63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI: LE RADICI DA PRESERVARE

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L'esclusione degli anziani dai trial clinici randomizzati: un problema ancora aperto? Popolazioni emergenti: anziani in RSA

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Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

A Systematic Sampling Review

- Patients were excluded due to age in 72.1% of all trials (60.1% in pediatric populations and 38.5% in older adults)
- Of all exclusion criteria, only 47.2% were graded as strongly justified in the context of the specific RCT
- Multivariable analyses revealed independent associations between the total number of exclusion criteria and drug intervention trials (RR, 1.35; 95% CI, 1.11-1.65; P=.003) and between the total number of exclusion criteria and multicenter trials (RR, 1.26;95% CI, 1.06-1.52;P=.009).
- Industry sponsored trials were more likely to exclude individuals due to concomitant medication use, medical comorbidities, and age. Drug intervention trials were more likely to exclude individuals due to concomitant medication use, medical comorbidities, female sex, and socioeconomic status

Van Spall H, JAMA 2007

SPECIAL ARTICLE

Fighting Against Age Discrimination in Clinical Trials

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Table 1. Age ageing randomised controlled trials published between January 2008 and July 2010

Reference	Topic	Setting and type of trial	*n*, needed to recruit	*n*, screened	*n*, recruited	*n*, excluded	*n*, refusing	Period of follow-up	Dropout	Power achieved?	Comment
Randomised trials											
Peri *et al.* (2008) [20]	Activity levels	Residenti… cluster									…lts likely contaminated by cross …ver between clusters
Azad *et al.* (2008) [5]	Heart failure clinic	Outpatien… blinde…									…recruitment due to frailty and …imited resources'
Harrari *et al.* (2008) [21]	Health risk appraisal	Primary c… self-re…									…e-scale questionnaire intervention
Crotty *et al.* (2008) [22]	Home versus day hospital post-hospital stay	Communi… blinde…									
Harris *et al.* (2008) [6]	Methods of increasing study recruitment	Postal an… telepho… unblin…									…(43%) were recruited into the …ain study
Spice *et al.* (2009) [23]	Falls	General p… second… cluster									…of setting/style of care
Moseley *et al.* (2009) [24]	Increased exercise after hip fracture	Rehab un… home, blinde…									…differences shown with higher …ercise levels
Gleason *et al.* (2009) [25]	Soy supplement	Communi… blind p…									…umably healthy volunteers …erhaps from a panel?
Neyens *et al.* (2009) [26]	Falls	Nursing h… cluster									…ntion to treat; may be select …roup of homes participated as 34 …ut of 119 homes agreed and 12 …elected
Meyer *et al.* (2009) [27]	Falls	Nursing h… cluster									…rvention was a risk assessment …ol for falls—all residents …cluded automatically so no …dividual refusals
Ciaschini *et al.* (2009) [28]	Falls	Communi… blind, one centre									…erts and direct clinician referral
Forster *et al.* (2009) [29]	Post-stroke support	Community, single blinded, two centres				163 (33.5%), not disabled	59	6 month	23 (8.7%), 16 died, 7 withdrew	Yes	
Salonoja *et al.* (2010) [30]	Medicine, reduction	Community, not blind, one centre	Not specifi…		591	21 (3.4%), multiple reasons	All agreed through adverts in a single town	1 year	61 (10.3%)	Yes	Recruited by adverts so selective population: one time counselling to reduce sedatives
Boxer *et al.* (2010) [31]	Drug treatment for sarcopenia	Community, double blinded, placebo	Not made clear	728 responses then 725 screened	99	329 (45%), not frail or normal DHEA levels	47 1st wave, 23 2nd wave, =70 total	6 months	12	Yes	Recruited by mailing

- **Only 18 papers devlivered in 18 months (2008-2010)**
- **Topics for trials very variable**
- **Methods of recruitment very variable.**
- **Nearly three participants needed to be screened on average for every subject included.**
- **Exclusion rates very variable, (3.4%-49%).**
- **Refusal rates were as high as 54% but more typically around 12–15%.**
- **Although the precise factors affecting recruitment were not clear from most papers, one trial clearly highlights '(patient) frailty and limited resources'.**
- **Drop out rates ranged from 5 to 37%. More specifically drop out rates at 1 year for the two community-based falls prevention studies were 12 and 14%, and for the two falls studies in nursing homes were 19 and 37%**

McMurdo M et al, Age Ageing 2011

Frequencies of exclusion criteria that might negatively affect the inclusion of older individuals in ongoing clinical trials regarding hematologic malignancies.

Exclusion criterion	Frequency, N. (%)
Upper age limit	35 (41.18)
Reduced life expectancy	23 (27.06)
Drug therapy (at least one drug)	53 (62.35)
Abnormal laboratory result (at least one)	69 (81.18)
Cognitive impairment	5 (5.88)
Physical disability	62 (72.94)
Inability to give informed consent	32 (37.65)
Inability to attend follow-up visit	5 (5.88)
Physician's judgement	23 (27.06)
Reduced compliance	28 (32.94)
Comorbidity (at least one disease)	77 (90.59)
Specific disease	
Renal failure	60 (70.6)
Cardiovascular	56 (65.9)
Infectious	47 (56.6)
Hematologic	39 (45.9)
Lung	33 (38.3)
Psychiatric	31 (36.5)
Previous cancer	18 (21.2)
Gastrointestinal	17 (20)
Neurological	15 (17.6)
Liver	8 (9.6)

Cherubini A et al. Haematologica 2013;98:997-1000

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Baseline clinical characteristics of populations of the included DOACs phase III trials

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE-AF
>75 years	39%	43%	31%	38%
Perm vs parox AF	67%	81%	85%	75%
Previous stroke	20%	55%	20%	29%
HF	32%	63%	36%	58%
CHADS score 3-6	33%	87%	30%	54%
Individual TTR	67%	58%	66%	68%

Pazienti ≥ 75 anni esposti a DAB studio RE-LY	4828	40%
Pazienti ≥ 75 anni esposti a RIV studio ROCKET	3082	44%
Pazienti ≥ 75 anni esposti a API studio ARISTOTLE	2850	31%
Pazienti ≥ 75 anni esposti a EDO studio ENGAGE	5654	27%

SPRINT: A Randomized Trial of Intensive versus Standard Blood-Pressure Control

Table 1. Baseline Characteristics of the Study Participants.*

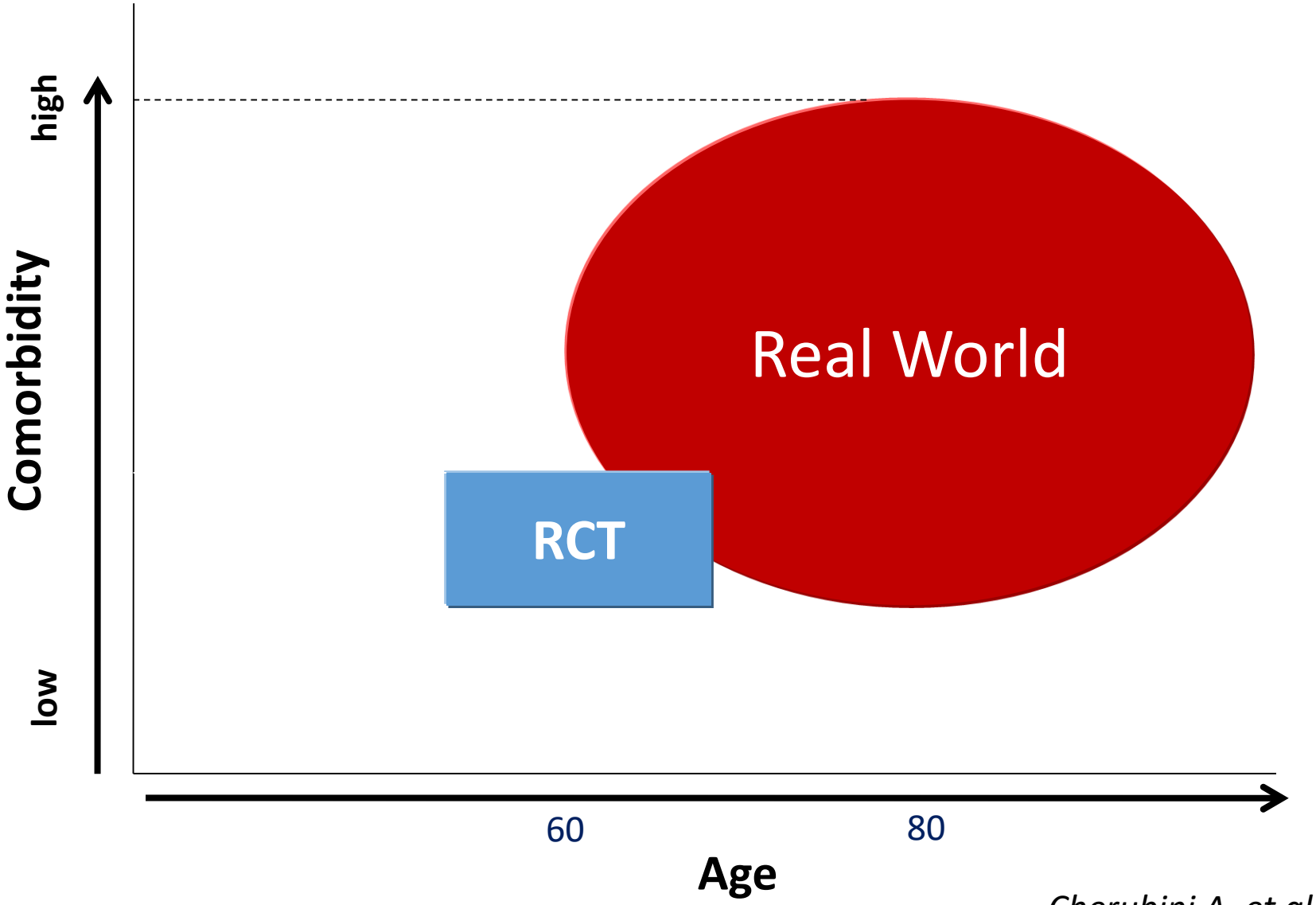
Characteristic	Intensive Treatment (N=4678)	Standard Treatment (N=4683)
Criterion for increased cardiovascular risk — no. (%)†		
Age ≥75 yr	1317 (28.2)	1319 (28.2)
Chronic kidney disease‡	1330 (28.4)	1316 (28.1)
Cardiovascular disease	940 (20.1)	937 (20.0)
Clinical	779 (16.7)	783 (16.7)
Subclinical	247 (5.3)	246 (5.3)
Framingham 10-yr cardiovascular disease risk score ≥15%	2870 (61.4)	2867 (61.2)
Female sex — no. (%)	1684 (36.0)	1648 (35.2)
Age — yr		
Overall	67.9±9.4	67.9±9.5
Among those ≥75 yr of age	79.8±3.9	79.9±4.1
Race or ethnic group — no. (%)§		
Non-Hispanic black	1379 (29.5)	1423 (30.4)
Hispanic	503 (10.8)	481 (10.3)
Non-Hispanic white	2698 (57.7)	2701 (57.7)
Other	98 (2.1)	78 (1.7)

The SPRINT Research Group. N Engl J Med 2015;373:2103-2116.

SPRINT: Exclusion criteria

- Known secondary cause of hypertension
- Proteinuria (within the past 6 months)
- Arm circumference too large or small to allow accurate BP measurement
- Diabetes mellitus
- History of stroke (not CE or stenting)
- eGFR < 20 ml/min /1.73m^2 or end-stage renal disease (ESRD)
- CV event /procedure/ hospitalization for unstable angina (last 3 months)
- Symptomatic HF (past 6 months) or LVEF (by any method) < 35%
- Medical condition likely to limit survival to less than 3 years or a malignancy other than non-melanoma skin cancer within the last 2 years
- Any factors to be likely to limit adherence to interventions
- Failure to obtain informed consent from participant
- Unintentional weight loss > 10% in last 6 months

Evidence B(i)ased Medicine



Cherubini A. et al

Consequences of the exclusion of older subjects from clinical trials

- The drugs we are using in older people have not been properly evaluated.
  - The efficacy and safety of pharmacological and non pharmacological treatments is unknown in older subjects
  - High risk of inappropriate prescription, including under-treatment
- Under-recruiting trials are bad for patients, bad for science, and bad for economy

Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents

The PARTAGE Study

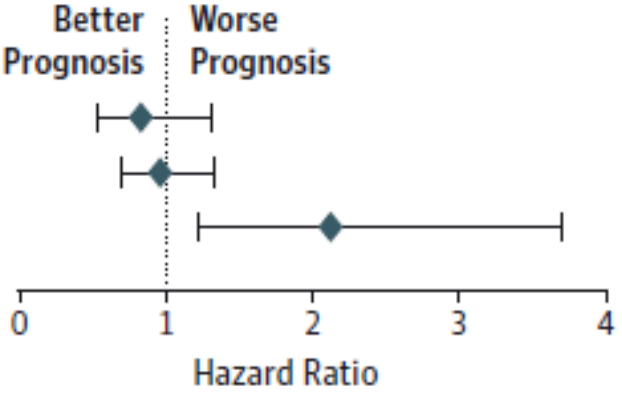
DESIGN, SETTING, AND PARTICIPANTS This longitudinal study included elderly residents of nursing homes. The interaction between low (<130 mm Hg) SBP and the presence of combination antihypertensive treatment on 2-year all-cause mortality was analyzed. A total of 1127 women and men older than 80 years (mean, 87.6 years; 78.1% women) living in nursing homes in France and Italy were recruited, examined, and monitored for 2 years. Blood pressure was measured with assisted self-measurements in the nursing home during 3 consecutive days (mean, 18 measurements). Patients with an SBP less than 130 mm Hg who were receiving combination antihypertensive treatment were compared with all other participants.

JAMA Intern Med. 2015;175(6):989-995. doi:10.1001/jamainternmed.2014.8012
Published online February 16, 2015.

Figure 1. Hazard Ratios (HRs) for All-Cause Mortality According to Systolic Blood Pressure (SBP) Levels, Number of Antihypertensive (Anti-HTN) Drugs, and Interaction Between SBP and Number of Anti-HTN Drugs

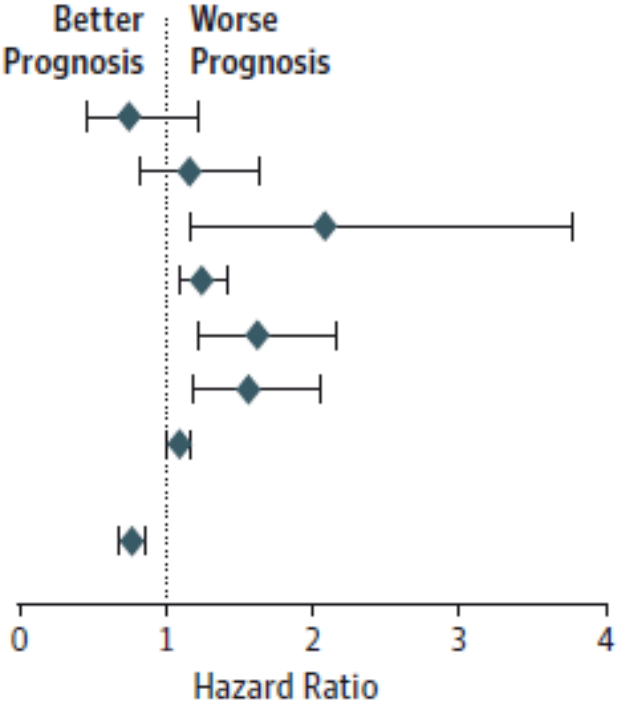
A

Unadjusted analysis	HR (95% CI)	*P* Value
SBP <130 mm Hg	0.83 (0.53-1.31)	.42
≥2 Anti-HTN drugs	0.97 (0.70-1.33)	.83
SBP <130 mm Hg and ≥2 anti-HTN drugs	2.13 (1.23-3.69)	.007



B

Adjusted analysis	HR (95% CI)	*P* Value
SBP <130 mm Hg	0.75 (0.46-1.22)	.25
≥2 Anti-HTN drugs	1.16 (0.82-1.64)	.41
SBP <130 mm Hg and ≥2 anti-HTN drugs	2.09 (1.16-3.77)	.01
Age, per 5 y	1.25 (1.10-1.42)	<.001
Male sex	1.63 (1.22-2.17)	<.001
BMI ≤25	1.57 (1.19-2.06)	.001
Charlson Comorbidity Index score, per 1-point increase	1.09 (1.03-1.16)	.005
ADL score, per 1-point increase	0.77 (0.68-0.86)	<.001



Successful Clinical Trial Research in Nursing Homes: The Improving Decision-Making Study

Hanson L et al, Clin Trials 2010; 7:735-743

Despite the compelling individual and public health impact of NH care, clinical research, particularly clinical trials, rarely includes this population. Among 5000 original articles published in 6 leading medical journals in 2008, not one focused on nursing home care.

Suffering in Silence: Addressing the Needs of Nursing Home Residents

Morrison RS L et al, J Palliative Med 2009; 12:no 8

- Indeed, of the nearly 5000 articles (including 394 clinical trials and 244 reviews) published in the New England Journal of Medicine, Journal of the American Medical Association, Lancet, Annals of Internal Medicine, Archives of Internal Medicine, and the British Medical Journal in the past year, not a single article focused on this vulnerable and needy population

Perché i NH residents non sono reclutati nei clinical trials

- Patient's related factors
- Organization's related factors

Perché i NH residents non sono reclutati nei clinical trials

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Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2018;46:27–41
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A Point Prevalence Study of Delirium in Italian Nursing Homes

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- 71 nursing homes from 18 Regions in Italy

Table 1. Demographic and clinical characteristics of patients with and without delirium according to 4-AT score

Patient characteristics	Delirium (n = 535, 36.8%)	No delirium (n = 919, 63.2%)	p value
Age, years	85.0±7.0	84.0±7.8	0.015
Female gender	653 (71.1)	362 (67.7)	0.174
Education, years	5 (3–7)	5 (5–8)	<0.001
ADL score	1 (0–1)	1 (1–4)	<0.001
0 functions spared	237 (44.3)	131 (14.3)	
1–5 functions spared	286 (53.5)	696 (75.7)	<0.001
6 functions spared	12 (2.2)	92 (10.0)	
Nutritional status			
Well nourished	328 (61.3)	669 (72.8)	<0.001
At risk of malnutrition	160 (29.9)		
Malnourished	47 (8.8)	24 (2.6)	
Charlson Index score	1 (1–3)	2 (1–3)	0.010
Dementia	401 (75.0)	353 (38.4)	<0.001
Drugs	5.1±2.1	5.6±2.1	<0.001
Diuretics	218 (40.7)	457 (49.7)	0.001
Antihypertensives	250 (46.7)	533 (58.0)	<0.001
Antiplatelet drugs	290 (54.2)	534 (58.1)	0.148
Antiarrhythmic drugs	36 (6.7)	74 (8.1)	0.357
Statins/hypolipidemic drugs	61 (11.4)	187 (20.3)	<0.001
Antidiabetics (including insulin)	88 (16.4)	176 (19.2)	0.197
Antiulcer drugs	311 (58.1)	612 (66.6)	<0.001
Benzodiazepines	192 (35.9)	331 (36.0)	0.960
Antipsychotics	295 (55.1)	290 (31.6)	<0.001
Antidepressants	166 (31.0)	349 (38.0)	0.008
Antiepileptic drugs	75 (14.0)	99 (10.8)	0.066
Tracheotomy	0 (0)	2 (0.2)	0.280
Nasogastric tubes or PEG	7 (1.3)	4 (0.4)	0.064
Urinary catheter	35 (6.5)	28 (3.0)	0.002
Physical restraints	134 (25.0)	62 (6.7)	<0.001

Perché i NH residents non sono reclutati nei clinical trials

- Patient's related factors
- Organization's related factors

Challenges in Carrying Out Research in the Nursing Home Setting – organization's related barriers

- Inadeguatezza dei supporti informatici nelle RSA (mancanza database informatizzati)
- Difficoltà logistiche nell'effettuare alcuni esami che richiedono attrezzature speciali (esempio imaging)
- Spazi dedicati, telefoni, fax, etc.
- Timore dello staff di distrarre troppo tempo dalle attività ruotinarie (ad esempio per preparare e trasportare gli ospiti nelle attività specifiche)
- Mancanza di competenza da parte dello staff nel somministrare assessment e interventi e nel valutare le misure di outcome

Simmonds S et al, Clinical Trials in Older Adults Wiley-Blackwell, 2013

Challenges in Carrying Out Research in the Nursing Home Setting –patient's related barriers

- Scarsa attitudine nel partecipare ai clinical trials (errori nel riportare i dati)
- Difficoltà nell'ottenere consenso informato/determinare la capacità decisionale / surrogate decision making
- Necessità di testimoni nell'ottenere consenso informato
- Assicurazioni
- Difficoltà a raggiungere il sample size (consenso informato, failure to meet screening criteria, attrition rate per malattie intercorrenti, decesso, o dimissioni).

Simmonds S et al, Clinical Trials in Older Adults Wiley-Blackwell, 2013

Potenziali barriere e possibili soluzioni

	Paziente-associate	Medico-associate	Trial-associate
Barriere	Logistiche Finanziarie Scarsa consapevolezza circa i potenziali benefici del trial Dipendenza fisica e cognitiva	Percezione di scarsa utilità dei trial Cultura Mancanza di interesse a fare ricerca su anziano (anziano vissuto come problema)	Criteri di inclusione rigorosi Metodi di valutazione stato funzionale Scarsità di fondi dedicati anziani
Soluzioni	Fornire trasporti e sistemazioni Formazione (geriatrica, research nurses, trial coordinat) Database nazionali Miglioramento dei sistemi di comunicazione	Studi specifici su anziani e in NH (PPI) Miglioramento dei sistemi di comunicazione Promozione della formazione geriatrica nelle NH	Promozione cultura geriatrica anche a livello aziende del farmaco Aumento dei fondi dedicati a ricerche su anziani Trials specifici su anziani in NH (QIP?)