44, 1011 Lausanne, email : jacques-cornuz@hospvd.ch

1.3 Statistician ("Biostatistician")

Dr Isabella Locatelli, PhD, Statistician

Department of ambulatory care and community medicine (DACCM), University of Lausanne, 10, route de la Corniche, CH - 1010 Lausanne

Email: isabela.locatelli@hospvd.ch

Phone: +41 21 314 72 41

1.4 Laboratory

No laboratory is involved in the trial

1.5 Monitoring institution

No external monitor is involved in the study. Internal monitoring will be performed by the study staff.

1.6 Data Safety Monitoring Committee

There is no data safety monitoring committee for this trial, as the risks associated with the intervention can be considered minimal.

1.7 Any other relevant Committee, Person, Organisation, Institution

Steering committee:

The role of the steering committee is to monitor study progress, review monitoring reports and results after the intermediate analysis. It is composed of all investigators mentioned above. According to needs, the steering committee can invite members of the FP committee and geriatric expert group.

FP committee:

The role of the FP committee is to revise and pilot CRF and study procedures involving FPs. It consists of three family practitioners, not otherwise participating in the trial:

- Dr Nicole Jaunin, Cugy, Email: nicole.jaunin@cabmedcugy.ch
- Dr Sébastien Martin, Lausanne, Email: seb.martin@bluewin.ch
- Dr Jean-Marc Bidaux, Palézieux, Email: jean-marc.bidaux@svmed.ch

Geriatric expert group: The role of the geriatric expert group is to review the management recommendations included in the AGE tool, to participate in the training of the FP allocated to the intervention group on the AGE tool, and to make the link with FPs and geriatricians in their respective regional networks. It consists of: specialists in geriatrics part of the association of geriatricians of the Canton de Vaud, Switzerland, and directly involved in ambulatory care.

- Dr Annelore Sautebin, Hôpital Riviera-Chablais, Email: annelore.sautebin@hopitalrivierachablais.ch
- Dr Ahmed Jabri, Réseau Santé Nord Broye, Email: ahmed.jabri@rsnb.ch
- Dr Stéphane Rochat, Epalinges, Email : stephane.rochat@vidymed.ch
- Dr Serge Félix, Hôpital Riviera-Chablais, Email: serge.felix@hopitalrivierachablais.ch

Department of geriatrics, CHUV, Lausanne

The department of geriatrics has been a key partner in the different steps of the AGE program. It has provided academic expertise and has actively participated in the first steps of the program (AGE0 to AGE2).

Contact: Prof Christophe Büla, MD, CHUV, department of Geriatrics, Rte du Bugnon 44, 1011 Lausanne, Email: christophe.bula@chuv.ch

Centre de recherche Clinique (CRC) of the Lausanne University Hospital (CHUV): the CRC is mandated to develop the database for the trial (eCRF).

Contact: Plateforme de soutien en recherche clinique, Dr Isabelle Guilleret, CHUV Mont-Paisible 14 MP14 /02/ 204, 1011 Lausanne. Email : Isabelle.Guilleret@chuv.ch

Qualitative study methodologist

Mrs Joëlle Schwarz, sociologist, Department of ambulatory care and community medicine (DACCM), University of Lausanne, 10, route de la Corniche, CH - 1010 Lausanne

2. ETHICAL AND REGULATORY ASPECTS

2.1 Study registration

The trial will be registered in clinicaltrials.gov, as well as in the Federal Office of Public Health's (FOPH) portal for human research in Switzerland.

2.2 Categorisation of study

Category A: the trial will involve neither medicinal product nor medical device. The intervention under study has only limited risks and is associated with minimal constraints.

2.3 Competent Ethics Committee (CEC)

The responsible investigator ensures that the clinical study will be submitted for approval to the competent ethics committee (CEC), in this case the "Commission cantonale d'éthique de la recherche sur l'être humain" of the canton Vaud, Switzerland.

All changes in the research activity and all unanticipated problems involving risks to humans; including in case of planned or premature study end and the final report will be reported within the allowed time frame: premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

No other specific approval is sought.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

The investigators have no conflict of interest to declare.

2.7 Patient Information and Informed Consent

Participating FPs and their practice staff (eg medical assistant) can be designated by the principal investigator to inform the participants about the study.

The designee (FP or medical assistant) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The participant will be asked to sign the consent form within one week after being informed about the study by his family practitioner, and send the signed consent by mail. The participant will be allowed to sign the consent form directly during the consultation. Actual inclusion will take place at the subsequent consultation.

The patient information sheet and the consent form will be submitted to the CEC and to the competent

authority (as applicable) to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the family practitioner (as the investigator's designee) and it will be retained as part of the study records.

If the FP considers that a patient lacks capacity of discernment, written consent will be asked to his/her legal representative, a patient's relative or another trustworthy person not otherwise involved in trial conduct, and the FP will seek patient's assent.

The participant will also be asked to sign a relative information form (see 4a_Info_proche_AGE_3_20160315), authorizing the investigators to collect data on level of functioning from a relative named by the participant, if the participant is temporarily or permanently unable to provide the information himself. This information form will only be sent to the relative in case it is needed to call him.

All participants invited for the qualitative sub-study will be provided an additional participant information sheet and a consent form describing the sub-study and providing sufficient information for participant to make an informed decision about their participation in the sub-study. The patient will be informed about the study by study staff by phone/postal letter. The information sheet will be read with the patient and signed during the home visit.

Physicians invited to participate in the qualitative sub-study will be provided a participant information sheet describing the sub-study and providing sufficient information for participant to make an informed decision about their participation in the study. The physician will be informed orally about the sub-study during the AGE training sessions conducted as part of the AGE trial, where he will also receive the information sheet. The consent form will be signed during the visit to the physician's practice.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's and family practitioner's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants and family practitioners shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

Confidentiality of the information disclosed by the subject to the study staff may only be revealed to the FP if there is an immediate danger to the patient or another individual (for example suicidal ideas revealed during phone interview).

Some identifying information (contact information, date of birth) needs to be collected, but this information will only be available to the person needing (for example, contact information available to the person in charge of phone interviews), and it will be removed from the data extracts used for data monitoring and analysis (see section 12.1 for details).

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

Patients will be informed that the content of their interview will be handled confidentially and not disclosed to their physician. Only general findings will be presented to the physicians, which will not be able to recognize their specific patients.

2.9 Early termination of the study

The sponsor-investigator may terminate the study prematurely if it is considered as unethical not to provide any specific intervention for the patients enrolled in the usual care group based on the results of the intermediate analysis. At that moment, if a difference on the main outcome (IADL) of 2 or more is observed, the AGE tool will be proposed to the FPs in the usual care group. This decision will be made in collaboration with the steering committee that will be set up for this study. Finally, the FP's included in the "usual care" arm will be offered to use the AGE tool after completing the study.

2.10 Protocol amendments

The principal investigator is authorized to amend the protocol. All important protocol modifications will be communicated to the relevant parties (investigators, CEC, participating FPs, trial registries).

Substantial amendments will only be implemented after approval by the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

According to demographic projections, a significant increase in the proportion of the elderly population is anticipated worldwide. By 2030, in industrialized countries, the proportion of persons over the age of 65 years will increase from 15% at present to 22%.⁽²⁾ The population over the age of 80 years is the one that will grow the fastest. This aging of the population will lead to an increase in the prevalence of chronic diseases and functional impairment,⁽³⁾ and will result in a growing use of the health care system for which western societies are largely unprepared.⁽⁴⁾ In that regards, family practitioners (FP) are in the front line of this huge epidemiological challenge.

Current perspectives in the management of elderly persons consider that it is more important to reduce morbidity and improve the quality of life rather than increasing life expectancy. Therefore, tailoring interventions that target the prevention of functional decline and quality of life improvement should be the main objectives. Many chronic diseases such as cardiovascular diseases, stroke, osteoarthritis, depression and geriatric syndromes (cognitive impairment, falls, urinary incontinence, visual impairment,...) ⁽⁵⁻⁷⁾ have a strong impact on functional performances in elderly persons. If chronic diseases are often well defined, it is less the case of *geriatric syndromes*, which are multifactorial clinical conditions that share common features such as older age.⁽⁸⁾ Tinetti and colleagues proposed the following definition: “ *Geriatric syndromes are multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render [an older] person vulnerable to situational challenges*». ⁽¹⁾

If timely recognized, adapted preventative measures can be initiated to reduce part of the burden.^(9, 10) Particularly, comprehensive geriatric assessment associated to intensive management interventions has proven efficient to prevent or delay functional decline and institutionalization, and improve quality of life (QoF) in elderly patients.⁽⁹⁾

However, while primary prevention and management of common chronic conditions such as hypertension, diabetes, or cardiac ischaemic diseases are more or less routinely and adequately performed in primary care, screening, prevention and management of geriatric syndromes are often incomplete.⁽¹¹⁻¹³⁾ In one study measuring adherence of family practitioners (FP's) to recommendations using quality indicators, it was observed that only half of their elderly patients had a cognitive testing performed routinely and one quarter were annually screened for the risk of falls.⁽¹⁴⁾

Several reasons can explain this low rate of early diagnosis of geriatric syndromes in primary care. First, primary care physicians remain mostly unfamiliar with interventions to improve quality of life and reduce functional decline. Moreover, FP often question the relevance of early diagnosis of age-related problems and are doubtful about the efficacy of interventions aiming at functional decline prevention, still seen as a fatality. Finally, the lack of time available for primary care physicians to perform a comprehensive geriatric assessment and a global screening for geriatric syndromes is a serious limitation.

In this project, we aim at assessing the efficacy and efficiency on functional decline and quality of life of a structured intervention administered by FP's in real-world setting: the Active Geriatric Evaluation (AGE tool).

Development of the Active Geriatric Evaluation (AGE tool) for the screening, diagnosis and management of geriatric syndromes in family practice

Numerous screening tests for specific geriatric syndromes have been developed, but few were specifically designed for a comprehensive geriatric assessment in primary care and even those suffer some limitations.^(15, 16) For example the Comprehensive Geriatric Assessment Tool developed by Mann *et al* in Austria took more than half an hour to administer in a pilot study, which is long when a standard consultation in primary care lasts 15 to 20 minutes on average.⁽¹⁷⁾

In order to develop an instrument better suited for the screening and management of geriatric syndromes by FP's, the Active Geriatric Evaluation program (AGE) was launched in 2011 by the investigators of the present study. It consists in 4 steps: 1) a literature review to identify suitable screening tools for geriatric syndromes and design a Brief Assessment Tool (BAT), development of a theoretical framework and construction of a comprehensive assessment and management tool for FP's (**AGE 0**) ⁽¹⁸⁾; 2) Validation of the geriatric consultation as a gold standard for assessing geriatric syndromes (study named **AGE 1**) ⁽¹⁹⁾; 3) a prospective study to assess the performances (sensitivity, specificity,...) of the BAT (study named **AGE 2**, completed in October 2014); and 4) assessment of the efficacy and efficiency of the AGE tool implemented in family practice (present proposal).

The BAT was developed for the screening of eight geriatric syndromes in primary care. But because screening for geriatric syndromes might provide by itself only a limited impact on functional decline, it was further integrated to a global tool that includes also diagnostic complementary investigations and management strategies (**AGE tool**). **Figure 1** displays a schematic view of the tool (including preliminary results on the performances of the screening instrument) are presented under point 3.2.

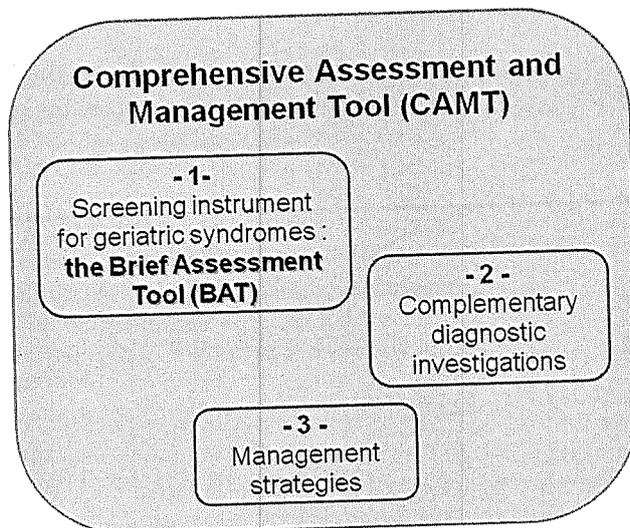


Figure 1: The three components of the AGE tool, a comprehensive assessment and management tool

While research on elderly patients' preferences often focussed on end-of life choices or place of care (home versus hospital or institution), perception of age-related health issues themselves and health choices available to patients have rarely been explored.

Using a structure-agency framework, our work aims to describe the interactional dynamics of patient-centered care as developed by Shim 2013(20). We use Bourdieu's concept of capitals (social, economic and cultural), as well as more recent developments by Abel (21) about health-relevant cultural capital, that help to understand inequalities in health status and health care. In combination with a biomedical model, we also include biological capital among a person's capitals. For example geriatric syndromes, such as visual impairment or gait imbalance, can be conceived as limitations in biological capital, which in turn affect the other individual capitals. The other way around, aspects of social, economic and cultural capitals may alter the impact of time itself on the individual and therefore the expression of ageing. As a result, individuals of the same biological age may show great variability in the development of a specific geriatric syndrome.

Patients consider their autonomy to be very important for their quality of life (23). We hypothesize that family physicians, within the physician-patient relationship, can play an important role to preserve their patient's autonomy. Indeed, many health-interventions delivered by physicians have a motivational component to induce change within the individual using his or her own resources (e.g. smoking, physical activity, nutrition, adherence to medication), and physicians are familiar with the concept of motivational interviewing (Miller 1983), that uses Prochaska – Di Clemente transtheoretical model of change (1983). Moreover, all motivational approaches have in common to work on patients ambivalence ("I know it is bad for my health to smoke but on the other hand I feel more confident when I smoke"). Working on ambivalence could be thus a strong determinant of behavioural changes but has been rarely explored with elderly patients.

While motivational interview focuses on patient's autonomy, drawing on self-determination theory (Markland 2005), limited attention is given to what constrains or enables individual health choices. Furthermore, physicians may mobilize resources in a patient's environment (relatives, home-based care,

social services), which could have an impact on the subject's passivity and actually limit the choices he/she is allowed to make regarding his/her own health. Using a structure-agency approach will help us to describe the various elements that may impact a patient's autonomy. The AGE3 trial provides an opportunity to explore these aspects within the context of a standardized intervention.

Rationale

The AGE tool is designed to be performed by independent FPs. It was developed step by step and the screening instrument (BAT) that composes the core of the tool proved to perform well in excluding geriatric syndromes (see below). However, the efficacy of the global tool (AGE) aiming to preventing functional decline has not yet been tested in family practice. **Our hypothesis is that the AGE administered by FPs in routine family practices could prevent or delay functional decline and improve the quality of life in elderly patients.**

If the AGE tool is adopted, it will have important implications: changing FPs' habits, time investment, training of FP's or increase interdisciplinary approach. Therefore, there is an absolute necessity to carefully assess its efficacy prior to its implementation. This means to investigate carefully how much the intervention impacts on patients' health in routine practice. This information is of prime importance in order to convince FP's to adopt a tool like AGE. The present study aims at addressing these questions through a cluster randomized trial in family practice.

The AGE3 trial provides a unique opportunity to address various aspects of patient and physician perceptions around the issue of functional decline and loss of autonomy. The qualitative study will also contribute to an in-depth understanding of the implementation of the AGE tool. This information will be crucial for proper further dissemination if the tool is shown to be effective, and for developing a better-adapted intervention otherwise.

State of research performed by the investigators

This study is part of the larger AGE program (<http://www.pmu-lausanne.ch/pmu-recherche-medecine-premier-recours.htm>) that was developed by the investigators (Nicolas Senn & Stefanie Monod). This is a collaborative and complementary project between a primary care institution (the Department of Ambulatory Care and Community Medicine of the University of Lausanne, DACCM), an institute of Family Medicine (IUMF), an academic geriatric institution and a public health organization (Public Health Department of the Canton de Vaud). The overall aim of the AGE program is to develop and assess a comprehensive evaluation & management intervention (AGE tool) for elderly patients in primary care that could potentially reduce functional decline. This program was conceived by the investigators from the beginning as a coherent development that should lead to the implementation and evaluation of new and more efficient interventions in real world primary care setting. The literature review was performed by both investigators, while AGE 1 and AGE 2 (validation of the geriatric BAT) was conducted by N. Senn at the DACCM and in selected private practices.

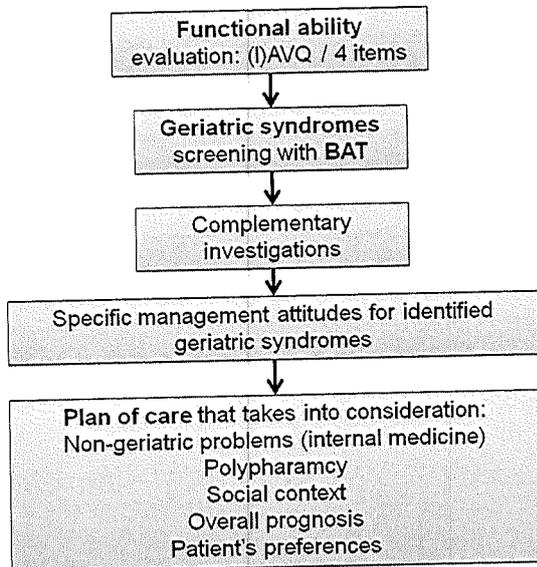
3.2 Investigational Product (treatment, device) and Indication

Study intervention: AGE arm

The Brief Assessment Tool (BAT) was developed for the screening of eight geriatric syndromes in primary care. But because screening for geriatric syndromes might provide by itself only a limited impact on functional decline, it was further integrated to a global tool that includes also diagnostic

complementary investigations and management strategies (AGE tool). The FP's randomly assigned to the AGE arm will be responsible to perform the AGE tool within the framework developed for the AGE program which is displayed in the **figure 3**.

Figure 3: theoretical framework of the Active Geriatric Evaluation (AGE)



Indeed it is essential that, in order to take the maximum benefits of the screening instrument, the BAT is not performed on its own, but should be part of a comprehensive management process that considers not only the specific management options for the different geriatric syndromes, but also put it in a larger perspective that includes individual patients' specificities. The **Table 1** details the BAT screening instrument and its interpretation.

Table 1: Brief Assessment Tool (BAT) for the early diagnosis of geriatric syndromes

| Assessing the level of functional dependency (prior to screening for geriatric syndromes) | | 4 items of (I)ADL: • Can you dress yourself? • Can you prepare your meals alone? • Can you make your own shopping? • Can you make your payments alone? |
|---|--|---|
| Syndrome | Test | Interpretation |
| Cognitive impairment | <p>Mini-Cog: 1. Ask the patient to remember 3 words (insure that he/she retained them properly) 2. Ask the patient to draw a clock with numbers and ask him/her to write 11h10 or 8h20. <i>Instructions may be repeated but not other direction must be given</i> 3. Ask the patient to repeat the 3 words</p> | <p>Clock: 2 points if the numbers are properly and time is correct, otherwise 0 points 3 words recall: 1 point/recalled word Interpretation: 0-2 points: Probable cognitive impairment 3-5 points: probable absence of cognitive impairment</p> |
| Mood disorder | <p>Two questions test: 1. During the past month have you often been bothered by feeling down, depressed, or hopeless? 2. During the past month have you often been bothered by little interest or pleasure in doing things?</p> | <p>If one answer is "yes", depression is suspected</p> |
| Gait and balance | <p><i>1 question:</i> Did you fall during the past year? <i>Observation:</i> • How does the patient gets up from his chair • The standing balance (grabs a support, faltering, enlargement of the polygon). • His/her walk (gait symmetry, continuity, deviation from a path). • If he/she must stop walking when talking • How does the patient sits (drops back)</p> | <p>Increased risk of falls if "yes" to question</p> |
| Visual impairment | Near vision Snellen pocket card | according to test's results |
| Hearing impairment | <p>Whisper test: Whisper a question in each ear of the patient, standing back to him/her</p> | <p>Suspicion of hearing impairment if the patient can't answer the question</p> |
| Urinary incontinence | <p>4 questions: • Do you have difficulty holding urine or urge feelings? • Do you sometimes find it difficult to reach the toilet in time? • Do you have involuntary urine loos when coughing or effort? • Do you sometimes wear pads?</p> | <p>If one answer is "yes": probable urinary incontinence</p> |
| Malnutrition | Loss of weight > 5% within 1 month, or > 10% within 6 months | Present if positive |

The BAT takes 20 minutes on average and can be administered during a normal consultation (data from AGE2). **Table 2** presents preliminary results on BAT's performances (AGE 2) performed by FP's on 85 patients (gold standard was a full geriatric consultation of two hours). As displayed, the performances of the BAT are good for most syndromes, especially with good negative predicative values (except for vision), which allow to reasonably excluding the diagnosis and prevent further investigations.

Table 2. Performance of the BAT for the main syndromes (preliminary results of the AGE program part 2, N=85 patients)

| Syndrome | Sensitivity | Specificity | PPV | NPV |
|----------------------|--------------------|--------------------|--------------------|--------------------|
| Cognitive impairment | 64.0 (42.5 - 82.0) | 67.2 (53.7 - 79.0) | 45.7 (28.8 - 63.4) | 81.3 (67.4 - 91.1) |
| Mood disorder | 65.6 (46.8 - 81.4) | 64.2 (49.8 - 76.9) | 52.5 (36.1 - 68.5) | 75.6 (60.5 - 87.1) |
| Urinary incontinence | 76.5 (58.8 - 89.3) | 85.4 (72.2 - 93.9) | 78.8 (61.1 - 91.0) | 83.7 (70.3 - 92.7) |
| Gait and balance | 67.9 (47.6 - 84.1) | 73.6 (59.7 - 84.7) | 57.6 (39.2 - 74.5) | 81.3 (67.4 - 91.1) |
| Visual impairment | 81.4 (69.1 - 90.3) | 45.8 (25.6 - 67.2) | 78.7 (66.3 - 88.1) | 50.0 (28.2 - 71.8) |
| Hearing impairment | 82.1 (66.5 - 92.5) | 86.0 (72.1 - 94.7) | 84.2 (68.7 - 94.0) | 84.1 (69.9 - 93.4) |
| Malnutrition | 25.0 (9.8 - 46.7) | 87.7 (76.3 - 94.9) | 46.2 (19.1 - 74.9) | 73.5 (61.4 - 83.5) |
| Osteoporosis | 77.8 (60.8 - 89.9) | 65.9 (49.4 - 79.9) | 66.7 (50.5 - 80.4) | 77.1 (59.9 - 89.6) |

PPV = positive predictive value; NPV = negative predictive value

Once the presence of one or more geriatric syndromes is suspected using the BAT, a management strategy is proposed as displayed in **table 3**. It is divided in two distinct steps: 1) perform additional tests to confirm or exclude the diagnosis and 2) to propose specific management attitudes. Proposed attitudes are based on literature review (24). The recommendations were reviewed by two geriatric experts who graded each recommendation as minor (supported by limited evidence; there could be good reasons not to follow this recommendation in a specific context) and major (supported by good evidence).

Table 3. Proposed strategies when screening using the BAT is positive

| Syndrome | Additional investigation if BAT screening positive (diagnostic confirmation) | Level of recommendation | Proposed management attitudes !! Need to be integrated to overall management plan!! | Level of recommendation |
|----------------------|--|-------------------------|--|-------------------------|
| Urinary incontinence | Complete focused medical history and examination: sensation of emptying, dysuria, pollakiuria, urogynecological problems, urinary retention, constipation, prolapsus, rectal examination | Major | Prescription of urinary protection | Major |
| | Voiding calendar (timing of mictions, nycturia) | Major | Consider specialized physiotherapy and rehabilitation, usually after specialist advice | Minor |
| | Urinary dipstick | Minor | 4. Voiding behavioral hygiene, liquid intake restriction in case of nycturia. | Major |
| | Radiological examination for post-mictional residue | Minor | Consider anticholinergic | Minor |
| | Review medication | Minor | Refer to gynaecologist / urologist for specialty care / ev surgery | Minor |
| Mood disorder | Complete medical history. | Major | Initiate depression follow-up | Major |
| | Ev perform eventually Geriatric Depression Scale (GDS, short form, or Hospital Anxiety and Depression Scale HAD). | Minor | Antidepressant drug | Minor |
| | Assess alcohol consumption | Major | Motivational intervention on alcohol consumption | Major |
| | | | Review psychotropic medication | Major |
| Cognitive impairment | Medical history, compare with functional status (ADL IADL) | Major | Home care support | Major |
| | MMSE or Moka test | Major | Meet family / network to plan the future (including management of finances) | Major |
| | Consider referral to memory clinic/geriatrician), +/- MRI. | Minor | Consider specific treatment according to diagnosis (hypothyroidism) | Major |

| | | | | | |
|--------------------|---|-------|--|--|-------|
| | Lab tests: simple blood count, HbA1c, creatinine clearance, ASAT, ALAT, Gamma-GT, Na, K, Ca, vitamin B12, folic acid, TSH | Major | Consider procognitive treatment (acetylcholinesterase inhibitors, memantine, eventually ginkgo biloba) | Minor | |
| | Review medication (diuretics, psychotropes, opiates, anticholinergic) | Major | Adapt medication | Major | |
| | Assess driving ability | Major | Write advance directives | Major | |
| Visual impairment | Complete visual acuity assessment (Snellen scale) | Major | Ergo-therapist to check indication for auxiliary means | Major | |
| | Refer to ophthalmologist for full assessment (cataract, glaucoma,..) | Major | | | |
| Hearing impairment | Perform otoscopy (cerumen impaction) | Major | | | |
| | Refer for audiometry | Major | Prescription of hearing aid | Major | |
| Gait and balance | Complete medical history and examination: cardiovascular, neurological, osteoarticular, Schellong test. Examine feet and shoes. | Major | Home hazard assessment (ergo-therapist) & home care support | Major | |
| | Refer to specialty care if needed (neurology,...) | Major | Recommend exercise, physiotherapy, adapted shoes | Major | |
| | Review medication (psychotropes, antihypertensive) | Major | Adapt medication | Major | |
| | Assess alcohol consumption | Major | Motivational intervention on alcohol consumption | Major | |
| | Check calcium and vitamin D | | Major | Prescribe calcium and vitamin D prescription | Major |
| | | | | Evaluate auxiliary means, telealarm system | Major |
| Osteoporosis | Perform osteodensitometry | Minor | Recommend exercise, physiotherapy. | Major | |
| | Check calcium and vitamin D | Major | Consider calcium & Vit D supplementation | Major | |
| | | | Consider treatment with biphosphonates | Major | |
| Malnutrition | Perform digestive (including constipation) and dental examination | Major | Treat other causes (depression,...) | Major | |
| | Review medication | Major | Review meal organization (cooking, shopping, meal delivery) | Major | |
| | Assess financial situation | Major | Hyperproteic supplements | Minor | |
| | Consider home evaluation (ergo-therapist or dome-based care) | Minor | Promote snacking | | |
| | Consider nutritionist evaluation | Minor | | | |

4.1 Preclinical Evidence

Not applicable

4.2 Clinical Evidence to Date

See points 3.1 and 3.2. In addition, the AGE 2 results showed that the intervention was well accepted by both FP's and patients.

4.3 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

Not applicable

4.4 Explanation for choice of comparator (or placebo)

Usual care arm

This arm called "usual care" will serve as control group. In this arm, FP's will be responsible to recruit 12 patients each. No specific intervention will be provided to these patients, except what FP's usually

do. In that regard, it is possible that some FP's might use structured interventions similar to AGE. This will be neither encouraged nor discouraged. This might be the case if two FP's are belonging to the two different arms and know each other's or participate to quality groups. This will be reported in the study records. The same inclusion/exclusion criteria as for the other arm will apply to these patients. Patients of this arm will also have the same follow-up as described below.

4.5 Risks / Benefits

The potential risk of the therapeutic intervention in comparison to standard of medical care is judged comparable. The proposed investigations and management strategies are all part of routine optimal care. No invasive procedure or medication prescription is directly related to the intervention. It may happen that some of the syndromes detected may be a source of anxiety. If this occurs, the patient's physician will do his best to mitigate the new fears and ensure optimal care. For post-trial care, patients continue to be managed by their physician.

Quality of life assessment contains some questions that can stir emotions. If the interviewer feels that the subject needs further support at the end of the phone interview, he may refer the patient to his/her FP, or contact the FP directly.

The study participants may benefit from improved screening and management of geriatric syndromes. Besides, if the intervention is shown to have a positive effect on functional decline, dissemination of the study results could lead to better care for all elderly patients in primary care.

Interviews conducted in the qualitative sub-study exploring aspects of autonomy as perceived by elderly patients may stir emotions in the interviewee. If the interviewer feels that the subject needs further psychological support and/or information, he/she may refer the patient to his/her FP, or contact the FP directly with consent from the patient. Risk of unauthorized data access and/or unwanted identification of project participants will be limited by the study procedures.

Vulnerable patients such as patient lacking discerning capacity will not be included in the qualitative study, although they may have been enrolled in the AGE3 trial, based on the fact that they may be less able to control which information they wish to share with the interviewer.

We do not expect immediate participant benefit for either physician or patient. Study results may lead to better care for all elderly patients in primary care, and better understanding of elderly patients' realities and perceptions of autonomy for all family physicians.

4.6 Justification of choice of study population

The AGE tool is designed to be used by FP in routine setting. Therefore, participant FP should dedicate a significant amount of their time to FP care (at least 20 hours per week on average). They should not hold a subspecialty title in geriatrics. FPs planning to retire or handover their practice within the next 2 years will be excluded. To limit cross-contamination between FPs, only one FP per group practice can participate in the study.

The study aims at identifying subjects at risk of functional decline, at a stage where the planned measures are expected to make a difference. Institutionalized patients already suffer from a significant degree of functional decline, which is why they are excluded from this study. The same logic applies if they had a geriatric or memory consultation in the past 6 months.

The BAT has been validated in patients 70 years and older specifically addressed to a geriatric consultations. The basic level of functioning is expected to be better among patients followed in routine primary care. In order to ensure that there will be a sufficient prevalence of geriatric syndromes in the study population, the inclusion criteria for age has been chosen at 75 years and older.

Other inclusion / exclusion criteria are based on practical reasons: patients are expected to understand French, in order to have the outcome measures taken during a phone interview. They must have visited

their FP at least twice during the past year, to ensure that they are under a regular follow-up, and they are expected not to leave the study area or to change FP during the next 2 years.

The FP committee of primary care physicians not participating in the study is set up in order to safeguard participant interest and ensure proper medical care.

5. STUDY OBJECTIVES

5.1 Overall Objective

The aim of the project is to determine whether an active geriatric evaluation performed in family medicine, combining a brief assessment tool (BAT) for the early diagnosis of geriatric syndromes with a structured diagnostic and management strategy (AGE tool), impacts on the functional decline and quality of life of elderly patients.

5.2 Primary Objective

The primary objectives of this project are to determine whether the AGE tool used in family medicine:

1. reduces the functional decline of elderly patients.

5.3 Secondary Objectives

The secondary objectives of this project are to determine if the AGE tool used in family medicine:

1. improves the quality of life of elderly patients.
2. reduces the incidence of hospital admissions
3. reduces the incidence of institutionalizations
4. reduces the incidence of emergency visits
5. impacts on the number of FP outpatient visits
6. improves the processes of care (diagnoses and management) of elderly patients
7. is acceptable and feasible for patients and family practitioners
8. is cost-effective

5.4 Safety Objectives

We do not expect any safety issue related to the intervention. Besides, serious adverse events such as hospitalizations and death are expected to occur regularly, independently of the intervention, in the study population aged 75 and above. Our hypothesis is rather that they will be lower in the intervention group, which is why these events are among our primary and secondary objectives.

However, detecting geriatric syndromes may be a source of stress for the individual patient and may have an impact on his quality of life that may annihilate the potential benefits expected from the intervention.

The **safety objective** of this project is to determine if the AGE tool administered in family medicine impacts the quality of life, hospitalization and death rate of elderly patients.

Hospitalization and death will be announced to the principal investigator by FPs within the week. They will also be recorded retrospectively during the annual review of the patient file combined with the phone interview to the patient or his relative.

6. STUDY OUTCOMES

Several measures of efficacy will be used within this study (see below), but the main outcome will be functional ability, which can be measured in several ways. The use of (instrumental) "activities of daily living" scales (IADL and ADL) is the simplest and most reliable way to assess functional decline. According to previous studies using this outcome in similar populations, one point (= one activity) lost avoided out of 8 activities (for IADL) over 1 year can be considered as a significant and meaningful improvement.(9, 25) Other outcomes such as the quality of life can complement the measure of the impact of this intervention on the functional decline.

Because it is a complex intervention that combines an initial screening tool with possible management strategies, it is also very important to understand the processes used by the FP's for using the instrument. In other words how the screening is performed and what is done with the screening results. For this specific purpose, we will also measure several process outcomes that are detailed below.

6.1 Primary Outcome

1. Activities of daily living (ADL) score and instrumental ADL (IADL) score

Specification of the main outcome measures

The overall aim of this study is to assess if the AGE tool can prevent the functional decline in elderly patients. Designed as a pragmatic cluster randomized trial in real-life setting, it needed to use appropriate and feasible outcome measures.

First, in order to assess the **functional status**, we propose to use the most validated instruments for assessing functional status, which are the activities of daily living (ADL) and instrumental ADL (IADL) developed by Katz et al and Lawton et al.(26, 27) These two instruments have been used in numerous studies, are sensitive to change and foremost can be reliably administered by phone(27, 28) .

6.2 Secondary Outcomes

1. Health related quality of life (WHOQOL-OLD) score
2. Incidence of hospital admissions
3. Incidence of institutionalization
4. Incidence of emergency visits
5. Incidence of outpatient visits
6. Process outcome measures: number of geriatric syndromes identified / confirmed, managements strategies adopted (medication adaptation, referral to specialty care, supportive measures,...)
7. Qualitative assessment of acceptability and feasibility of the intervention, and of perceptions of autonomy in elderly patients and family physicians

Second, in order to assess comprehensively the **quality of life** of elderly people, we propose to use the WHOQOL-OLD questionnaire composed of 24 items. This broadly validated instrument is composed of six facets: 1) Sensory abilities, 2) Autonomy, 3) Past, present and future activities, 4) Social participation, 5) Death and dying and 6) Intimacy. (29) Like with ADL and IADL, this questionnaire can be administered by phone.

Among the most important consequences of functional decline is the constant increase of the use the health care system. This is best measured by the **rates of hospitalization, emergency visits, ambulatory primary care visits and institutionalization**. However, at least for the two first, the measure of the rates based exclusively on retrospective self-reporting has poor reliability and important variability, especially in elderly who have frequent cognitive impairment. Therefore, we plan to use FP's

medical records and crosscheck the information with that obtained directly through the patient or their relatives.

Acceptability will be assessed by physicians' adherence with the BAT and AGE tool. For the BAT, we will assess the proportion of physicians using the tool once or twice during the study follow-up, and whether they skip some of the items.

AGE feasibility will be assessed by physicians' adherence to the recommendations, namely the proportion of investigations and interventions fulfilled among those recommended.

In addition, acceptability and feasibility will be assessed by semi-structured interviews conducted among a subset of physicians and patients allocated to the intervention arm (see 6.3 for more details).

6.3 Other Outcomes of Interest

Passive Surveillance

Additionally to this active follow-up, patients are encouraged to visit their FP's in case of medical problem (with or without hospitalization). FP's will be asked also to report on study forms any events that can be useful to the measure of outcomes.

Specification of the process outcomes

If it is clear that the main interest of the performing this study is to assess the overall benefits in terms of functional decline and quality of life, it is also important to understand how the intervention works. This is especially true for a complex intervention as this one, as many factors may influence the impact of the AGE. For example, it is not because the screening was made properly by the FP that the recommended management strategy is initiated. For this specific reason, we measure a relatively large number of process outcomes related to different steps of the entire process as displayed in **figure 2**.

Qualitative study

Quality of life and activities of daily living are well-validated patient-centered outcomes, and selection of the geriatric syndromes to be included in the AGE tool was based on known impact on either of these two outcomes. However, while these outcome measures were chosen for their psychometric properties, it is also important to explore how the subjects themselves relate to them in their own context. Independence in daily activities is not equivalent to autonomy in terms of freedom of choices. Therefore, we need to understand how the AGE intervention, by addressing issues of functional decline and geriatric syndrome, affects patient's capabilities.

In addition, we aim to assess how patients - physicians relationships affect the intervention itself, focussing on the health-relevant cultural capitals in interaction with the other social, economic and biological capitals. From the physician's perspective, various aspects of cultural health capital (suspicions towards evidence-based medicine, perceived threat to practitioner's autonomy, fear of role modification) may be relevant to understand how the AGE tool is used. Besides, in a comprehensive perspective, we will explore whether and how the introduction of AGE tool as component of patient management may impact the process of care.

Finally, we aim to assess how the AGE tool is being implemented and how it is perceived and accepted by patients and physicians. Beliefs, perceptions, values, social status and interactions as well as a broad range of relevant social determinants of health might emerge from respondents and represents crucial points to critically review the implementation processes.

Specification on the cost-effectiveness analysis

Such a study context offers ideal condition to collect all necessary information to assess the cost-effectiveness the AGE intervention. Indeed, it will be possible to have access at limited cost to all information related to the efficacy of the intervention and the cost that it induces (or not in the usual care group) and allow a valid assessment. Cost-effectiveness analysis will be based on incremental cost-effectiveness ratio par preserved ADL.(30)

Our hypotheses are the use of the AGE tool will increase ambulatory costs (number of consultations, referrals, and investigations), decrease medication costs, and decrease the number of hospitalization, institutionalization, and use of home-based care.

6.4 Safety Outcomes

FPs will be asked to report severe adverse events (SAE), defined as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

SAE will be announced by FPs to the sponsor-investigator within the week through the eCRF (or fax for paper-based data collection). SAE possibly linked to the intervention (Suspected Unexpected Serious Adverse Reaction) will be announced to the sponsor-investigator within 24 hours, who will report them to the competent ethical committee within 15 days.

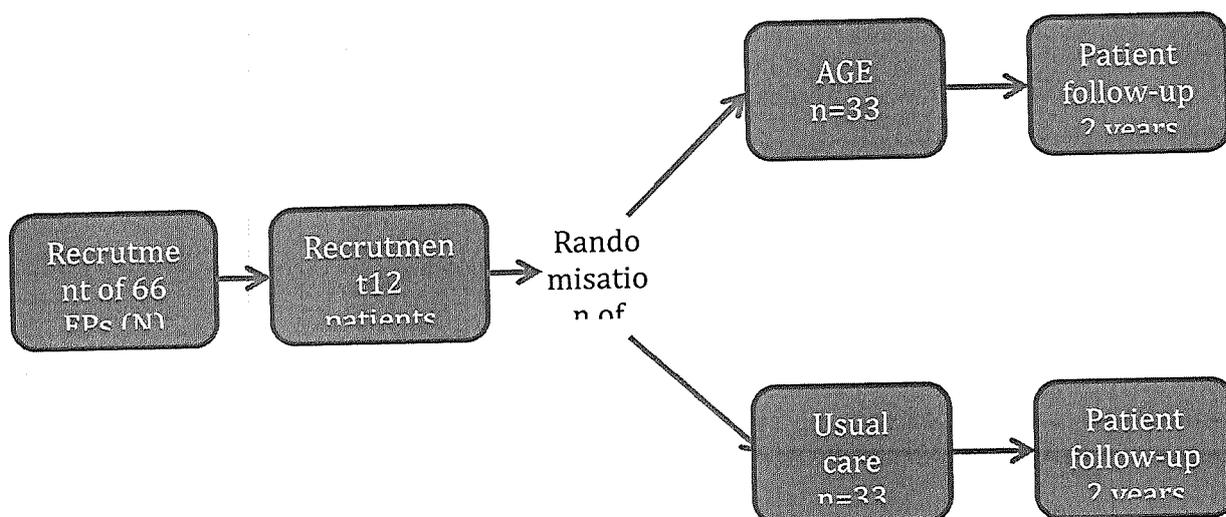
Quality of life of elderly people will be estimated by the WHOQOL-OLD questionnaire composed of 24 items. This broadly validated instrument is composed of six facets: 1) Sensory abilities, 2) Autonomy, 3) Past, present and future activities, 4) Social participation, 5) Death and dying and 6) Intimacy.

7. STUDY DESIGN

7.1 General study design and justification of design

This is a controlled, open label, cluster randomized superiority trial. The unit of randomization will be a family practitioner (FP). FP will be recruited in french-speaking Switzerland and randomly allocated (1:1 ratio) to one of the two parallel arms (AGE or usual care). A total of 33 FP's will be recruited by arm. Twelve patients aged 75 years and over will be recruited per FP. Therefore in total 66 FP's and 792 patients will be involved (see sample size estimate below). The follow-up of patients will be for 2 years per patient. **Figure 2** displays the design of the study.

Figure 2: Study design



Assessing the efficacy of complex interventions such as the AGE can be achieved only in real life setting, in this case FP practices. To avoid contamination and to take into account the clustering effect related to FP's, randomisation will be performed at FP level and patients will be followed-up at an individual level. There can only be one participating FP per practice. The FP allocated to the "usual care" arm will

be also offered to use AGE at the end of the study. A cluster randomized trial is indeed considered the most appropriate design to assess clinical efficacy, even though analyses are more complex.

Participants and FPs will be unblinded, as we could not imagine a sham intervention without effect on functional decline, but main evaluators will be blinded (primary outcome assessment: study coordinator and study statistician).

The qualitative study will focus on patients and family physicians within the intervention arm of the AGE3 trial. Data collection will take place after enrolment of the patients in the main trial and repeated after one year.

7.2 Methods of minimising bias

Randomisation

The randomisation unit will be the family practitioner, allocated on a 1:1 ratio to the intervention or usual care group. Randomisation will take place during training sessions organised during half a day for FPs participating in the study.

Participating FPs will be given a unique ID at the time of the previsit by the study staff. An independent statistician will generate a randomisation list based on uneven block size. He will then prepare sealed opaque envelopes containing the allocation arm, with a printed number (identification number, ID) on the outside. When attending the training session, the FP will open the envelope corresponding to his unique ID. The allocation lists (containing the identification number and allocation after each randomisation session) will be kept in sealed envelopes by the PI.

Blinding procedures

FPs and study participants will be unblinded to their allocation. The study staff (medical assistant) performing the main outcome measures (phone interviews) will be blinded to the allocation. The study coordinator in charge of study and data monitoring will also be blinded to the allocation. The study assistant that will conduct the annual visits to the family practice will not be blinded to the allocation. Data related to the BAT specifically will be monitored by the unblinded study assistant and an external statistician. The study statistician in charge of the interim and final analysis will be blinded to the allocation.

Allocation masking

Allocation will be recorded into the eCRF because this information is necessary to determine which forms the FP has to complete, but it will not be visible to users (study staff). The forms recording information on the AGE tool will not be accessible to users apart from FP and study assistant conducting annual visits. Data monitoring of AGE-specific sections will be performed on unlinked datatables, after recoding of the identifier by an external datamanager so that it cannot be linked to patient or FP. Queries will be transmitted back to the FP through this data manager.

Other methods of minimising bias

To avoid differential patient selection according to allocation, participating FPs will be asked to recruit 12 patients before being allocated to the intervention or control group.

Recruitment of patients will be planned during two months before the training and randomisation session. The study should be proposed to all eligible patients presenting during the planned recruitment period. In line with the pragmatic nature of the trial, exclusion criteria are limited in order to limit selection of patient participants. In particular, procedures were planned to include vulnerable patients (cognitive impairment, hearing or visual impairments; see section 7.1). Although not a strict random sample of the patient population, hardly feasible in the absence of a proper sampling frame (list of patients by age) in most FP practices, screening of all eligible patients in a predefined timeframe (with random selection if more than one attends on a specific day) should limit patient selection.

To limit selection of FPs, FPs lacking internet connection and/or not willing to use electronic data

collection can also participate. However, we are aware that FPs willing to participate in the study might not be representative of all FPs in the study area.

To avoid contamination between FPs allocated to the intervention and the usual care arm, limited information will be given on the BAT and the AGE tool to FPs before allocation is determined. Two FPs belonging to the two different arms may know each other or participate to the same quality groups. FPs allocated to the intervention arm will be advised to refrain from sharing with their colleagues about the content of the intervention until the study has ended. However, because some degree of contamination seems unavoidable, this was taken into account in the sample size calculation. Also the "process outcomes" will measure which components of the AGE tool are actually deployed in both arms.

By using purposive sampling for the qualitative study, we aim to ensure that patient characteristics are balanced between participants. As recruitment is planned over 4 to 5 months, we can adapt the participant selection based on the initial results.

Although the AGE trial has already started, and about one third of the physicians have already been randomised, we expect that there are sufficient remaining physicians to be included to ensure good diversity in physician and patient characteristics.

7.3 Unblinding Procedures (Code break)

Patient and physician are not blinded to the allocation.

8. STUDY POPULATION

8.1 Eligibility criteria

The study will be conducted in primary care practices located in the canton of Vaud. Because target of FP recruitment proved difficult to achieve in only one canton, the study was extended to FPs working in other french-speaking cantons of Switzerland (Valais, Neuchâtel and Fribourg) in January 2017.

Population

AGE is designed to be used by FP in routine setting to prevent as early as possible the functional decline of community elderly people. Therefore the intervention will be performed with any patients aged 75 years or older being followed-up in a FP practice.

Inclusion criteria

The participating FP should fulfill the following criteria:

- Working as family practitioner (≥ 20 hours per week)
- Family medicine being their main activity
- Working in the french-speaking part of Switzerland
- Willing to recruit twelve patients into the study

The patients should fulfill the following criteria:

- Aged 75 years or more
- Consider the enrolling physician as his/her reference FP
- Able to understand French
- Living at home (not in institutions)
- Visited his/her FP at least twice during the past year
- Giving signed informed consent (or, in the absence of discerning capacity, giving assent in the presence of a surrogate signing the consent form)

Exclusion criteria

For FP's

- Having participated in the AGE2 study
- If another FP from the same practice is already participating to the study
- Planning to handover the practice within the next 2 years
- Holding a subspecialty title in geriatrics (in french: "formation approfondie en g eratrie")

For patients

- Having had a geriatric or specialized memory consultation in the past 3 months
- Planning to leave the study area or to change of FP in the next 2 years

Comments:

- Patients with hearing deficits can be recruited, as this is part of the geriatric syndromes to be detected. If the hearing deficit is known by the FP at time of recruitment and likely to affect the feasibility of the phone interviews, this can be communicated to the study team who will organize a physical visit to the patient's home.
- Patients with visual impairment can be recruited. If he-she is unable to read the information sheet, it will be read directly to him by the FP or his designee.
- Patients with severe comorbidities can be recruited, even if their life expectancy is expected to be shorter than 2 years, in line with the pragmatic nature of the trial
- Some of the patients to be recruited can be considered vulnerable, mainly because of cognitive impairment. Excluding such patients would artificially shift the population towards better functioning level, and would hamper the pragmatic nature of the study. Although beneficiaries might not benefit from the study directly, the risks and study constraints are minimal and the study results should lead to essential improvements in the management of similar patients in the future.
- Patients without discerning capacity will not be recruited for the qualitative interviews
- It may happen in this ageing population that judgment capacity is temporarily or permanently altered over the course of the study. Therefore, all recruited patients will be asked to nominate a relative (husband, child,...) who can be contacted in case the patient is unable to answer questions during the follow-up.

8.2 Recruitment and screening

Recruitment of FP's

Study information (see appendix: 4a_InfoBref_m edecin_AGE_3) will be targeted to the FPs most likely to participate: it will be sent by email and/or post to the contact list of the University Institute of Family Medicine, cantonal FP professional association, and to physicians known to the investigators for their interest in research. Information about the study will be given during medical association meetings and continuous training sessions ("cercle de qualit e"). Posters will be depicted at the Policlinique M edicale Universitaire and CHUV, at locations attended by FPs for continuous training. Information about the study (See appendix: 4a_Info_m edecin_AGE_3) will also be made available on the website of the Policlinique M edicale Universitaire.

Once FPs have shown interest, they will be contacted by phone by the study coordinator who will briefly explain the next steps. If they are still willing to participate into the study, a first practice visit will be organized with the study coordinator and one of the medical assistant, to explain the initial procedures regarding patient recruitment and informed consent. Unique FP ID will be attributed at the time of this visit.

Physicians participating in the AGE3 trial that are randomised to the intervention will be informed about the qualitative study during the AGE training sessions that are conducted after patient recruitment and during which they are randomised. If willing to participate in the qualitative study, an appointment will be

made with a subset of physicians at their practice at the time of a planned consultation with one of their included patients, and two activities will take place: (1) (non-participant) observation during the consultation using the AGE tool; and (2) an interview with the physician alone. The physician consent form will be signed during this visit. The subset of physicians participating in the qualitative study should provide a balance of rural/urban/semi-urban and female/male characteristics.

Enrolment of patients

All participating FP's will be responsible to recruit 12 patients on average. Enrolment of patients will be planned during the first practice visit by the study staff. The date for the training and randomisation session will be set with the FP. All patients aged at least 75 with a planned consultation date during the two months before the randomisation (based on the FP's consultation agenda) will be recorded in a designated prescreening registry. This registry will be filled prospectively on a weekly basis during the recruitment period. Before starting enrolment, FP decide whether they prefer to propose the study consecutively to all eligible patients until 12 are enrolled, or whether they prefer to propose the study to only one patient per consultation day, selected randomly. Random selection is done by tossing a coin (if two patients) or drawing a number from a bag containing numbered chips corresponding to the numbers of eligible patients.

When the selected patients come for their consultation, the FP (or his designee within the practice) will check the inclusion criteria and provide written and oral study information to the patient. The patient can choose to consent during the consultation, or to send back the signed consent form within the week. Additionally, all recruited patients will nominate a relative (husband, child,...) who agrees to be contacted in case the patient is unable to answer questions during the follow-up. An appointment is planned within the next 3 months with the FP.

Recruitment can be stopped before the end of the recruitment period once 15 patients have been included.

For the in-depth interviews to be conducted at home for the qualitative study, patients will be selected among the patients recruited by each participating physician. Ideally, the patients who were observed (by the researcher) during their consultation will be recruited first for an in-depth interview at home, upon consent. The other participants are to be recruited (with the support from the physicians) following a purposive sampling accounting for sex, socio-demographic and familial context. Participants will be informed about the qualitative interview during the observation (by the researcher) and/or by phone/postal letter upon selection by the researcher (together with the physician). The consent form will be signed during the interview. Patients that refuse to take part in the qualitative evaluation can be replaced.

The same interview procedure will be repeated after one year.

8.3 Assignment to study groups

After enrolling his patients, the FP will participate at a half-day training-randomisation session. These sessions will be planned at least once a month at the Policlinique Médicale Universitaire in Lausanne during the recruitment period. Depending on specific regional physicians' interest, additional sessions can also be organized elsewhere. The session will be accredited as continuous training by the Swiss Society of Family Medicine.

Table 1. Content of FP training

| Time | Content | By |
|-------------|------------------|-------------------|
| 0h45 | GCP crash course | Study coordinator |

| | | |
|----------------------------|--------------------------------------|----------------------------------|
| 0h30 | Study procedures and data collection | Study coordinator |
| 0h15 | Randomisation | PI |
| 0h15 | Coffee break | |
| 1h30 Intervention arm only | AGE tool (intervention arm) | Geriatrician / study coordinator |

A randomisation list using uneven block sizes will be prepared. Allocation will be enclosed in sealed envelopes numbered sequentially. Randomisation will take place during the training. On the day of the training, each FP will take the envelope corresponding to his previously attributed unique ID. The FPs open their envelopes when every physician present at the session has taken one. The PI records the number on the envelope (physician's ID), the physician's name, and his/her allocation in the allocation list, which is then concealed in a sealed envelope at the end of the session and kept by the PI.

Individual randomisation

For various reasons, some FPs may not be able to attend a training session and will be randomised during the second visit of the study staff (visit 2)

8.4 Criteria for withdrawal / discontinuation of participants

Individual patients may discontinue the study at any point in time, by informing his physician or the study team. In this case, the study team can use the data recorded in the medical file up to the date that the patients informs of his wish to discontinue the study. The physician remains free to complete investigations and interventions recommended in AGE of his/her own will. Patients discontinuing the study will not be replaced.

An individual patient may also choose to refuse the phone interview, without discontinuing the study itself. In this case, the investigators can access the medical file until the end of the planned 2 years. If authorized by the patient, they can collect some information by the authorized contact person designated initially.

Patients that are institutionalized remain under study follow-up and their outcome will be assessed directly (if they are able to answer a phone interview) or indirectly (through a relative) if not.

There are no foreseeable reasons for investigators to withdraw a patient from the study. Patients that miss clinical appointments and outcomes assessment will be kept in the intention-to-treat study population and this belongs also to the feasibility assessment.

Physicians may choose to discontinue the study. If so, they are responsible of informing the study team. If discontinuation occurs before the training and randomisation session, he/she may be replaced by another willing physician. If discontinuation occurs after patient recruitment, training and randomisation, patient outcomes will still be collected by the study staff until the end of planned follow-up. Access to the medical files will be discussed on a case by case basis with the physician.

There is no foreseeable reason for the investigators to withdraw a physician from the study once he participated in patient recruitment, training and randomisation.

9. STUDY INTERVENTION

9.1 Identity of Investigational Products (treatment / medical device)

There are no investigational products used in this study. The trial intervention consists of the AGE tool.

Experimental Intervention (treatment / medical device):

AGE tool

The AGE tool consists of the brief assessment tool (BAT) and accompanying investigations and

management as described above (section 3.2). The FPs allocated to the AGE arm are invited to perform the BAT annually with the included patients. Once the presence of one or more geriatric syndromes is suspected using the BAT, a management strategy is proposed (**table 3**). It is divided in two distinct steps: 1) perform additional tests to confirm or exclude the diagnosis and 2) to propose specific management attitudes. All proposed attitudes are based on literature review (Senn & Monod, in press) and geriatrician expertise. The FP remains free to follow the proposed attitudes.

Control Intervention

This arm called “usual care” will serve as control group. In this arm, no specific intervention will be provided to the patients, except what FP’s usually do. In this regard, it is possible that some FP’s might use structured interventions similar to AGE. This will be neither encouraged nor discouraged. FPs in the “usual care” arm will be asked to perform one BAT after 2 years of follow-up, at the final patient visit.

Packaging, Labelling and Supply (re-supply)

Not applicable

Storage Conditions

Not applicable

9.2 Administration of experimental and control interventions

Experimental Intervention

Timing

The BAT should be administered yearly by the FP. The first BAT should occur within 3 month of patient recruitment and corresponds to day 0 of follow-up. The second and third BAT should occur after one and two years, respectively (including a 3 month window). Total follow-up time is 2 years after the initial BAT. Timing of the additional investigations and management will be freely decided by the participating FPs. Medical record review and outcome assessment by phone interview are planned annually by the study team, without direct relation to the physician’s consultation schedule.

Training of FP’s

All FPs will attend a training session on basics of good clinical practice (basic principles and legal framework in Switzerland; 45 minutes) and study procedures including data collection (45 minutes), in addition to a one-to-one training directly in their private practice on patient enrolment and informed consent.

All FP’s in the AGE-arm will follow a brief training on how to use the AGE tool. This will consist of 1hr30 of face-to face meeting with a geriatrician and/or the study coordinator who will explain how the AGE tool is constructed and how it should be used. This training will be provided as a group presentation with several FPs or directly in the practice (for those who could not attend for example). Training content was standardized between the different geriatricians participating in the training sessions.

Control Intervention

Timing

FPs in the control arm were asked to plan a follow-up appointment within the 3 months after recruitment. If a FP is randomised to the “usual care” group and there is no need for this consultation, he may cancel it after randomisation. Start of follow-up period will be at the first visit after randomisation. Medical record review and outcome assessment by phone interview are planned annually by the study team, without direct relation to the physician’s consultation schedule.

Training of FP’s

All FPs will attend a training session on basics of good clinical practice (basic principles and legal framework in Switzerland; 45 minutes) and study procedures including data collection (45 minutes), in addition to a one-to-one training directly in their private practice on patient enrolment and informed consent.

After randomisation, FPs’ allocated to the usual care arm will be dispensed of the rest of the training.

The AGE tool will be shared just before their first patient reaches the end of follow-up, without specific training. A specific training on the AGE tool will be proposed to FPs of the control arm after the end of the study.

9.3 Dose / Device modifications

The FPs may modify the allocated intervention or administer components of the intervention at time points not prespecified. This will be reported as part of the feasibility and acceptability assessment.

9.4 Compliance with study intervention

A tick-box chart (or an equivalent electronic tool) displaying the BAT, the specific complementary diagnostic investigations and management strategies proposed will be provided to the FP for each recruited patient in the intervention arm. This document will accompany the medical file of the patient and should serve both as a reminder for the FP and a record for what was done. This should enhance adherence to the intervention. The FP will also receive a compilation of reference articles on the topic in french. Otherwise, the training is kept to minimal on purpose, because we would like to test the efficiency of the AGE tool in real-life conditions. Thus, a too intensive training will not be realistic and sustainable if implemented.

Adhesion to recommendation will be defined according to the level of recommendations prespecified by the geriatrician experts: FPs will be expected to follow major recommendations that are supported by good evidence, while deviations to minor recommendations will not be considered non-adherent. Adhesion with the intervention by FPs will be assessed after one and two years. Non-adhering FPs will remain allocated to the intervention arm, because we want to assess the tool in real-life conditions.

Non-compliance with study schedule will not lead to withdrawing of study participant, but will be recorded as protocol deviations. If the patient is unable to complete himself the final assessments (end visit and/or phone interview) within 3 months of the planned date, for example because of illness, the evaluation will be based on information obtained from a relative.

9.5 Data Collection and Follow-up for withdrawn participants

Data of subjects who withdraw from the study will be collected until the date of withdrawal. Data can be extracted from the medical file about events up to the date of the withdrawal. FPs will inform the PI or the study coordinator within one day of a subject's wish to withdraw, and all data will be collected within one month.

If a FP wants to withdraw participation from the study, data will be collected from medical files about events up to the date of the withdrawal. The date of withdrawal corresponds to the date the FP informs the PI or the study coordinator of his wish to withdraw. All data will be collected within one month. Phone interviews of patients followed by a FP that withdrew from the study will still be conducted until the end of the study.

9.6 Trial specific preventive measures

Not applicable

9.7 Concomitant Interventions (treatments)

Concomitant interventions related to the study intervention are permitted in both arms. Their use will be recorded in the CRF. This includes:

- Comprehensive geriatric evaluation
- Geriatric readaptation
- Memory consultation
- interRAI assessment and other community-based interventions, if recorded in the medical file

9.8 Study Drug / Medical Device Accountability

Not applicable

9.9 Return or Destruction of Study Drug / Medical Device

Not applicable

10. STUDY ASSESSMENTS

10.1 Study flow chart(s) / table of study procedures and assessments

| Visit type | Study Periods | Filled by | Pre study | Screening | Intervention Period | | | | | | Follow-up | | | Unplanned |
|---|---------------|-----------|-----------------------|-----------|---------------------|-----------------|---------------------|--------------------|---------------------|-------------------|-------------------|-------------------|--------------------------------------|-----------|
| | | | | | Screening | Inclusion visit | Phone 0 | 1-year visit | Phone 1 | Phone 2 | 2-years visit | Phone 2 | Close visit | |
| Patient visits to FP | | | | Screening | Inclusion visit | | 1-year visit | | | 2-years visit | | | Extra-visits | |
| Phone interviews with patient | | | | | | Phone 0 | | Phone 1 | | | Phone 2 | | | |
| Study staff visits to FP (without patient) | | | FP visit 0 | | | FP visit 1 | | FP visit 2 | | | | Close visit | | |
| Time (hour, day, week) | | | minus 1 day to 6 mths | 0 | 0 to 14 days | 1 day to 3 mths | 1 year (+/- 3 mths) | 1 year (+/- 1 mth) | 1 year (+/- 3 mths) | 2 years (+3 mths) | 2 years (+3 mths) | 2 years (+3 mths) | Any visit between D0 and final visit | |
| Physicians form (CRF 1) | FP | x | | | | | | | | | | | | |
| Patient Information and Informed Consent | FP | | x | | | | | | | | | | | |
| Screening log | FP | | x | | | | | | | | | | | |
| Screening (CRF 2) | FP | | x | | | | | | | | | | | |
| Contact details (CRF 0) | FP | | x | | | | | | | | | | | |
| Inclusion (CRF 3) | FP | | | x | | | | | | | | | | |
| If intervention arm: BAT (CRF 4) | FP | | | x | | | x | | | x (both arms) | | | | |
| Primary Variables (phone interview): IADL, ADL, WHOQOL-OLD (CRF 5) | SA2 | | | | x | | | x | | | x | | | |
| Cormorbidities (CRF 6) | SA1 | | | | | x | | | | | | x | | |
| Secondary Variables (from FP records): hospital admissions, institutionalizations, emergency visits, number of falls, outpatient visits (CRF 6) | SA1 | | | | | | | | x | | | | | |
| Process evaluation (CRF 6) | SA1 | | | | | x | | | | x | | | x | |
| Plan of care (CRF 10) | FP | | | | | | | | | | | | x | |
| Visit date (CRF 7) | FP | | | | | | x | | | | | | x | |
| Current medication (CRF 12) | FP | | | x | | | x | | | | x | | x | |
| Adverse Events (CRF 11) | FP | | | x | | | x | | | | | | x | |
| Check contact details (CRF 6) | SA1 | | | | | x | | | | x | | | | |
| End of follow-up (CRF 8) | FP | | | | | | | | | x | | | | |

| Qualitative sub-study - PATIENT | Visits (if applicable) | |
|---------------------------------|------------------------|---------------|
| Visit | 1 | 2 |
| Time (hour, day, week) | 1d to 2 months | 1 years +/-3m |
| Participant Information | x | |
| Informed consent signature | x | |
| In-depth interview | x | x |

| Qualitative sub-study - PHYSICIAN | Screening | Visits (if applicable) | |
|-----------------------------------|-------------------|------------------------|---|
| Visit | 1 (AGE3 training) | 2 | 3 |

| Time (hour, day, week) | Min -1d | 1d to 2 months | 1 years +/-3m |
|-----------------------------|---------|----------------|---------------|
| Participant Information | x | | |
| Informed consent signature | | x | |
| In-depth interview | | x | x |
| Observation of consultation | | x | |

10.2 Assessments of outcomes

Assessment of primary outcome

The following information will be collected to assess **functional ability** and **quality of life** (See next section for details):

- ADL (6 items)
- IADL (8 items)
- Quality of life with WHOQOL-OLD (24 items)

This information will be collected through a phone interview. One, respectively two years after enrollment, the patient will receive a letter reminding him of the call from the study staff. In case the patient is unable to answer the questions, a close relative of the participants will be asked to answer the questions (for the activities of daily living but not quality of life).

Assessment of secondary outcomes

Patients will be also asked (or their relatives) if:

- They have been admitted to hospital in the previous year
- They are now living in a nursing home
- They visited the emergency department in the previous year

The information concerning hospitalization, emergency visit and institutionalization will be cross-checked using FP's medical records.

Assessment of other outcomes of interest

Finally at each time point, a number of additional information will be collected to assess the **process outcomes** that are related to the use of AGE. This information will be collected directly with the FP (self-administered questionnaire) or collected on the medical files of the patients as well as cross-checked on existing databases when they are accessible (such as the prescriptions records of pharmacists, number of outpatient visits or home care institutions). These data are not the main outcomes of the study, but will provide important information on how the AGE tool is used (adherence), which additional diagnostic interventions were performed and which management strategies are implemented following the identification of syndromes. In brief, this will allow a better understanding on how the AGE is used and performed in family practices. Details on all outcomes' measures of the AGE & related framework are discussed in the next section.

Assessment of costs

Intervention cost will be approximated by the additional time during FP consultation for the use of AGE tool, assessed in a previous study. With the consent of the FP, billing data for patients included in the study will be collected and anonymously recorded in SecuTrial® software. These data will lead to compare consultation time and management strategies by the FP between both arms. The other costs, associated to process outcomes beyond FP's intervention, can be valued according to available average data in this population or by expert opinion. Medication cost can be approximated from the therapeutic plan available in medical file of the patient and according to the current public prices of the official drug list. Costs will be estimated for medications showing at least 5% prescription difference between both arms. The comparison of the process outcomes in the two arms at baseline and during the follow-up will be used to assess the potential additional investigations induced by the intervention.

Qualitative assessment

Interviews will be guided by an interview guide that contains the topics to be discussed. Interviews will

be recorded entirely and transcribed literally by students. During the observed consultations, observations will be recorded by hand by the study staff on an ad-hoc questionnaire.

Assessment of safety outcomes

10.2.1.1 Adverse events

The FP will be asked to record any serious adverse events (hospitalization, death) within 7 days into the eCRF. Any new recording of SAE will be automatically notified to the PI. For each serious adverse event, the following information will be collected: time of onset, duration, resolution, action to be taken, assessment of intensity, and relationship with study intervention.

See section 10 for further details on serious adverse events definition and procedure.

10.2.1.2 Laboratory parameters

Prescription of laboratory tests will be at the discretion of the participating physicians. They will follow their usual routine, either for tests performed in house or sent to an external laboratory. No actual recording of test results is planned, apart from the interpretation of the physician ("normal/abnormal"). No additional quality control or standard procedures are planned for this aspect.

10.2.1.3 Vital signs

Weight and height will be assessed by each FPs with the material available in his practice. No calibration or standard procedures are planned, as this is expected to reflect routine practice. No vital signs will be recorded.

Assessments in participants who prematurely stop the study

For patients willing to withdraw from the study, see point 8.5.

Patients that are admitted, institutionalized, or suffer from a SAE remain under study follow-up until the end of the planned follow-up period. If the outcome assessments are not feasible because of their condition, functional capacity is assessed with the help of the initially appointed relative.

Patients will be considered lost-to-follow-up if both themselves and their appointed relative cannot be reached between the planned date of end-of-follow-up and the 3 following months, and they do not visit their FP during this period. As a last resort, final functional level can be assessed by the FP himself of the patient visits during this time.

A patient may change FP over the course of the study, without this affecting his participation in the study. Secondary variables obtained from the medical file will be considered missing after the last consultation to the participating FP, except if the patient switches to another FP also participating in the study. Phone interviews will continue.

10.3 Procedures at each visit

Screening visit (day -90 to -1)

(e.g. Screening visit, Day (e.g., -10 to 0): List all exams/tests and other actions to be performed

- Patient information
- Inclusion and exclusion criteria (CRF 2)
- Patient consent form signed by FP and given to the patient to sign and send back to study staff (alternatively, patient can sign the form on site)
- Consent to contact relative
- Patient contact details and contact details of relative (CRF 0)
-

Inclusion visit (day 0)

- Physical aids (hearing, visual, dental)

- CMS support
- Family contextBAT (if intervention)

Baseline phone visit = phone visit 0 (day 0 to 14)

- Patient and contact availability
- Schooling and profession
- Physical aids (hearing, visual, dental)
- Driving
- CMS support
- Family context
- IADL
- ADL
- WHOQOL-OLD
- Inform of next phone call in one year

Baseline study visit to FP = FP visit 1 (day 1 up to 3 months)

A study nurse visits the FP once all patients have been recruited and they have come for baseline visit. The study nurse extracts the following information from the medical file.

- Last weight recorded and date
- Last height recorded and date
- Comorbidities
- Current medication
- Within past year:
 - o Investigations
 - o Interventions
 - o Specialized consultations
 - o Prescriptions
 - o Number of hospital admissions, reason, duration
 - o Number of consultations
 - o Number of emergency consultations
 - o Number of readapation / rehabilitation / short stays in institutions
- Contacts with family member
- CMS information

The study nurse may ask the GP for clarifications if needed.

Qualitative patient interview (day 1 up to 3 months)

A researcher will conduct the patient interviews. He/she may be accompanied by the qualitative methodologist.

List of main topics for the interviews:

- Perception of AGE intervention – points raised during the brief assessment or the phone interview
- Exploration of patient's autonomy regarding health choices
- Autonomy enablers and constrainers, including financial aspects

Qualitative FP interview (day 1 up to 3 months)

A researcher will conduct the interview with the FP. He/she may be accompanied by the qualitative methodologist. The FP interview may be combined with the FP visit 1.

List of main topics for the FP interview:

- Perception of AGE intervention
 - Ease-of-use or problems faced
 - Items that would probably not have discussed with their patients without the intervention
 - Things they did not know about their patients that were uncovered by the AGE assessment

- Feelings about discussing activities of daily living
- Autonomy enablers and constrainers according to FP

Direct observation of AGE consultations:

- How the active geriatric evaluation is introduced
- Order of the items and variations compared with proposed order
- Explanations given during the course of the evaluation
- Parts that are omitted, voluntarily or unvoluntarily
- Patient reactions to the questions and examinations

Additional patient visits

At any visit occurring during the study follow-up, the FP records:

- Date of visit
- Occurrence of SAE yes/no
- Change in medication yes/no

If in the AGE arm, the FPs is also asked to complete the investigations and interventions recommended in the tool.

1-year visit (1 years + up to 3 months)

- BAT (intervention arm)
- Date of visit
- Occurrence of SAE yes/no
- Change in medication yes/no

Phone visit 1 (1 year +/- 3 month), phone visit 2 (2 years + up to 3 month)

- Physical aids (hearing, visual, dental)
- Driving
- Family context
- CMS support
- IADL
- ADL
- WHOQOL-OLD
- Inform of next phone call in one year (phone visit 1)

1-year visit (1 years + up to 3 months)

- BAT (intervention arm)
- Date of visit
- Occurrence of SAE yes/no
- Change in medication yes/no

Visit 2 to FP follow-up (1 year +/- 3 months)

Data extracted from medical file

- Weight
- Height
- Check current medication according to information in eCRF
- Death
- Within past year:
 - o Investigations
 - o Interventions
 - o Specialized consultations
 - o Prescriptions
 - o Number of hospital admissions, reason, duration
 - o Number of consultations
 - o Number of emergency consultations
 - o Number of readapation / rehabilitation / short stays in institutions

Qualitative patient interview (year 1 +/- 3 months)

- Perception of AGE intervention after one year
- Exploration of patient's autonomy regarding health choices
- Autonomy enablers and constrainers

Qualitative FP interview (year 1 up to 3 months)

- Perception of AGE intervention after 1 year
 - Ease-of-use or problems faced
 - Items that would probably not have discussed with their patients without the intervention
 - Things they did not know about their patients that were uncovered by the AGE assessment
- Feelings about discussing activities of daily living
- Autonomy enablers and constrainers according to FP

2-years visit (2 years + up to 3 months)

- Final outcome
- BAT (both arms)

CRF closure, visit 3 to FP (2 years + up to 3 months)

Data extracted from medical file

- Weight
- Height
- Check current medication according to information in eCRF
- Death
- Comorbidities
- Within past year:
 - o Investigations
 - o Interventions
 - o Specialized consultations
 - o Prescriptions
 - o Number of hospital admissions, reason, duration
 - o Number of consultations
 - o Number of emergency consultations
 - o Number of readapation / rehabilitation / short stays in institutions
- o CRF closure

11. SAFETY

Only severe adverse events (SAE) will be recorded as part of this trial, defined as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

Congenital anomalies/birth defects are not relevant for our study.

SAE will be announced by FPs to the sponsor-investigator within the week through the eCRF (or fax in case of paper-based data collection). SAE linked to the intervention (Suspected Unexpected Serious Adverse Reaction) will be announced to the sponsor-investigator within 24 hours, who will report them to the competent ethical committee within 15 days.

Relationship with the intervention will be graded as probable, possible or unlikely, based on the definitions of WHO-UMC.

SAEs should be followed by the FP until resolution or stabilisation. Occurrence of a SAE (apart from death) will not lead to study withdrawal. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

11.1 Drug studies

Not applicable

11.2 Medical Device Category C studies

Not applicable

11.3 Medical Device Category A studies

Not applicable

12. STATISTICAL METHODS

This is a superiority trial aiming at showing a difference in functional status assessed by the IADL between elderly patients followed by a family practitioner using the AGE assessment and management tool and elderly patients followed in usual care. The test of the null hypothesis will be two-sided and use a level of significance of 0.05.

Protocol amendment 04/09/2017: Preliminary analysis of baseline data of the first 247 patients showed that the majority of patients had a baseline IADL score of 8. Therefore, initial assumption of a mean score of 5 and use of a Poisson model were not appropriate anymore. We reformulated our hypothesis to show a difference in "incident disability", i.e. patients that lose at least one IADL{Rosso, 2013 #250}. Also, we refined the intraclass correlation estimation, because by contrast with our previous AGE1 and AGE2 study, IADL are assessed by a single rater in AGE3. However, the effect of the intervention itself might differ by FP, causing some degree of intracluster correlation after 2 years in the intervention arm.

Protocol amendment 19/12/2018: after reviewing our calculation and the recruitment data, we realized that for many patients normal functioning did not correspond to 8/8 IADL score, because of activities of daily living in which they never took part, such as preparing meals or doing laundry. There, we considered it was better to base the sample size calculation based on a hypothesis of loss of

independence in at least one activities, independently of IADL score at baseline, which we considered a better way to capture functional decline. Number of patients recruited by FPs was found to have sufficient power (>90%) based on the reviewed sample size calculation.

In addition, as no formal sample size calculation had been made for WHOQOL-OLD score, this outcome was considered a secondary outcome instead of a primary one.

12.1 Hypothesis

The null hypothesis is that there is no difference in the proportion of patients having lost at least one IADL after 2 years of follow-up between elderly patients followed by a family practitioner using the AGE assessment and management tool and elderly patients followed in usual care.

The alternative hypothesis is that there will be a difference of at least 15% in the proportion of patients having lost at least one IADL after 2 years of follow-up, between elderly patients followed by a family practitioner using the AGE assessment and management tool and elderly patients followed in usual care. We assume that 25% are expected to lose at least one IADL after 2 years without intervention.

12.2 Determination of Sample Size

In order to estimate the sample size needed for our purposes, we assumed that 10% of patients would lose independence in at least one activities (IADL) in the intervention group, compared with 25% in the control group. This is in line with what was observed in other similar interventional studies(9). A mixed effect logistic model was adopted in order to describe data, with a doctor-related random effect. With these parameters, cluster data were generated with n FP's per group and m patients per FP ($n = 5, 10, \dots, 55, 60$; $m = 5, 10, \dots, 25, 30$). For each combination of n and m , 10'000 datasets were generated and the power was empirically calculated as the percentage of datasets on which a significant ($\alpha=0.05$) difference between the two arms was obtained via the logistic mixed effect model, for different levels of ICC. Results are shown in Figure 1. In the absence of available data of intracluster coefficient (ICC) for such a type of interventions, and with an ICC of 0 at baseline, we expect only a cluster effect in half of the participants after 2 years (intervention arm), which we postulated to be 0.10 considering the standardized nature of the intervention.

This approach allows choosing the best cluster combination that includes also feasibility considerations. For example to achieve a power of 90%, 8 patients per FP are sufficient if we have 20 FP's per arm, based on an ICC is 0.10. Taking into account the patient loss to follow-up estimated at 15%, we increased the number of patients per FP to $8/(1-0.15)=10$, corresponding to a total of 40 FP's and 400 patients., corresponding to a final sample size of **40 FPs for a total of 400 patients**.

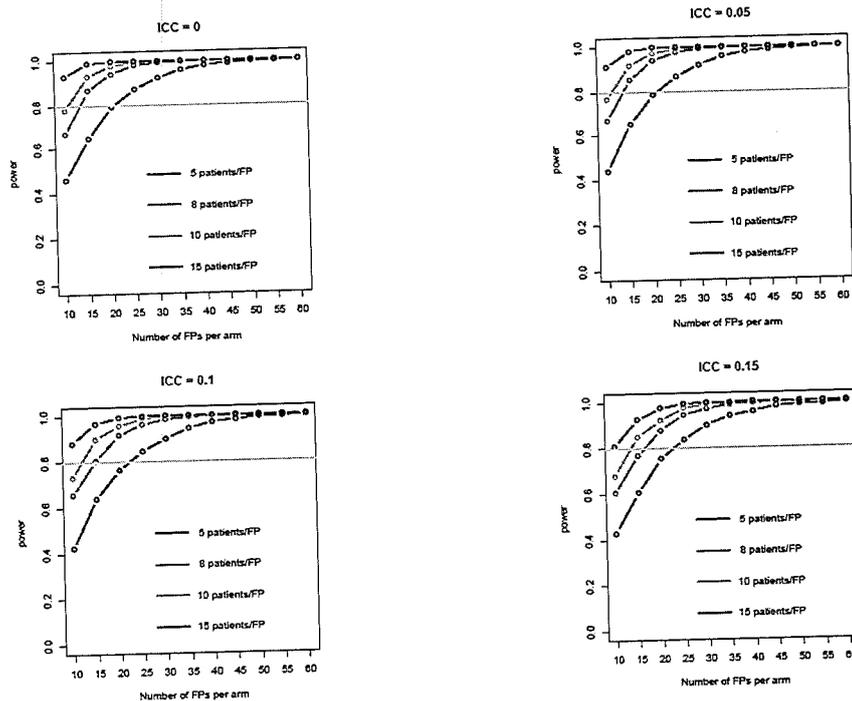


Figure 1. Power simulation according to number of participating physicians per arm and patients per physician, for different levels of intraclass correlation coefficient.

Qualitative sub-study

The study population for the qualitative evaluation is a subset of the AGE3 trial study population. We aim to recruit about 20 patients and 6 to 8 physicians, before reaching data saturation.

The sample size for patients has been estimated in order to cover the main patient constellations in terms of age, gender, support by home care, level of profession, and geography (rural/semi-urban/urban residence).

For physicians, we aim for a balanced age and sex distribution. In addition, we will consider group versus single practice and canton (Vaud versus other), as well as their practice location (rural/semi-urban/urban).

12.3 Statistical criteria of termination of trial

It might be perceived as unethical not to provide any specific intervention for the patients enrolled in the usual care group. Therefore we will perform an interim analysis at midterm (after first annual outcome assessment of at least 50% of the study participants). At that moment, if a difference on the main outcome (proportion of patients having lost at least one IADL) of 15% or more is observed, the AGE tool will be proposed to FPs of the usual care group. This decision will be made in collaboration with the steering committee set up for this study. Finally, the FP's included in the "usual care" arm will be offered to use AGE after completing the study.

12.4 Planned Analyses

Datasets to be analysed, analysis populations

The analysis will be performed in intention to treat (pragmatic trial). The analysis population will comprise all patients included by the randomised FPs. The primary analysis (ITT) will include all patients with

IADL measure at baseline and after 2 years. The per protocol population will exclude subjects in the intervention group who received less than two almost complete BAT (at least 7 out of 8 items screened) and had less than 50% of the recommended interventions done.

Primary Analysis

The primary analysis will compare the difference in proportion of patients having lost at least 1 IADL after 2 years between intervention and control group, using a generalised 2-level linear mixed model with a logit distribution. Clustering by FP will be taken into account by the mixed model („physician effect“). Baseline and 1-year IADL will be included in the model if available (repeated measures).

The primary analysis will be performed after closure of the database by the study statistician. Important determinants of FP variance will be explored and included in the model if relevant (practice size and type, age, gender of FP, specialty type, comprehensiveness of care)

Secondary Analyses

The following analyses are also planned to be performed by the study statistician after database closure:

- Difference in proportion of patients having lost at least 1 ADL after 2 years between intervention and control group, using a generalised linear mixed model
- Difference in WHOQOL-OLD after 2 years between intervention and control group, using a generalised linear mixed model
- Difference in WHOQOL-OLD difference (delta) between baseline measurement and after 2 years between intervention and control group, using a generalised linear mixed model
- Number of hospital admissions, institutionalizations, emergency visits and routine visits using a linear mixed model
- Survival analysis of time to institutionalization and time to death

Basic sociodemographic and clinical characteristics (comorbidities) of patients and FP characteristics will be described for both groups.

For process evaluation, the number of geriatric syndromes suspected, confirmed and acted upon will be compared after 2 years. Implementation of management strategies (investigations, medication adaptation, referral to specialty care, supportive measures) included in AGE will be compared between both groups, based on the information in the medical file. Based on a predefined scale, FP adherence to the AGE tool will be estimated for each patient.

For the primary outcome, subgroup analysis will be performed by patient characteristics (gender, age category, baseline disability, comorbidities) and FP characteristics (gender, age, urban/rural/semi-urban)

Sensitivity analyses

We will also whether the primary outcome is dependent of the % adherence to AGE. A complier average causal effect analysis will be used to estimate the effect of the intervention in the intervention group, had all FPs adhered to it [15, 16].

A more classical “per protocol” analysis will restrict the analysis to the population of patients in the intervention group which had both BAT performed (at least 7 out of 8 items screened) in the planned timeframe, and at least 50% adherence of FP to the AGE tool.

Interim analyses

Data monitoring will be done continuously (at least monthly) by the study coordinator, blinded to group allocation. BAT data will be monitored separately, after unlinking of the data with patient and FP identifier.

Analysis of baseline data will be conducted by the coPI once recruitment is complete. Mean and variance of IADL were assessed in slightly different patient populations than the AGE3 study population. If the

analysis of baseline data shows important discrepancies compared to the assumptions made for the initial sample size calculation (baseline IADL, intra-class correlation), a new sample size estimation may be performed. If recruitment of additional FPs is needed to need sufficient power, this will be discussed with the steering committee and the protocol will be amended accordingly.

One interim analysis will be performed when at least 50% of patients have had their one year assessment. The interim analysis will be performed by the study statistician. If a difference on the main outcome (IADL) of 2 or more is observed between the two groups, the code will be broken and if it is shown that the difference is in favor of the intervention arm, the AGE tool will be offered to the patients of the usual care group. This decision will be made in collaboration with the steering committee. No futility rule is planned, as we acknowledge that the effect of the intervention may be somewhat delayed and therefore not necessarily apparent after one year only.

Safety analysis

An annual safety analysis will be done by the study coordinator, comparing the incidence of hospital admissions and deaths between both groups. This will be included in the annual safety report submitted to the steering committee and the Ethics committee.

If there is a significant difference ($p < 0.05$) between the two groups in terms of hospital admissions and deaths, the steering committee can decide to halt the study.

Qualitative analysis

A thematic analysis will be performed throughout the data collection using MaxQDA. A first code system will be derived from the response to research questions. After review of the material by the first coder, the material will be coded again independently by a second researcher and results will be compared in order to ensure coding consistency (cross-checking procedure). Codes will be encompassed in themes with a broader level of meaning and organized in a way that answers the research questions.

Deviation(s) from the original statistical plan

Any deviation from the original statistical plan will be justified and reported in the final study report.

12.5 Handling of missing data and drop-outs

As recommended for pragmatic trials (and nowadays for clinical trials in general), we shall follow an Intention-to-treat approach. However, we shall face the problem of a high number of missing outcome data, considering that many patients approach end-of-life age.

Main outcome - ADL

Missing outcome data are expected to occur mainly because of death considering the age of participants, and because of consent withdrawal (patients refusing to answer phone questionnaire). Missing outcome data cannot be considered missing completely at random, as patients approaching end-of-life, usually with a worse functional status, are more likely to refuse to answer the questionnaire. However, ADL may be imputed (assuming a Missing at random MAR mechanism) using following covariates: age, sex, ADL and IADL at baseline (and at 1 year if available), schooling, previous profession, living alone, using home-based care, frequency of contact with children and "proches aidants", driving, intervention arm and GP random intercept.

We shall start by doing a complete case analyses, completed by the following simple imputations:

- Patients who died before end-of-follow-up are considered to have declined functionally
- Patients who are institutionalized before the end of the study and who withdrew (without measured outcome) are considered to have declined functionally

Sensitivity analyses

- Last observation carried forward: ADL result at 1 year carried forward to 2 years if missing and patient not dead
- Worst-case scenario: all missing cases considered as having lost at least one ADL
- Best-case scenario: all missing outcome considered as having maintained ADL
- Multiple imputation of ADL data, based on baseline and 1-year values, age, sex, schooling, previous profession, living alone, using home-based care, frequency of contact with children and “proches aidants”, driving, intervention arm and GP random intercept

As recommended by the guidelines for scoring WHOQOL, if one of the items of a specific domain is missing, a domain score should be calculated by substituting a person specific average across the completed items in the same scale. If two or more items are coded missing in these two domains, the domain score should not be calculated.

Completely missing WHOQOL:

- If the patient died, we shall consider his score to be 0 (standardised scale).
- Multiple imputation of WHOQOL-score, using baseline and 1-year values, age, sex, schooling, previous profession, living alone, using home-based care, frequency of contact with children and “proches aidants”, driving, intervention arm and GP random intercept

For time to event analysis (time to institutionalization, time to death), drop-outs will be censored. If date of end of follow-up is missing, we shall randomly select date between last consultation recorded and date of reported end of follow-up.

Other missing data are expected to be missing at random. We expect that missing data among the planned adjustment factors will be limited. Multiple imputation is therefore not planned for additional variables. Process data might be more difficult to obtain in the control group, resulting in a higher number of missing data. This will be checked in the interim analysis.

For extreme values, predefined checks included in the data collection software will prevent a number of aberrant values. For the main outcomes, model post-estimation will include assessment of outliers, which may be excluded on a case-by-case assessment.

13. QUALITY ASSURANCE AND CONTROL

The PI is responsible for proper training of all involved study personnel and for implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions

13.1 Data handling and record keeping / archiving

Case Report Forms

The study data will be recorded on electronic case report forms (e-CRF) using the secuTrial® software, which complies with regulatory requirements for clinical trials. An audit trail is included to keep track of any change in the data. Data will be handled and stored in Lausanne according to regulatory requirements.

Data will be collected by the study staff (baseline information, annual process evaluation, phone interviews) and the participating FPs (inclusion information, consultations, BAT visits and AGE plan of care, medication and SAE). FPs and study staff will specifically be authorized to perform entries only into their specific section. Data will be recorded directly into the eCRF.

Paper version of all CRF will also be available for FPs that do not want to use the electronic system. This will be decided at the initial visit before patient enrolment. In this case, data will be entered by the study staff during the annual visits to the FP. Information that the annual patient visits took place will be communicated by phone, fax, or secured email (for correct planning of the phone interviews).

Name, address and phone numbers of patients and their relatives need to be collected to enable phone

contacts. These data will only be accessible to the FP and the study staff in charge of phone interviews. The data manager will remove contact information (including names) from the data extracts shared with the study staff. Birth date will be collected but only recoded into number of years at enrolment will be used in the dataset for analysis.. The unique identifier will be entirely numeric for both FP and patient.

Audiorecordings will be transferred by the medical assistant from the recorder to the study folder on the CHUV computer network. This folder will only be accessible to the data manager and administrative personnel in charge of transcription. Each audio file will be identified by the patient anonymous study identifier. After validation of the transcription by the investigator, the audiorecording will be erased from the recorder.

Specification of source documents

The following sections of the eCRF will be considered themselves source data (inclusion information, BAT visits and AGE plan of care, phone interviews). The patient's medical file maintained by the FP is the other source of data and will be accessed by the study team to extract data on free visits, medication, SAE, annual process evaluation.

Apart from the eCRF, the following documents are considered to be source documents:

- Signed informed consent paper forms
- FP's randomisation number and allocation (paper received during randomisation)
- Data included in the medical records of the patients located at the participating FP's practice (visit dates, hospital admission information, previous medical history, examinations, investigations and treatments, relevant examinations, investigations, and prescriptions during the study follow-up, medication). These records may be electronic.

Informed consent forms and randomisation number will be stored safely by the FP, either in the medical file or a dedicated lockable space in the FP's office. In case a FP is using electronic medical records, the study assistant will only access the record at the FP's practice under supervision of a practice staff.

Record keeping / archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. Electronic data will be stored at the Lausanne University Hospital server. Paper study data (apart from source medical files which will remain in the FP's practice and stored according to specific regulation) will be stored at the Policlinique Médicale Universitaire in Lausanne for a period of ten years under the responsibility of the principal investigator.

13.2 Data management

Data Management System

The trial will use the secuTrial system, under the responsibility of the Centre de Recherche Clinique of the University of Lausanne. The system is hosted by the Information System Department of the Lausanne University hospital (CHUV).

The database will be developed by the Centre de Recherche Clinique in collaboration with the PI and the study coordinator. It will be tested by the study coordinator, the study assistants and, for the sections to be filled by the FPs, piloted by the FP piloting committee.

Data security, access and back-up

An individual family practitioner will only have access to the data of the patients he included himself and to the data he entered himself. The FP is asked to access the data at every contact with a patient included in the study. He will access the data through his own computer located in his practice. Access to secuTrial platform is password-protected. No data is stored in the individual computers. Back-ups will be performed automatically by the Centre de Recherche Clinique.

The study assistants will be authorized to enter and access data into the eCRF for the specific sections of which they are responsible. They can access these data for all the patients included in the study.

The study coordinator in charge of data monitoring will not be authorized to directly enter data. He will have access to all entered data, except contact details, BAT and AGE plan of care (which would reveal allocation).

The data manager has access to all study data (raw data extracts) and is in charge of preparing these extracts for data monitoring and analysis. In particular, he will remove contact details, recode age in years and remove date of birth, and unlink BAT and AGE related information from the unique identifier. He has no role in data analysis per se.

The study statistician cannot enter or modify data but has access to all the study data, except contact details. BAT and AGE plan of care (which would reveal allocation) will only be linked to specific patients after completion of the ITT analysis.

Analysis and archiving

Completion status of each section will be predefined during database development. The secuTrial system includes visual aid to inform of data entry completion.

Data will be extracted by the data manager on a monthly basis. The study coordinator will perform monthly data monitoring. These data extracts will be stored in a securised folder on the Polyclinique Médicale Universitaire's server until the final analysis is completed.

The database will be locked after all study data have been validated and monitoring review has been completed.

Electronic and central data validation

Predefined checks (validation rules) will be included to limit the occurrence of data entry mistakes. The checks to be performed by the system will be specified in a data management plan.

The study coordinator will analyse the data on a monthly basis, to identify missing items or discrepancies. If these are not, an electronic query is made in secuTrial to the person responsible of data entry for this section, who will see it and try to resolve it the next time the database is entered. Paper-based queries will be used for FP using paper data collection.

Source data validation (when applicable) will be performed by the study assistant during his/her annual visits to each practice ("review A"). These visits will also be an opportunity to solve all remaining queries.

A final data validation will take place when data entry is considered complete. After this final validation, the database is locked.

13.3 Monitoring

Our risk-adapted monitoring is based on the "Guidelines for Good Operational Practice Version 2.0–CTU Network – August 2014". As potential trial participant-related critical indicators, there is possibility of inclusion of vulnerable population (aged individuals with cognitive impairment), but other critical indicators are absent. Our primary endpoint is not "hard", in the sense that it may be influenced by the participant and investigator's subjectivity, but it is reliable and valid. The trial procedures can be considered simple. On this basis, the risk can be considered low to intermediate and the monitoring was adapted accordingly.

Monitoring will be performed internally by the the study coordinator and one of the study nurse (not involved in outcome assessment by phone interviews).

A site initiation visit will be done by the study coordinator or the PI and the study nurse to each participating practice:

- To inform the practice staff on the study (see Info_médecin_AGE_3_20151020)
- To train the practice staff on the recruitment procedure and data collection tool (screening log, informed consent, inclusion section of eCRF)
- To train the practice staff on the essential documents
- To sign the delegation log

After recruitment of all 12 patients of a specific site, a new visit is done by the study nurse, to assess:

- The physical existence of the trial participants (existing medical file)
- The correct filling of the screening log

- The presence of signed informed consent forms
- The eligibility criteria

Then, two additional visits are planned after one and two years, during which the study nurse will check

- For all participants, concordance between information given on the eCRF and source documents (medical file), in particular
 - o Visit dates
 - o Hospitalizations
 - o Medications
 - o Investigations performed
 - o Review SAE forms
- Solve pending queries

In addition, the study coordinator will join the study nurse on a random selection of 10% of the visits to proceed to source data verification for all included patients of a specific practice:

- The existence of the trial participants (existing medical file)
- The presence of signed informed consent forms
- Source data verification between medical files and data extracted by the study assistant in the eCRF

During these visits, trial conduct will also be audited.

Data collected in the eCRF will be submitted to ongoing monitoring and additional visits may be organised in case of issues detected during this monitoring (missing data, incomplete SAE reporting, no answer to queries, ...).

The PI will submit an annual report to the Ethics Committee, to inform on:

- Progress in study recruitment
- Annual safety report

13.4 Audits and Inspections

There are no independent audits planned.

All study documentation, source data and documents are accessible to inspections from the Ethics Committee.

13.5 Confidentiality, Data Protection

Data will be handled by the study staff in Lausanne at the DACCM following usual confidentiality regulation. Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. The study protocol will be made accessible to the public at the time of study publication. The dataset, apart from the information directly related to the family practitioner and removal of potentially identifying information (contact information, date of birth replaced by age in years at enrolment), will be made accessible in an open repository after the main study results are published.

Access to the raw data (audio recording and transcripts) will be restricted to the staff in charge of transcription and coding until publication of the results. After publication, the project leader and project methodologist can still access the data.

13.6 Coding

Patient and physician data will be identified through an anonymous identifier. Correspondence between patient name and code is defined in the paper prescreening list that is stored in the family physicians office. The coding key is only accessible to the study staff that need to contact the patient directly (for phone call or home visits).

Coding key of physicians is accessible to all study staff and will be handled confidentially.

Audio recordings may contain physician or patient identifying information and therefore will be accessed only by study staff in charge of transcription. Identifying information such as name, place of birth or place of living, date of birth, location of practice will be removed from the paper transcripts.

13.7 Storage of biological material and related health data

No biological samples are collected in this study.

14. PUBLICATION AND DISSEMINATION POLICY

A final clinical trial report will report the results of the clinical trial in a clear, complete and objective way.

All results of the present study will be published in peer-reviewed international journals. Because it is a pragmatic trial, special efforts will be made to communicate directly the main outcomes of the study to health authorities and primary care providers. Furthermore, investigators will make everything possible to help with implementation of the interventions if proved effective and efficient.

A short feedback including the main results of the trial in simple language will be provided to participating physicians, to distribute to the interested participants.

Authorship rules will follow the uniform requirements of the International Committee of Medical Journal Editors (ICMJE). In principle, the study coordinator will be the main and the PI final author of the main publication containing the study results. The other investigators will be named by alphabetical order. The participating physicians will be acknowledged as part of a group "the AGE3 study group". Other collaborators (geriatric experts) and members of the piloting committee will be acknowledged for their respective inputs. Use of professional writers is not planned.

The study protocol will be made accessible at the time of study publication. The dataset, apart from the information directly related to the family practitioner, will be made accessible in an open repository after the main study results are published.

15. FUNDING AND SUPPORT

15.1 Funding

The study is entirely financed by grant 32003B_159863/1 of the Swiss national Fund

15.2 Other Support

There is no other support than the one mentioned under 14.1.

16. INSURANCE

Category A trial, therefore exempted from specific insurance.

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18. APPENDICES

1. Other:

Case Report Form (e.g. CRF)
Patient Information and informed consent
Authorised surrogate consent form
Authorised relative information form
FP information
FP poster
Interview and observation guide

