



**The SYNERGY II Everolimus elutiNg stent In patients
Older than 75 years undergoing coronary
Revascularisation associated with a short dual
antiplatelet therapy (SENIOR) trial: rationale and
design of a large-scale randomised multicentre study**

Olivier Varenne, Thomas Cuisset, Aurès Chaïb, Marie-Claude Morice, Manel Sabaté, Tian-Hai Koh, Isabelle Durand-Zaleski, Olivier Hanon, Kris Bogaerts, Peter Sinnaeve

► **To cite this version:**

Olivier Varenne, Thomas Cuisset, Aurès Chaïb, Marie-Claude Morice, Manel Sabaté, et al.. The SYNERGY II Everolimus elutiNg stent In patients Older than 75 years undergoing coronary Revascularisation associated with a short dual antiplatelet therapy (SENIOR) trial: rationale and design of a large-scale randomised multicentre study. *EuroIntervention* , 2017, 12 (13), pp.1614-1622. 10.4244/EIJY15M12_02 . hal-01745875

HAL Id: hal-01745875

<https://hal.science/hal-01745875>

Submitted on 24 May 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

he SYNERGY II Everolimus eluting stent In patients Older than 75 years undergoing coronary Revascularisation associated with a short dual antiplatelet therapy (SENIOR) trial: rationale and design of a large-scale randomised multicentre study

Olivier Varenne^{1,2*}, MD, PhD; Thomas Cuisset³, MD, PhD; Aurès Chaïb^{1,2}, MD; Marie-Claude Morice⁴, MD; Manel Sabaté⁵, MD; Tian-Hai Koh⁶, MD; Isabelle Durand-Zaleski⁷, MD, PhD; Olivier Hanon^{2,8}, MD, PhD; Kris Bogaerts^{9,10}, PhD; Peter Sinnaeve¹¹, MD, PhD

1. AP-HP, Hôpital Cochin, Service de Cardiologie, Paris, France; 2. Université Paris Descartes, Université Sorbonne Paris Cité, Paris, France; 3. AP-HM, Hôpital de la Timone, Service de Cardiologie, Marseille, France; 4. Générale de Santé, Institut Cardiovasculaire Paris Sud, Massy, France; 5. Cardiology Department, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain; 6. Department of Cardiology, National Heart Center, Singapore, Singapore; 7. AP-HP, Hôpital Henri Mondor, Santé Publique, Créteil, France; 8. AP-HP, Hôpital Broca, Service de Gériatrie, Paris, France; 9. Interuniversity Institute for Biostatistics and statistical Bioinformatics, KU Leuven, Leuven, Belgium; 10. Université de Hasselt, Hasselt, Belgium; 11. Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium

Abstract

Aims: In the elderly population, bare metal stents (BMS) are often preferred over drug-eluting stents (DES) because of the longer duration of dual antiplatelet therapy (DAPT) associated with the latter. The SENIOR trial is designed to determine whether one of the latest generation of DES can reduce major cardiovascular events compared to BMS, despite a similar short DAPT duration.

Methods and results: The SENIOR trial is a multicentre, single-blind, prospective, randomised trial comparing the latest generation DES (SYNERGY™ II; Boston Scientific, Marlborough, MA, USA) to BMS (Rebel™; Boston Scientific) in 1,200 patients ≥75 years old. DAPT will be given for one or six months according to clinical presentation, irrespective of stent type. The primary outcome is the composite of all-cause mortality, non-fatal myocardial infarction, stroke or ischaemia-driven target lesion revascularisation at one year. Secondary endpoints include the rate of major bleedings and the rate of stent thrombosis at one year.

Conclusions: This trial is designed to evaluate a new revascularisation strategy combining DES and short duration DAPT in elderly patients. It has the potential to decrease the need for target lesion revascularisation without a significant DAPT-related increase in bleeding compared to BMS.

Introduction

Despite age being a strong predictor of major adverse cardiac and cerebrovascular events (MACCE) after percutaneous coronary intervention (PCI)^{1,2}, elderly patients have been largely excluded, under-represented or highly selected in randomised trials evaluating drug-eluting stents (DES). However, DES implantation in elderly patients could lead to a significant reduction in the rate of myocardial infarction (MI) and target vessel revascularisation compared to bare metal stent (BMS) implantation³.

New-generation DES have been demonstrated to be safer compared to first-generation DES^{4,5}. In the Patient Related Outcomes with Endeavor vs. Cypher stenting Trial (PROTECT), Camenzind et al reported a strong interaction between DES types and dual antiplatelet therapy (DAPT) use, suggesting different vascular healing responses according to the type of DES⁶. More recently, in order to limit the potential long-term harm and toxicity associated with durable polymers⁷, DES with bioresorbable polymers have been developed^{8,9}. Whether or not DES with a biodegradable polymer are safer than DES with a durable polymer is still a matter of debate^{10,11}. However, Stefanini et al reported a lower risk of stent thrombosis and MI at four years with a biodegradable polymer DES in a pooled analysis including 4,062 patients¹².

There is emerging evidence that reducing the duration of DAPT together with new-generation DES could represent a safe strategy. This might be particularly relevant for patients ≥ 75 years old, to reverse the unfavourable risk/benefit ratio associated with earlier-generation DES and long DAPT. Despite European Society of Cardiology and American Heart Association/American College of Cardiology guidelines recommending 12 months of DAPT^{13,14,15}, the optimal duration of DAPT after DES implantation remains largely unknown, particularly in patients ≥ 75 years old. Bleeding risk is higher in elderly compared to younger patients¹⁶, and is further increased with longer DAPT^{17,18,19} without clear reduction in stent thrombosis in several studies^{17,19,20}. The potential impact of bleeding complications may explain why cardiologists are often reluctant to expose patients ≥ 75 years old to prolonged DAPT and why BMS are often preferred for PCI in these patients. Indeed, in a very recent registry from two reputable European centres, only about one out of four consecutive elderly patients undergoing PCI received at least one DES²¹.

Several trials have reported similar efficacy and safety with short vs. long DAPT duration after PCI (Table 1). Three months of DAPT was non-inferior to 12 months of DAPT with respect to the occurrence of stent thrombosis or MACCE in the RESET (REal Safety and Efficacy of three-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation) trial²². MACCE at 12 months were non-inferior after six months vs. 12 months of DAPT (4.8% vs. 4.3%, $p < 0.001$) in the EXCELLENT (Efficacy of XIENCE/Promus versus Cypher to reduce Late Loss after stENTing) trial²³. DAPT beyond 12 months was not more effective than aspirin alone in reducing the rate of MI and cardiac death in 2,701 patients treated with DES (HR 1.65, 95% CI: 0.80-3.36, $p = 0.17$)²⁴. In the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study (PRODIGY), patients receiving clopidogrel for six vs. 24 months had a similar rate of ischaemic events and stent thrombosis at two years¹⁷. Furthermore, in 3,119 patients treated with zotarolimus DES, the rates of death, MI, stroke and major bleeding at one year were similar with three months or 12 months of clopidogrel²⁵. More recently, the SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Months Dual Antiplatelet Therapy) trial²⁶ and the ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of six months Dual Antiplatelet Therapy After drug-Eluting Stenting) trial²⁷ reported similar rates of MACCE in patients with 12 months of DAPT compared to six months only (3.7% vs. 4.5%; difference 0.8%; 95% CI: -2.4-1.7; $p = 0.469$, and 1.5% vs. 1.6%; HR 0.91, 95% CI: 0.55-1.50; p for superiority = 0.70, respectively). Similarly, in the ITALIC plus (Is There A Life for DES after discontinuation of Clopidogrel) trial, the 2,031 patients treated with new-generation DES (XIENCE V®; Abbott Vascular, Santa Clara, CA, USA) had a similar rate of MACCE (death MI, stroke, TVR, major bleeding) whether they were treated with clopidogrel for six or 24 months (1.6% vs. 1.5%; HR 1.07, 95% CI: 0.52-2.22; $p = 0.85$)²⁸.

Table 1. Major adverse cardiovascular events and stent thrombosis in clinical trials evaluating short duration of dual antiplatelet therapy (DAPT).

Trial	Short DAPT (months)	Long DAPT (months)	MACCE short vs. long	Hazard ratio/risk difference (%) (95% CI)	p-value	Stent thrombosis	Hazard ratio/ risk difference (%) (95% CI)	p-value
PRODIGY ¹⁷	6	24	10.0% vs. 10.1%*	0.98 (0.74 to 1.29)	0.91	1.3% vs. 1.5% [‡]	1.15 (0.55 to 2.41)	0.70
RESET ²²	3	12	4.7% vs. 4.7% [†]	0.0 (-2.5 to 2.5)	0.84	0.2% vs. 0.3% [§]	-0.1% (-0.5 to 0.3)	0.65
EXCELLENT ²³	6	12	8.0% vs. 8.5% [‡]	0.94 (0.65 to 1.35)	0.72	0.6% vs. 0.1%	6.02 (0.72 to 49.96)	0.10
OPTIMIZE ²⁵	3	12	8.3% vs. 7.4% [¶]	1.12 (0.87 to 1.45)	0.36	0.8% vs. 0.8% [§]	1.08 (0.49 to 2.36)	0.86
SECURITY ²⁶	6	12	4.5% vs. 3.7%**	1.22 (-2.4 to 1.7)	0.47	0.3% vs. 0.4% [§]	0.75 (-0.7 to 0.4)	0.70
ISAR-SAFE ²⁷	6	12	1.5% vs 1.6% ^{ΔΔ}	0.91 (0.55 to 1.50)	<0.001 ^{†‡}	0.3% vs. 0.2%	1.66 (0.4 to 6.96)	0.49
ITALIC ²⁸	6	24	1.6% vs 1.5% ^{ΔΔ}	1.07 (0.52 to 2.22)	0.85	0.3% vs. 0%	N/A	0.49

* Death from any cause, myocardial infarction (MI) or cerebrovascular accident at two years. ‡ Definite stent thrombosis (ST) at two years. † Death from cardiovascular cause, MI, stent thrombosis, ischaemia-driven target vessel revascularisation, or bleeding at one year post procedure. ‡ Definite or probable stent thrombosis at one year. ‡ Death, myocardial infarction, stroke, or any revascularisation. ‡ Death from all causes, MI, urgent coronary artery bypass graft surgery, or target lesion revascularisation at one year. ** Cardiac death, MI, stroke, definite or probable stent thrombosis or BARC type 3 or 5 bleeding. ΔΔ Death, MI, stroke, stent thrombosis, major bleeding. †‡ p for non-inferiority.

Registry data have shown increased one-year stent thrombosis rates after DAPT discontinuation within 30 days post PCI but not after one month (3.6% vs. 0.1%, log-rank $p < 0.001$). DAPT interruption > 1 -12 months was provocatively associated with a lower rate of stent thrombosis compared to patients with no DAPT interruption within a year (0.1% vs. 0.8%, log-rank $p < 0.001$)²⁹. In a real-world registry, Mehran et al reported that thrombotic events after PCI largely occur while patients are still on DAPT, with an early risk of events due to disruption, irrespective of stent type (DES or BMS)²⁰.

Finally, extending the duration of DAPT was not associated with a reduction in all-cause death (OR [95% CI] 1.15 [0.85-1.54], $p = 0.36$), MI (OR 0.95 [0.66-1.36], $p = 0.77$), stent thrombosis (OR 0.88 [0.43-1.81], $p = 0.73$), or cerebrovascular events (OR 1.51 [0.92-2.47], $p = 0.10$) in a meta-analysis including 8,231 patients¹⁸.

Recently, in the large Dual Antiplatelet Therapy (DAPT) study, patients treated with 30 months of DAPT exhibited a substantial reduction of stent thrombosis (0.4% vs. 1.4%; HR 0.29, 95% CI: 0.17-0.48; $p < 0.001$) and MACCE (4.3% vs. 5.9%; HR 0.71, 95% CI: 0.59-0.85; $p < 0.001$), associated with a higher all-cause mortality (2.0% vs. 1.5%; HR 1.36, 95% CI: 1.00 -1.85; $p = 0.05$) and increased rates of severe or moderate bleedings (2.5% vs. 1.6%; HR 1.61, 95% CI: 1.21 to 2.16; $p = 0.001$) compared to patients treated with only 12 months of thienopyridine³⁰.

However, only selected patients were included in the trial, since investigators randomised patients who had already safely completed twelve months of DAPT after DES implantation. This represents a significant selection bias and implies that the DAPT results are only applicable to a selected population with global low ischaemic as well as bleeding risks. In addition, a large number of the patients were treated with first-generation DES associated with known delayed vascular healing, pro-inflammatory polymer or limited antirestenotic effect. In subgroup analysis, the effect of prolonged DAPT on MACCE was not similar among the different DES subtypes (p for heterogeneity = 0.048)³⁰.

More recently, the ZEUS trial (Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates) used a different approach to tackle the issue of efficacy versus safety in patients at risk for bleeding and/or thrombosis. This trial tested a zotarolimus-eluting stent (ZES) with an ultra-fast drug-eluting profile, followed by a variable DAPT duration based on patient comorbidities. The study demonstrated that ZES combined with an abbreviated and tailored DAPT regimen resulted in a lower risk of one-year MACCE in these uncertain candidates for DES implantation³¹. Nevertheless, these ZES are associated with a less powerful inhibition of neointima hyperplasia compared with the latest generation, slower eluting DES³¹.

Altogether, the improved safety of new-generation DES and the lack of strong evidence supporting prolonged DAPT in the elderly population clearly support the need for a dedicated trial assessing the balance of efficacy and safety in patients ≥ 75 years old treated with PCI.

Methods

STUDY DESIGN

A total of 1,200 subjects will be enrolled in the SENIOR (SYNERGY II Everolimus eluting stent in patients Older than 75 years undergoing coronary Revascularisation associated with a short dual antiplatelet therapy) trial, a prospective, single-blind, randomised multicentre trial registered at www.clinicaltrials.gov Identifier: NCT02099617. The first patient was included on 25 May 2014.

OBJECTIVES

The primary objective of this superiority study is to assess the effectiveness and safety of new-generation DES (SYNERGY™ II; Boston Scientific), compared with BMS (Omega™ or Rebel; Boston Scientific), in patients ≥ 75 years old in preventing the composite endpoint of all-cause mortality, MI, stroke and ischaemia-driven TLR at one year.

The secondary objectives are to assess the safety of PCI with DES versus BMS with identical duration of DAPT with respect to the rate of definite and probable stent thrombosis (Academic Research Consortium definition) at one year³².

Additional secondary outcome measures include all-cause and cardiovascular mortality, MI (periprocedural, spontaneous, Q-wave and non-Q-wave)³³, stroke (all, ischaemic, and haemorrhagic) and all revascularisations (ischaemia-driven and non-ischaemia-driven) at 12 and 24 months. In addition, bleeding complications type 2, 3, and 5 according to the Bleeding Academic Research Consortium³⁴ will be evaluated at one year.

Quality of life will be measured at 30 days post-procedure and at six, 12 and 24 months, and economic evaluation including direct comparison of medical care costs will be calculated at 12 and 24 months. Final cost-effectiveness will be assessed by the incremental cost per quality-adjusted year of life at two years.

DEFINITIONS

All-cause mortality is defined as any cause of death from inclusion until latest follow-up. Acute MI is defined by the evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia according to the third universal definition of myocardial infarction³³. Stroke is defined as appearance of a new focal neurologic deficit, with symptoms lasting less or more than 24 hours. Confirmation of the diagnosis with computerised tomography or magnetic resonance imaging will be used to differentiate between haemorrhagic and ischaemic strokes. All reported focal neurologic deficits reported during the study will be adjudicated. Ischaemia-driven target lesion revascularisation (TLR) is defined as any TLR for myocardial ischaemia (clinical evaluation or non-invasive assessment) under optimal medical treatment. All clinical events reported as being part of the primary endpoint, bleeding complication, or stent thrombosis will be reviewed by a dedicated, independent, clinical endpoint committee, unaware of the patient's treatment group.

PATIENT POPULATION

The inclusion and exclusion criteria are summarised in Table 2. Recruitment flow is summarised in Figure 1. The steps in determining trial eligibility and obtaining informed consent are designed to mirror daily clinical practice closely in order to optimise recruitment.

Table 2. Inclusion and exclusion criteria.

Inclusion criteria (all)	Exclusion criteria (none)
1. Man or woman aged ≥ 75 years. 2. One or more significant coronary artery stenosis on conventional coronary angiography: a. $\geq 50\%$ in the left main trunk (visual assessment) OR b. $\geq 70\%$ for non-left main trunk coronary artery (visual assessment) OR c. $\geq 50\%$ (visual assessment) with fractional flow reserve (FFR) < 0.80. 3. Indication for myocardial revascularisation by percutaneous coronary intervention: a. significant silent ischaemia defined as stress-induced myocardial ischaemia $\geq 10\%$ of myocardium with an FFR < 0.80 OR b. stable angina despite optimal medical therapy OR c. acute coronary syndrome including: unstable angina, non-ST- and ST-elevation myocardial infarction. 4. Accepting to comply with all follow-up required study visits. 5. Understood and signed the informed consent form.	1. Indication for myocardial revascularisation by coronary artery bypass grafting. 2. Subjects unable to tolerate, obtain or comply with dual antiplatelet therapy for at least six months (acute coronary syndrome) or at least one month (stable angina and silent ischaemia). 3. Subjects requiring additional surgery (cardiac or non-cardiac) within one month. 4. Non-cardiac comorbidities with life expectancy less than one year. 5. Prior haemorrhagic stroke. 6. Known allergy to aspirin or P2Y₁₂ inhibitors. 7. At least one contraindication to all the authorised P2Y₁₂ inhibitors at the requested dose (in case of contraindication to only one or two of the P2Y₁₂ inhibitors, the investigators are allowed to use the only, or one of the two P2Y₁₂ inhibitors for which no allergy is known). 8. Coronary artery stenosis $< 50\%$ (visual assessment). 9. Coronary artery stenosis $\geq 50\%$ and $< 70\%$ by visual evaluation and FFR ≥ 0.80. 10. Concurrent enrolment in another randomised clinical trial.

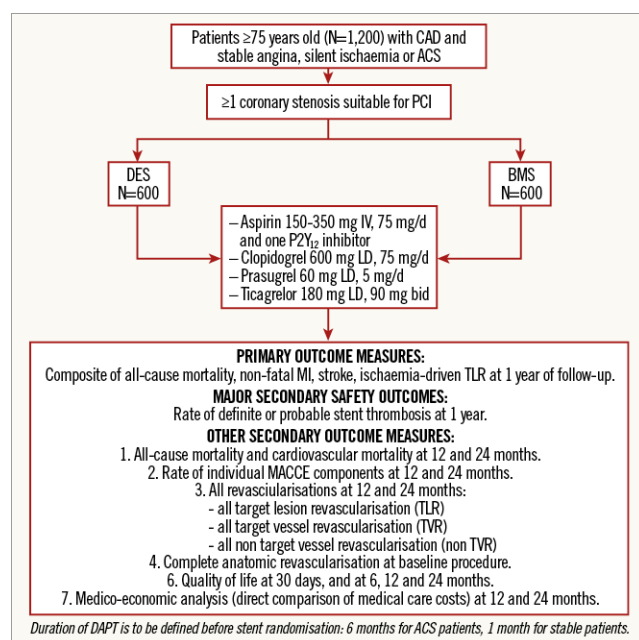


Figure 1. SENIOR study design.

Consecutive subjects above 75 years of age in whom revascularisation by PCI of at least one coronary artery stenosis with visually assessed diameter stenosis $\geq 70\%$ ($\geq 50\%$ in the left main) will be identified and screened for study eligibility. Subjects eligible for enrolment as per the general inclusion and exclusion criteria will be asked to sign an informed consent for the randomised trial.

INFORMED CONSENT

All subjects must provide informed consent in accordance with the local institutional review board (IRB)/ethics committee (EC), using an IRB/EC-approved informed consent form. Final eligibility for the trial will be confirmed based on the pre-intervention angiography. Local ethics committee approval was obtained on 16 April 2014 (Comité de Protection des Personnes Ile de France III: 2014-A00281-46).

RANDOMISATION

Randomisation is carried out through a web-based system available 24 hours per day, all year round, and maintained by a data coordinating centre (Cardiovascular European Research Center, CERC, Massy, France).

The choice of antiplatelet agent and duration of DAPT are stratified upfront and are required to be entered in the Interactive Web Response System (IWRS) at randomisation, to avoid inequality between the two groups based on an unblinded physician's decision.

MEASUREMENTS

Table 3 summarises the schedule of measurements at 24 hours, 30 days and 180 days post procedure and annually thereafter for the duration of the study. In addition, telephone interviews will be conducted semi-annually to control vital status and identify intervening MACCE since the last in-hospital visit. Quality of life and depression data will also be collected at six and 12 months in the hospital.

Table 3. Schedule of measurements.

	Post-procedure				Post-randomisation (months)			
	Baseline	Pre-procedure	24 hrs	30 days	6	12	18	24
Vital status/MACCE		x	x	x	x	x	x	x
12-lead ECG	x	x	x	x		x		x
Cardiac markers	x	x	x					
Angina status	x		x	x	x	x	x	x
CBC, platelet, INR	x	x						
Electrolytes	x	x						
Serum creatinine and clearance	x	x	x					
Coronary angiography	x							
Cardiac medication	x		x	x	x	x	x	x
Quality of life	x			x	x	x		x
Depression assessment	x			x	x	x		x
Healthcare use	x		x	x	x	x	x	x
Serious adverse events		continuous						

Cardiac marker design: CPK-MB or troponin to be checked before or 6-8 hours after the procedure. CBC: complete blood count; ECG: electrocardiogram; INR: international normalised ratio; MACCE: major adverse cardiac and cardiovascular events

REVASCULARISATION PROCEDURE

The transradial approach is recommended in experienced centres. The choice of guiding catheters, guidewires, predilatation, atherectomy devices, post-dilatation, and intracoronary imaging system is left to the investigator's discretion. A final inflation using non-compliant balloons is recommended. The final objective is to obtain a <20% residual stenosis with a TIMI grade 3 distal flow without the loss of any side branch ≥ 2.0 mm in diameter. Only one type of stent is allowed in a patient during the index procedure, should he receive >1 stent. The randomisation process will determine which stent is allocated for any patient. In case of a staged procedure, PCI will be performed within a month after inclusion with the same study stent(s).

ANTITHROMBOTIC REGIMEN

Antithrombotic regimens in the cathlab, including unfractionated heparin, low molecular weight heparin and bivalirudin are left to the physician's discretion. DAPT duration will be one month after PCI for stable angina and silent ischaemia, and six months after PCI for acute coronary syndromes, irrespective of the type of stent. Aspirin will be given at a loading dose of 150-300 mg (orally) or 80-150 mg (intravenously) and at an oral maintenance dose of 75-100 mg daily, indefinitely. The P2Y₁₂ inhibitors added to aspirin before or immediately after PCI could be either clopidogrel (600 mg loading dose and 75 mg/d), prasugrel (60 mg loading dose and 5 mg/d orally, half the maintenance dose given to <75-year-old patients) or ticagrelor (180 mg loading dose and 90 mg/bid orally). In case of a staged procedure, the duration of DAPT will be six months from the index procedure in patients with acute coronary syndrome at baseline or one month starting from the final PCI in patients with stable or silent ischaemia at baseline.

SAMPLE SIZE

The study is powered to test the superiority of DES with a relative 25% reduction in the primary endpoint compared to BMS. Assuming a primary endpoint event rate of 31% for BMS at one year (interpolated from the most contemporary and accurate references)^{14,15,16,17}, a minimum time to follow-up of one year and a constant dropout rate yielding 15% lost to follow-up at one year, then a sample size population of 560 subjects per arm will provide 80% power to demonstrate superiority using a chi-square test (two-sided alpha=0.05) comparing the event rates at one year from the Kaplan-Meier curves. A total of 1,200 patients (600 in each arm) will be randomised. The sample size calculation was performed in SAS version 9.2 (SAS Institute, Cary, NC, USA) using 10,000 simulations. Results from individual or secondary endpoints will only be considered to be hypothesis-generating.

QUALITY OF LIFE, AND DEPRESSION ANALYSIS

Quality of life will be assessed using the SF-12v2³⁵ and the EuroQol-5D³⁶ self-administered questionnaires. These questionnaires have been validated in populations with coronary artery disease³⁷. Quality-adjusted survival for each treatment group is estimated on the basis of observed clinical outcomes (survival) and country-specific utility weights.

Depression state will be assessed with the short version of the Geriatric Depression Scale used extensively in the elderly³⁸.

COST-EFFECTIVENESS ANALYSIS

Medical care costs for the initial hospitalisation and for the one- and two-year follow-up periods will be assessed by a combination of "bottom-up" and "top-down" methods using patient-level detailed resource utilisation from the CRF, and DRG-specific costs from the national hospital activity-based costing study.

CARDIAC CATHETERISATION LABORATORY COSTS

Detailed resource use will be recorded for each procedure, and the cost of each item estimated on the basis of the most recent hospital acquisition cost for the item. Costs of additional

disposable equipment, overheads, and depreciation for the cardiac catheterisation laboratory will be estimated from the DRG-specific average cost per procedure³⁹.

OTHER HOSPITAL COSTS

All other hospital costs will be determined by using the national cost schedules, which provide itemised DRG-specific costs on a yearly basis. Hospital costs will be determined by multiplying the per diem itemised hospital costs (excluding procedural costs) by the actual length of stay of each patient in the trial. The most recent cost study available will be used.

OTHER COSTS

Outpatient services will be assessed by patient self-report of medication and service utilisation, and their costs will be estimated from the most recent national cost schedules.

OUTCOMES

Since the primary endpoint is a reduction in MACCE, the primary endpoint for the cost-effectiveness analysis is the incremental cost per event avoided by DES compared with BMS. This disease-specific cost-effectiveness ratio will be calculated by dividing the difference in mean one-year and two-year medical care costs for the two treatment groups by the difference in event rates over the same time frame. Final cost-effectiveness will be assessed for cost per quality-adjusted year of life gained at two years.

STATISTICAL ANALYSIS

All primary analyses will be carried out using the intention-to-treat principle. The rates of the primary endpoint at one year in both groups will be determined from a Kaplan-Meier curve and compared by means of a chi-square test. In addition, a relative risk estimate with a 95% confidence interval will be provided. The rates of definite and probable stent thrombosis at one year will be analysed similarly. Cost data will be reported as both mean and median values and compared by t-tests. To estimate the uncertainty surrounding the cost-utility ratio, we will calculate bias-corrected CIs by the bootstrap method using 1,000 repeated samplings of the study population. All statistical analyses will be described in a statistical analysis plan, which will be finalised before the end of the study.

Limitations

The design of the SENIOR trial will only allow definite conclusions with regard to the primary combined endpoint, in view of the planned sample size. Given the expected relative scarcity of stent thrombosis and major bleeding complications, as well as all-cause mortality, dedicated trials in much larger populations of elderly patients will be needed to address the safety/benefit ratio of combining DES and short DAPT duration in these high-risk patients.

Conclusions

The SENIOR trial is designed to compare a new-generation DES with standard BMS in elderly patients receiving a similarly short duration of DAPT. A strategy combining the efficacy of this latest generation of DES to reduce ischaemia-driven revascularisations and re-

hospitalisations with the safety of a short duration of DAPT could be of particular benefit in a high bleeding risk population such as the elderly.

Impact on daily practice

Improved outcomes associated with newer-generation stents without increased bleeding risk may alter the unfavourable risk/benefit ratio associated with first-generation DES and thus modify PCI strategies in elderly patients with coronary artery disease.

Acknowledgements

Clinical trial operational management of the study is performed by CERC.

Funding

The study is funded by an unrestricted educational grant through the Investigator Research Program, from Boston Scientific.

Conflict of interest statement

O. Varenne has received speaker fees from Boston Scientific and Abbott Vascular. T. Cuisset has received consulting or speaker fees from Abbott Vascular, AstraZeneca, Biotronik, Boston Scientific, Cordis, Daiichi Sankyo, Edwards, Eli Lilly, Hexacath, Iroko Cardio, Medtronic, Servier and Terumo. M. Sabaté has received consulting fees from Abbott Vascular. O. Hanon has received consulting or speaker fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer, Boston Scientific, Novartis, Pfizer, Sanofi-Aventis, Servier, and Vifor. I. Durand-Zaleski has received consulting or speaker fees from AbbVie, Amgen, Sanofi, Janssen, BMS, Pfizer, and Medtronic. The other authors have no conflicts of interest to declare.

References

1. Anderson HV, Shaw RE, Brindis RG, McKay CR, Klein LW, Krone RJ, Ho KK, Rumsfeld JS, Smith SC Jr, Weintraub WS. Risk-adjusted mortality analysis of percutaneous coronary interventions by American College of Cardiology/American Heart Association guidelines recommendations. *Am J Cardiol.* 2007;99:189-96.
2. Munoz JC, Alonso JJ, Duran JM, Gimeno F, Ramos B, Garcimartin I, de la Fuente L, Gomez I, Fernandez-Aviles F. Coronary stent implantation in patients older than 75 years of age: clinical profile and initial and long-term (3 years) outcome. *Am Heart J.* 2002;143:620-6.
3. de Belder A, de la Torre Hernandez JM, Lopez-Palop R, O’Kane P, Hernandez Hernandez F, Strange J, Gimeno F, Cotton J, Diaz Fernandez JF, Carrillo Saez P, Thomas M, Pinar E, Curzen N, Baz JA, Cooter N, Lozano I, Skipper N, Robinson D, Hildick-Smith D; XIMA Investigators. A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or Vision Stents for the Management of Angina in the Elderly). *J Am Coll Cardiol.* 2014;63:1371-5.

4. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabaté M, Smits PC, Kaiser C, D'Ascenzo F, Frati G, Mancone M, Genereux P, Stone GW. Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2014;63:299-307.
5. Bangalore S, Toklu B, Amoroso N, Fusaro M, Kumar S, Hannan EL, Faxon DP, Feit F. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. *BMJ*. 2013;347:f6625.
6. Camenzind E, Boersma E, Wijns W, Mauri L, Rademaker-Havinga T, Ordoubadi FF, Sutorp MJ, Al Kurdi M, Steg PG; PROTECT Steering Committee and Investigators. Modifying effect of dual antiplatelet therapy on incidence of stent thrombosis according to implanted drug-eluting stent type. *Eur Heart J*. 2014;35:1932-48.
7. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol*. 2007;27:1500-10.
8. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372:1163-73.
9. Saito S, Valdes-Chavarri M, Richardt G, Moreno R, Iniguez Romo A, Barbato E, Carrie D, Ando K, Merkely B, Kornowski R, Eltchaninoff H, James S, Wijns W; CENTURY II Investigators. A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial. *Eur Heart J*. 2014;35:2021-31.
10. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Jüni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv*. 2013;6:777-89.
11. Navarese EP, Tandjung K, Claessen B, Andreotti F, Kowalewski M, Kandzari DE, Kereiakes DJ, Waksman R, Mauri L, Meredith IT, Finn AV, Kim HS, Kubica J, Suryapranata H, Aprami TM, Di Pasquale G, von Birgelen C, Kedhi E. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. *BMJ*. 2013;347:f6530.

12. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J.* 2012;33:1214-22.
13. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33:2569-619.
14. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banchoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hämäläinen M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons-Sel AE, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J.* 2013;34:2949-3003.
15. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44-e122.
16. Moscucci M, Fox KA, Cannon CP, Klein W, López-Sendón J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J.* 2003;24:1815-23.
17. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation.* 2012;125:2015-26.

18. Cassese S, Byrne RA, Tada T, King LA, Kastrati A. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. *Eur Heart J*. 2012;33:3078-87.
19. Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, Cuisset T, Elhadad S, Schiele F, Lhoest N, Ohlmann P, Carrié D, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Beygui F, Vicaut E, Montalescot G; ARCTIC investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet*. 2014;384:1577-85.
20. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet*. 2013;382:1714-22.
21. Mangiacapra F, Ricottini E, Di Giola G, Peace A, Patti G, De Bruyne B, Wijns W, Barbato E, Di Sciascio G. Comparison among patients ≥ 75 years having percutaneous coronary angioplasty using drug-eluting stents versus bare metal stents. *Am J Cardiol*. 2015;115:1179-84.
22. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y; RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol*. 2012;60:1340-8.
23. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation*. 2012;125:505-13.
24. Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, Han KH, Park SW, Yun SC, Lee SG, Rha SW, Seong IW, Jeong MH, Hur SH, Lee NH, Yoon J, Yang JY, Lee BK, Choi YJ, Chung WS, Lim DS, Cheong SS, Kim KS, Chae JK, Nah DY, Jeon DS, Seung KB, Jang JS, Park HS, Lee K. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. *N Engl J Med*. 2010;362:1374-82.
25. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB 3rd, Negoita M, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ Jr, Nicolela EL Jr, Perin MA, Devito FS, Labrunie A, Salvadori D Jr, Gusmão M, Staico R, Costa JR Jr, de Castro JP, Abizaid AS, Bhatt DL; OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310:2510-22.

26. Colombo A, Chieffo A, Frasher A, Garbo R, Masotti-Centol M, Salvatella N, Oteo Dominguez JF, Steffanon L, Tarantini G, Presbitero P, Menozzi A, Pucci E, Mauri J, Mario Cesana B, Giustino G, Sardella G. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol*. 2014;64:2086-97.
27. Schulz-Schüpke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tölg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wöhrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PW, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz KL, Schömig A, Mehilli J, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J*. 2015;36:1252-63.
28. Gilard M, Barragan P, Noryani AA, Hussam A, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Bosch J, Morice MC. 6- versus 24-month dual antiplatelet therapy after implantation of drug eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol*. 2015;65:777-86.
29. Silber S, Kirtane AJ, Belardi JA, Liu M, Brar S, Rothman M, Windecker S. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute zotarolimus-eluting stent implantation. *Eur Heart J*. 2014;35:1949-56.
30. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155-66.
31. Valgimigli M, Patialiakas A, Thury A, McFadden E, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Airolidi F, Ferlini M, Liistro F, Dellavalle A, Vranckx P, Briguori C; ZEUS Investigators. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol*. 2015;65:805-15.
32. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-51.
33. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of

Myocardial Infarction, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33:2551-67.

34. Merhan R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736-47.

35. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical Care*. 1996;34:220-33.

36. The EuroQol Group. Euro-Qol: a new facility for measurement of health-related quality of life. *Health Policy*. 1990;16:199-208.

37. De Smedt D, Clays E, Doyle F, Kotseva K, Prugger C, Pająk A, Jennings C, Wood D, De Bacquer D; EUROASPIRE Study Group. Validity and reliability of three commonly used quality of life measures in a large European population of coronary heart disease patients. *Int J Cardiol*. 2013;167:2294-9.

38. Wancata J, Alexandrowicz R, Marquart B, Weiss M, Friedrich F. The criterion validity of the Geriatric Depression Scale: a systematic review. *Acta Psychiatr Scand*. 2006;114:398-410.

39. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ*. 2013;346:f1049.