60° CONGRESSO NAZIONALE

NAPOLI

25-28 Novembre 2015

SPRINTT
Sarcopenia & Physical fRailty IN older people: multi-componenT Treatment strategies

SPRINTT: operazionalizzazione della fragilità

Francesco Landi, MD, PhD

Catholic University, Geriatric Center,

Gemelli Hospital - Rome, Italy

SPRINTT
Sarcopenia & Physical fRailty IN older people: multi-componenT Treatment strategies

UNIVERSITÀ CATTOLICA del Sacro Cuore

Problem statement

- ✓ Frailty is an Unmet Medical Need of Older Patients
- ✓ Frailty is a candidate for integrated therapeutic/preventive interventions
- ✓ Frailty/Sarcopenia are an opportunity to develop Innovative Treatments

A private - public partnership – will be a good approach to answer these complex questions

SPRINTT
Sarcopenia & Physical fRailty IN older people: multi-component Treatment strategies

"Developing innovative therapeutic interventions against physical frailty and sarcopenia (ITI-PF&S) as a prototype geriatric indication"

Innovative Medicines Initiative

efpia

SANOFI

gsk
GlaxoSmithKline

NOVARTIS

Lilly

SERVIER

IMI Call n.9
(call for interest)
was published on
July 9th, 2013

efpia

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

Innovative Medicines Initiative

Consortium Partners

- 5 EFPIA partners: Sanofi (lead), GSK (co-lead), Novartis, Servier and Eli Lilly

- 12 Academia institutions and 2 SMEs partners:

  - **Università Cattolica del Sacro Cuore – Italy**
  - **Centre Hospitalier Universitaire de Toulouse - France**
  - **Univerzita Karlova v Praze (CUNI)- Czech Republic**
  - **Roessingh Research and Development BV (RRD), the Netherlands**
  - **Helsingin yliopisto (University of Helsinki)- Finland**
  - **Servicio Madrileno de Salud - Spain**
  - **Universitaetsmedizin Goettingen, Georg-August-Universitaet, - Germany**
  - **Université Paris Descartes (UPD) - France**
  - **Università degli Studi di Firenze - Italy**
  - **Friedrich- Alexander- Universitât Erlangen-Nürnberg - Germany**
  - **Uniwersytet Jagiellonski - Poland**
  - **Istituto Nazionale di Riposo e Cura per Anziani- INRCA - Italy**
  - **CARETEK s.r.l. (Italy)**
  - **EU-Open s.r.l. (Italy)**

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

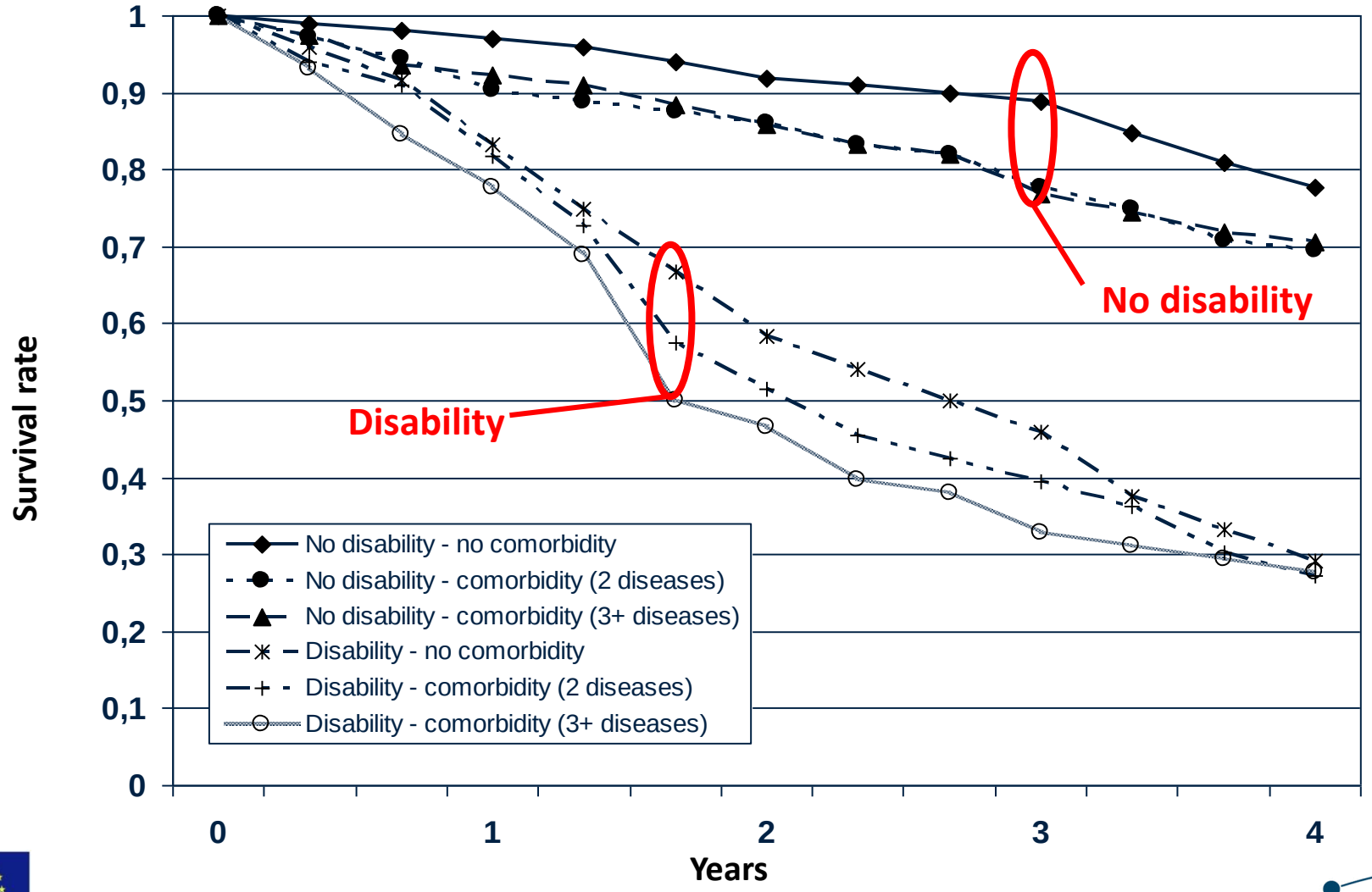
Developing innovative therapeutic interventions against physical frailty and sarcopenia (ITI-PF&S) as a prototype geriatric indication

- The SPRINTT project was designed in response to the IMI 9th Call for proposals launched in 2013
- Broadly, SPRINTT is geared to:
  - ✓ Provide a clear operationalization of the presently vague concept of frailty
  - ✓ Identify a precise target population of older persons at risk of disability, whose medical needs are presently unmet
  - ✓ Evaluate the effectiveness of a multicomponent intervention at preventing (mobility) disability in such population
  - ✓ Identify and validate diagnostic and prognostic biomarkers for physical frailty & sarcopenia

Identifying an at-risk older population

- The functional capacity of an older person is highly predictive of many important health outcomes (e.g., morbidity, loss of independence, falls, nursing home admission, mortality).
- Physical function impairment is the unique core output of frailty and sarcopenia, regardless of the operational definition(s) considered.
- The progression of frailty and sarcopenia is marked by increased morbidity, disability, frequent and often inappropriate healthcare use, nursing home admission, and poor quality of life.

Disability, more than multimorbidity, predicts mortality in advanced age



Landi et al., J Clin Epidemiol 2010

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

BMJ open

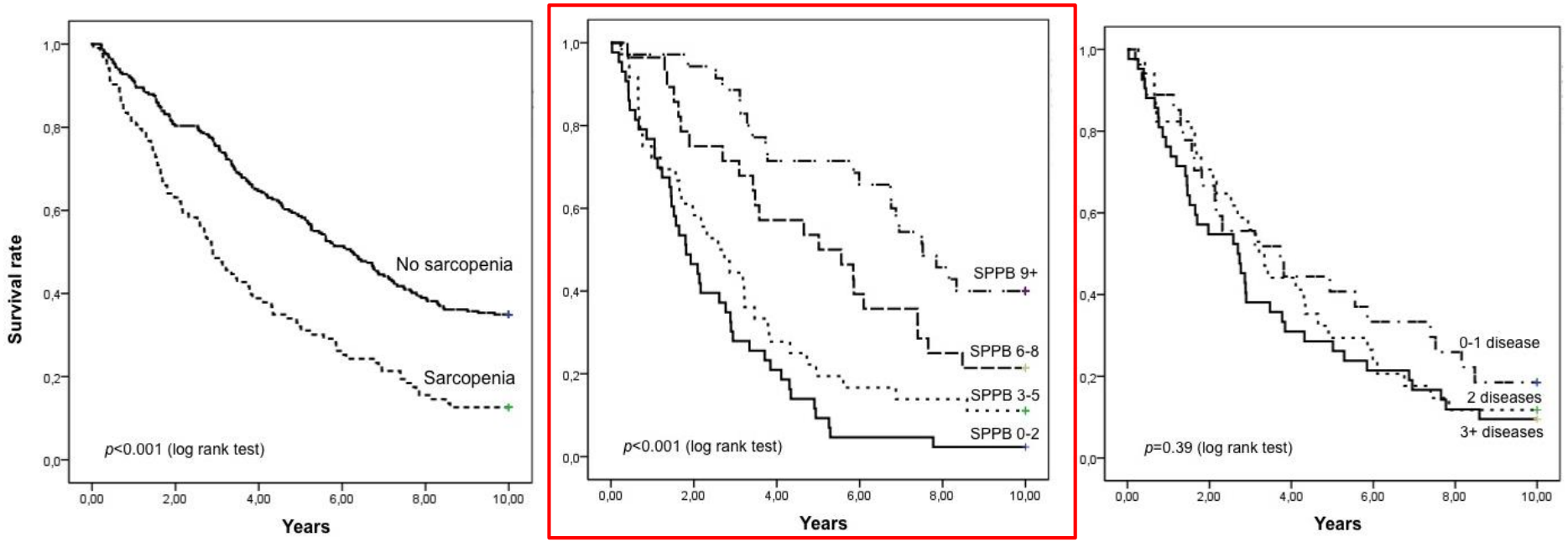
Impact of physical function impairment and multimorbidity on mortality among community-living older persons with sarcopenia: results from the *ilSIRENTE* prospective cohort study

In press

Francesco LANDI, MD, PhD,* Riccardo CALVANI, PHD, Matteo TOSATO, MD,

Anna Maria MARTONE, MD, Roberto BERNABEI, MD, Graziano ONDER, MD, PhD,

Emanuele MARZETTI, MD, PhD



efpia

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

imi
Innovative Medicines Initiative

Identifying an at-risk older population: operationalization of frailty

frontiers in
AGING NEUROSCIENCE

OPINION ARTICLE
published: 28 July 2014
doi: 10.3389/fnagi.2014.00192

Sarcopenia and physical frailty: two sides of the same coin

Matteo Cesari[1,2], Francesco Landi[3], Bruno Vellas[1,2], Roberto Bernabei[3] and Emanuele Marzetti[3]*

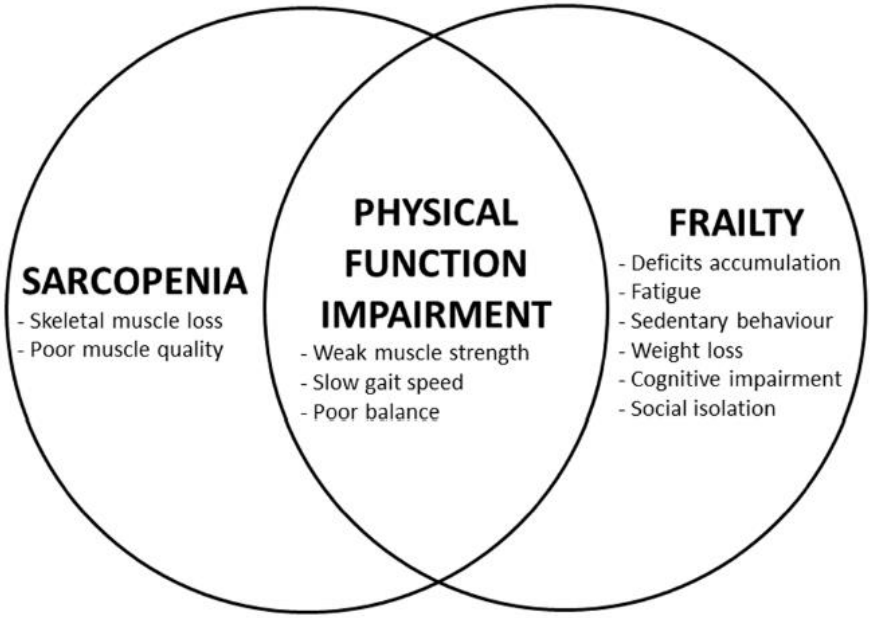


FIGURE 1 | Relationship among sarcopenia, frailty, and physical function impairment.

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Identifying an at-risk older population

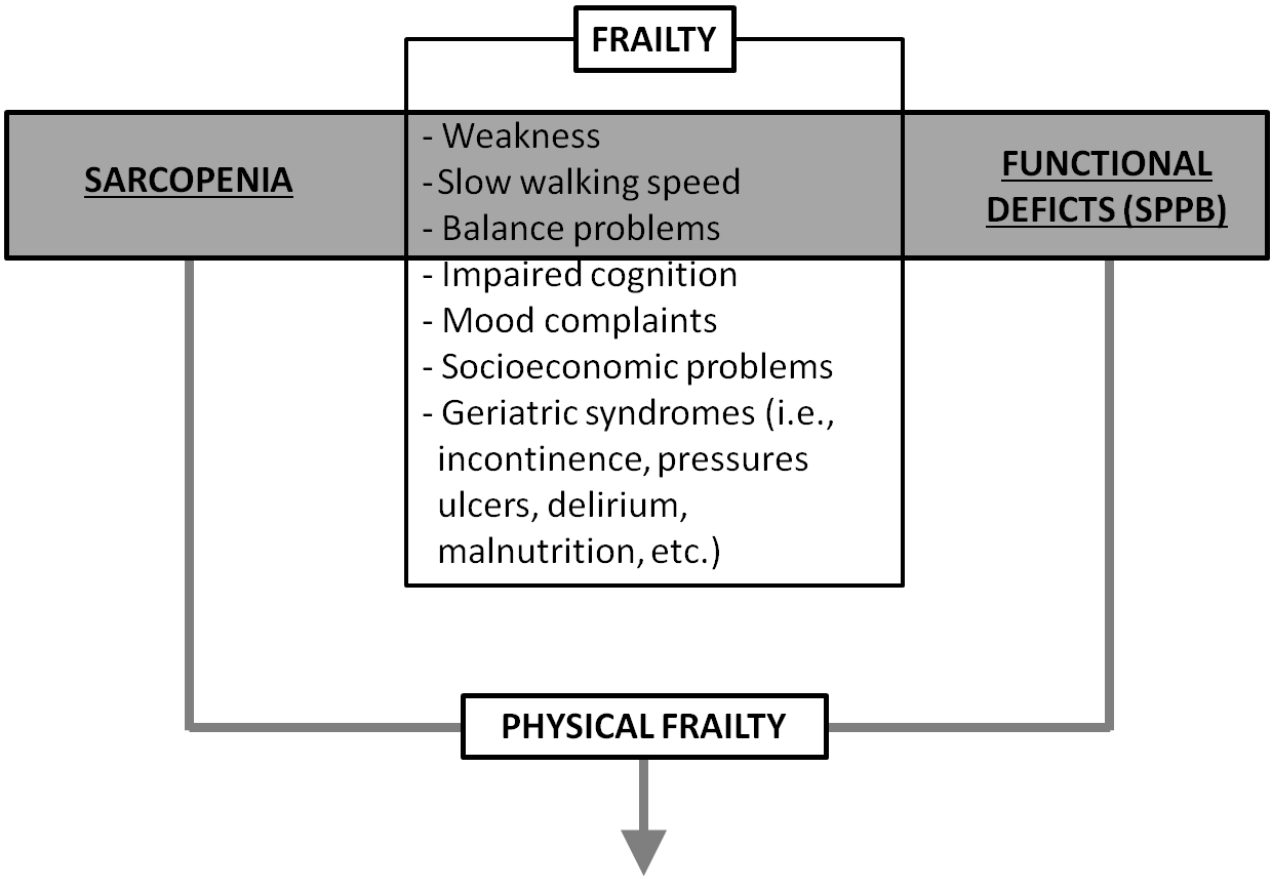
Clin Geriatr Med ■ (2015) ■–■
http://dx.doi.org/10.1016/j.cger.2015.04.005

Sarcopenia as the Biological Substrate of Physical Frailty

Francesco Landi, MD, PhD[a,*], Riccardo Calvani, PhD[a,1], Matteo Cesari, MD, PhD[b,1], Matteo Tosato, MD, PhD[a], Anna Maria Martone, MD[a], Roberto Bernabei, MD[a], Graziano Onder, MD, PhD[a], Emanuele Marzetti, MD, PhD[a]

Clin Geriatr Med - (2015) -–-
http://dx.doi.org/10.1016/j.cger.2015.04.005

Identifying an at-risk older population



Clin Geriatr Med - (2015)

Identifying an at-risk older population

The target population will be comprised of individuals with target organ damage (low muscle mass), specific clinical phenotype, and impaired physical performance

Table 1
Conceptual framework of physical therapy and sarcopenia—resemblance to common conditions of advanced age

Condition	Measurable Biological Substrate	Measurable Clinical Manifestations	Measurable Function
CHF	Myocardial dysfunction (echocardiography)	• Shortness of breath • Fatigue	6-min walking test
COPD	Airways destructive changes (spirometry)	• Dyspnoea • Cough • Sputum	6-min walking test
PAD	Arterial stenosis (Doppler echocardiography)	• Intermittent claudication • Numbness • Ulcers	Treadmill walking distance
PF&S	Reduced muscle mass (DXA)	• Slow walking speed • Poor balance • Weakness	SPPB

Clin Geriatr Med - (2015)

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

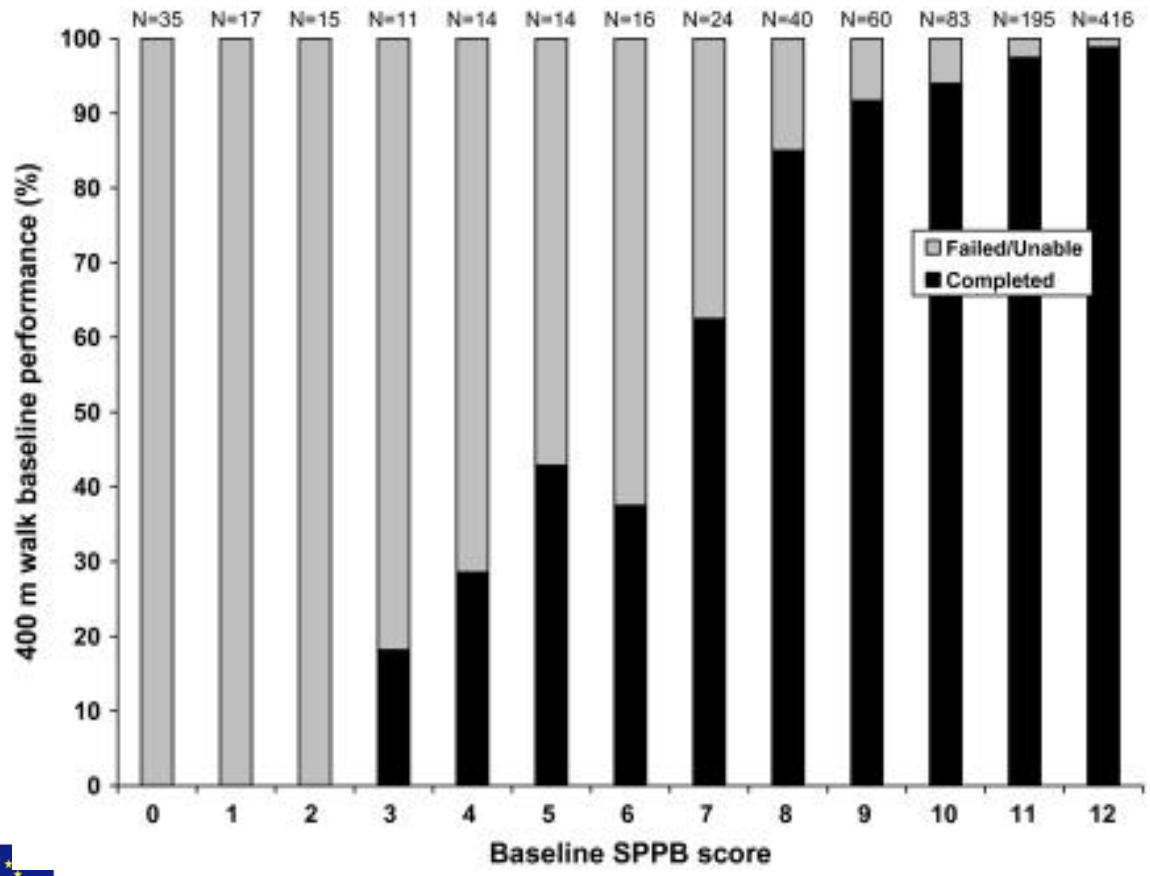
Innovative Medicines Initiative

Setting the SPPB range

- The identification of physically frail/sarcopenic older persons with unmet medical needs will rely on 3 key elements:
  1. Target organ deterioration (i.e., low muscle mass as measured by DXA = sarcopenia)
  2. Clinical signs and symptoms of physical frailty (i.e., weakness, slow walking speed and poor balance) objectively measured through the SPPB and corresponding to a summary score between 3 and 7
  3. Ability to complete the 400-m walk test at usual pace within 15 minutes

Setting the SPPB range

Four hundred-metre walk baseline completion by SPPB score. Older people with SPPB < 3 are unable to complete the test



- Older adults scoring 10+ on the SPPB are commonly considered high-functioning (Guralnik et al., J Gerontol 1994)
- A cut-off of 9 in the SPPB has good sensitivity and specificity in discriminating frail from non-frail older adults (da Câmara et al., JAGS 2013)

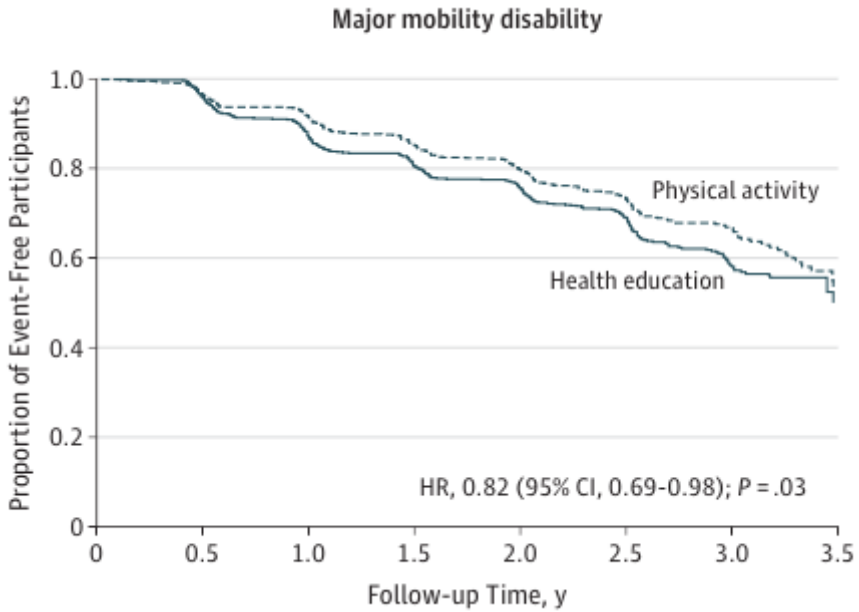
Vasunilashorn et al., J Gerontol A Biol Sci Med Sci 2009

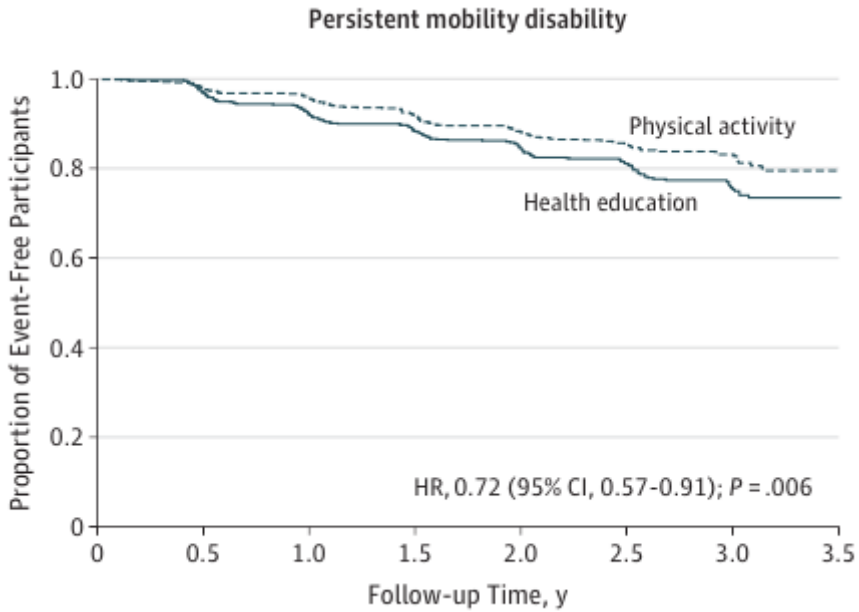
Original Investigation

Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults

The LIFE Study Randomized Clinical Trial

Marco Pahor, MD; Jack M. Guralnik, MD, PHD; Walter T. Ambrosius, PhD; Steven Blair, PED; Denise E. Bonds, MD; Timothy S. Church, MD, PhD, MPH; Mark A. Espeland, PhD; Roger A. Fielding, PhD; Thomas M. Gill, MD; Erik J. Groessl, PhD; Abby C. King, PhD; Stephen B. Kritchevsky, PhD; Todd M. Manini, PhD; Mary M. McDermott, MD; Michael E. Miller, PhD; Anne B. Newman, MD, MPH; W Jack Rejeski, PhD; Kaycee M. Sink, MD, MAS; Jeff D. Williamson, MD, MHS; for the LIFE study investigators



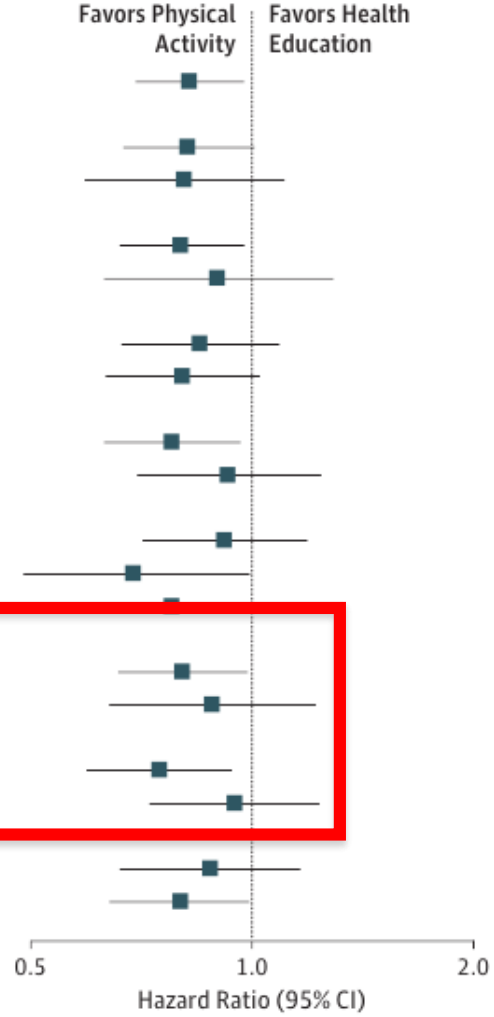


Sprintt CLINICAL TRIAL

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

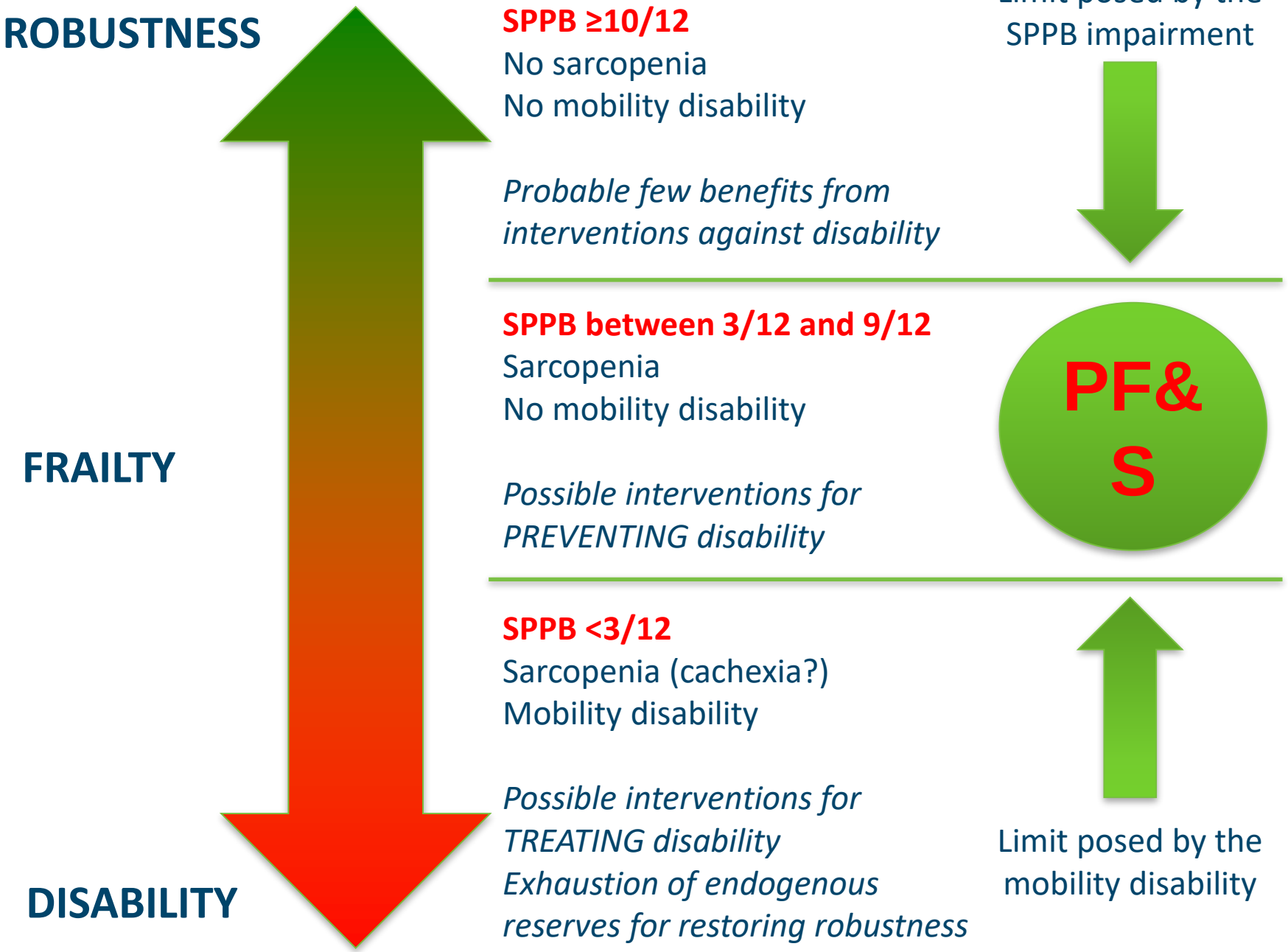
JAMA. doi:10.1001/jama.2014.5616
Published online May 27, 2014.

Subgroup	Physical Activity Events, No.	Physical Activity Total Participants	Health Education Events, No.	Health Education Total Participants	Hazard Ratio (95% CI)	Interaction *P* Value
Overall	246	818	290	817	0.82 (0.69-0.98)	
Sex						
Women	171	547	204	551	0.82 (0.67-1.01)	.95
Men	75	271	86	266	0.81 (0.59-1.11)	
Ethnicity/race						
Non-Hispanic white	182	604	234	635	0.80 (0.66-0.98)	.58
Other	64	211	56	180	0.90 (0.63-1.29)	
Age, y						
70-79	123	477	138	455	0.85 (0.67-1.09)	.76
≥80	123	341	152	362	0.81 (0.63-1.03)	
History of CVD						
No CVD	155	582	187	563	0.78 (0.63-0.97)	.34
CVD	91	236	103	254	0.93 (0.70-1.24)	
History of diabetes						
None	114	406	126	414	0.92 (0.71-1.19)	.41
Impaired fasting glucose	59	192	68	165	0.69 (0.49-0.99)	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
Gait speed						
<0.8 m/s	173	485	210	508	0.81 (0.66-0.99)	.63
≥0.8 m/s	73	333	80	309	0.88 (0.64-1.22)	
SPPB						
<8	135	353	177	378	0.75 (0.60-0.94)	.19
8 or 9	111	465	113	439	0.95 (0.73-1.23)	
[illegible]						
<90	95	261	108	261	0.88 (0.66-1.16)	.58
≥90	151	557	182	556	0.80 (0.64-0.99)	



JAMA. doi:10.1001/jama.2014.5616
Published online May 27, 2014.

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli


ROBUSTNESS
FRAILTY
DISABILITY
SPPB ≥10/12
No sarcopenia
No mobility disability
Probable few benefits from interventions against disability
SPPB between 3/12 and 9/12
Sarcopenia
No mobility disability
Possible interventions for PREVENTING disability
SPPB <3/12
Sarcopenia (cachexia?)
Mobility disability
Possible interventions for TREATING disability
Exhaustion of endogenous reserves for restoring robustness
Limit posed by the SPPB impairment
PF&S
Limit posed by the mobility disability

Population to treat in SPRINTT

Relevance to future drug trials

- Two potential populations for drug trials:
  - Patients with existing mobility disability and sarcopenia
  - Patients with sarcopenia but no mobility disability (yet)
- Prevention of mobility disability is a key public health goal for elderly populations
- Physical activity is expected to be synergistic – and perhaps required – for most drugs in this area/indication to be fully effective
- It seems more difficult to reverse rather than prevent mobility disability
- Therefore, the first point of entry for drug treatment of sarcopenia should be to PREVENT mobility disability
  - The population of patients with sarcopenia but no mobility disability is appropriate
  - 400 m walk test is an appropriate primary endpoint for this population

Clinical Study implementation and Operations

SPRINTT
Sarcopenia & Physical fRailty IN older people: multi-componenT Treatment strategies

DIAGNOSIS AND CRITERIA FOR SELECTION, EXCLUSION, AND INCLUSION OF PARTICIPANTS IN THE SPRINTT CLINICAL TRIAL

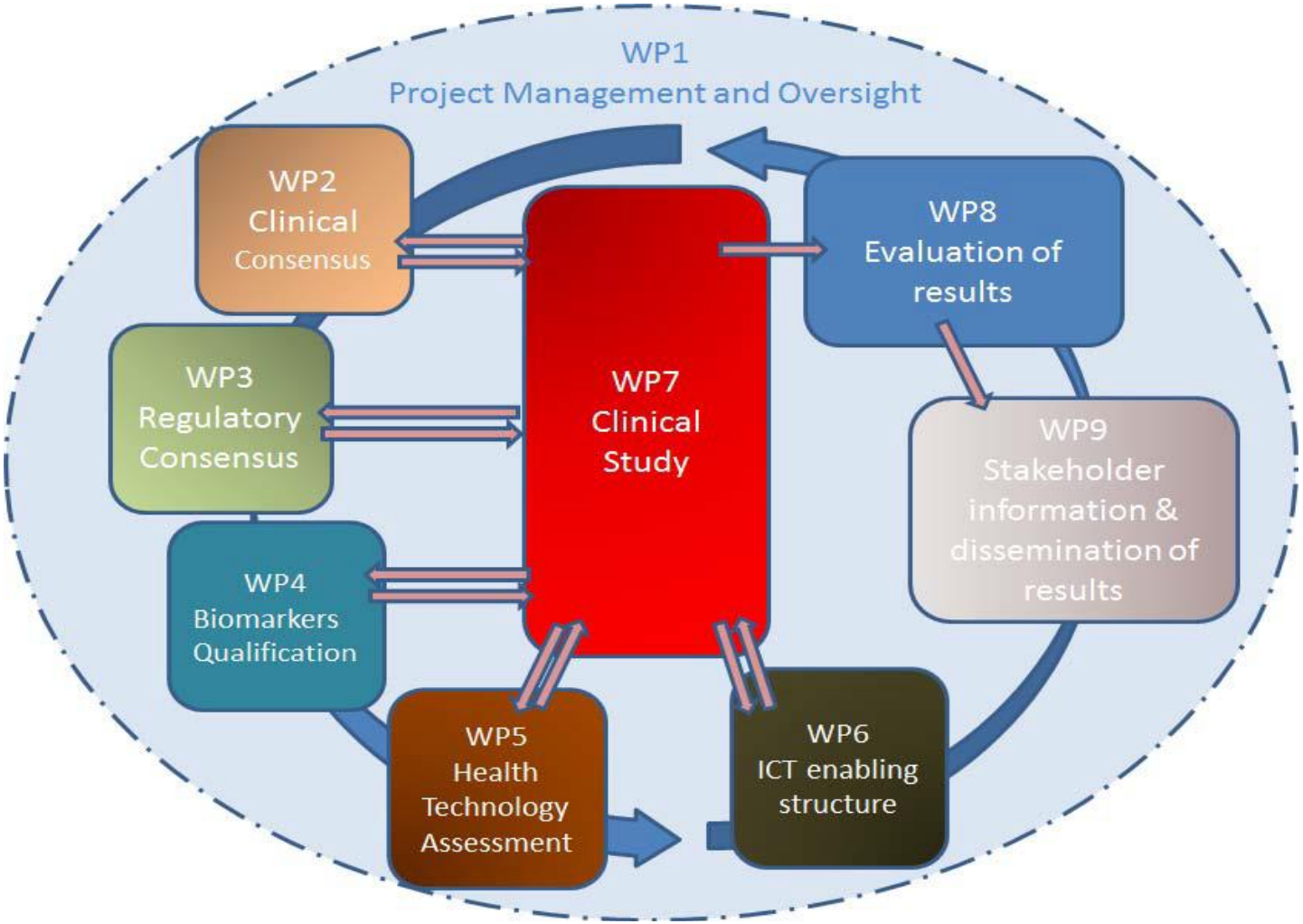
Sprintt
CLINICAL TRIAL

efpia

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

imi
Innovative Medicines Initiative

Clinical Study implementation and Operations



Clinical Study implementation and Operations

- **1500 patients**
- Patient Follow up : **24 months**
- 14 sites
- 11 European Countries
- 7 regional areas

9 backup sites

Pre-selected study site

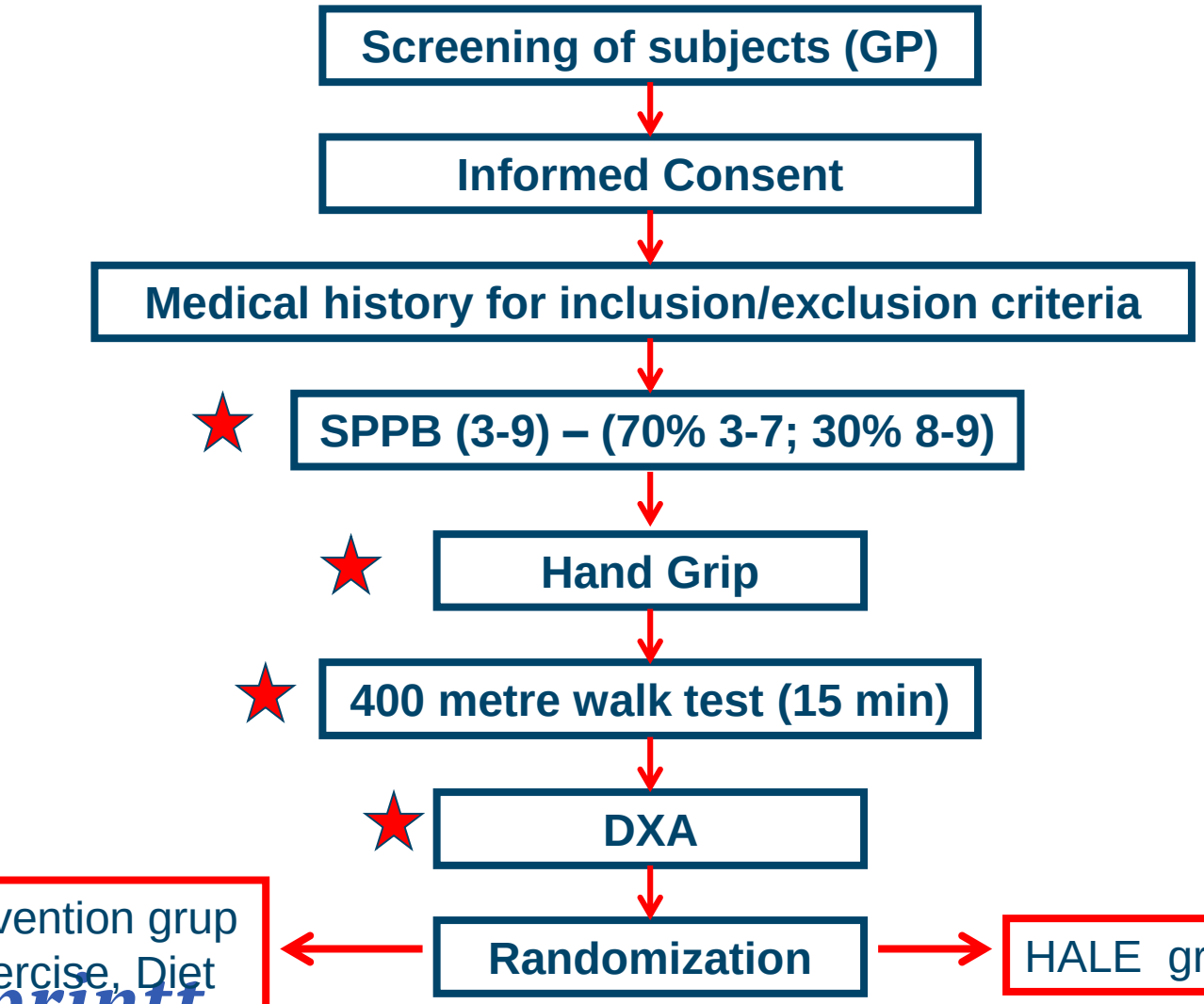
Backup study sites

Sprintt
CLINICAL TRIAL

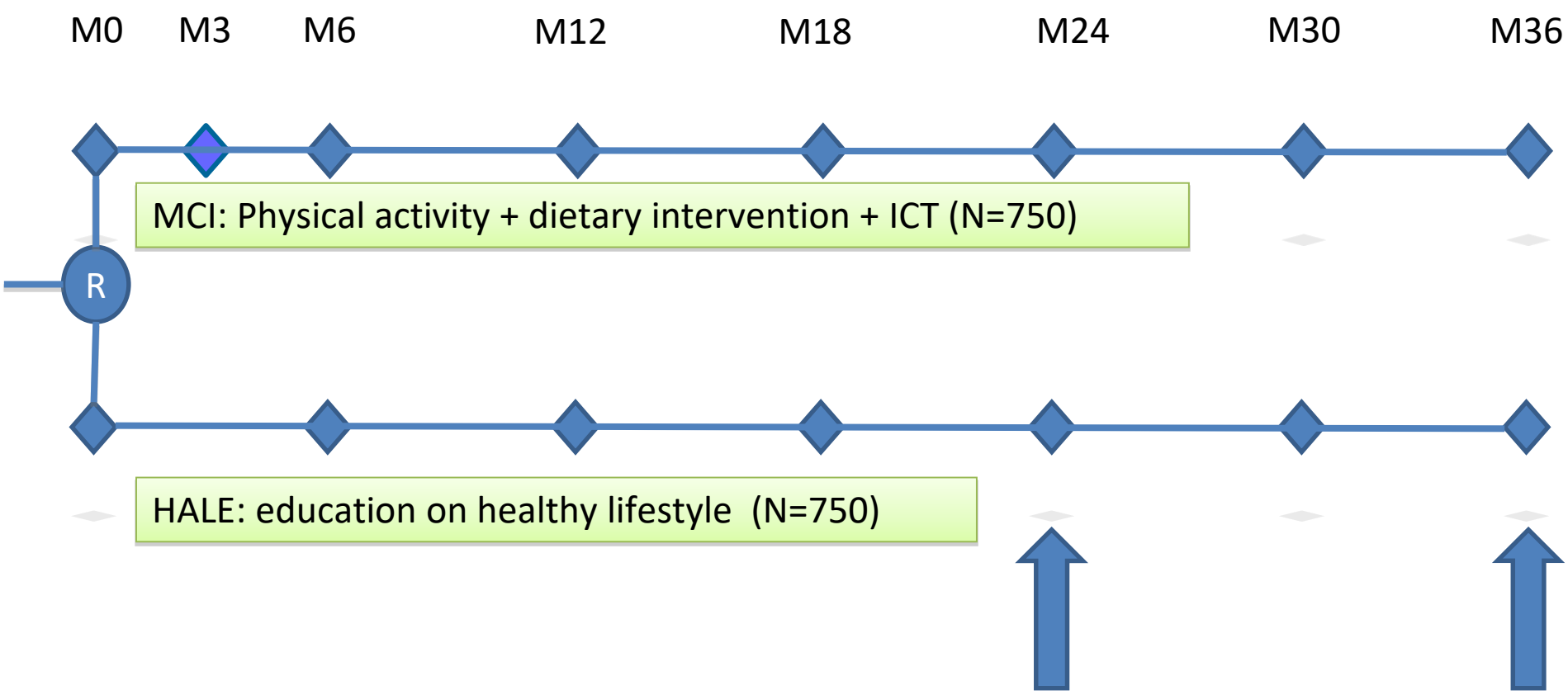
SPRINTT RCT

- 1,500 community-dwellers, aged 70+ years
- Low muscle mass (DXA, FNIH)
- SPPB 3-7 (n = 1,200) and 8-9 (n = 300)
- Able to walk 400 metres at usual pace in 15 minutes
- Two treatment arms: multicomponent intervention and successful aging programme

Clinical Study implementation and Operations



SPRINTT RCT chart



Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Multi-Component Intervention (MCI)

Physical activity intervention

Structured exercise and PA (LIFE study protocol)

Nutritional assessment and dietary intervention

Personalised dietary recommendations

Health technology intervention

Remote monitoring of daily physical activity, walk speed, falls, support for nutritional counselling, reinforcement of intervention compliance

Conclusions

- ✓ A two-step approach: initial hypotheses for generating clinical data; refinement of the target population based on results of the randomized clinical trial
- ✓ Key messages
  - ✓ Rationale: Prevention of disability in the older people is a key public health goal and fulfills a major unmet medical need
  - ✓ Definition of population: Functionally impaired with target organ deterioration (physical frailty and sarcopenia)
  - ✓ Entry: the proposed eligibility criteria defines a population at high risk of disability but not yet irreversibly disabled
  - ✓ Endpoint: 400 m walk defines mobility disability, predicts broader disability (ADL, IADL) and death
  - ✓ Impact: The population will have direct relevance to drug trials, will define the « comparator » intervention effect size, and will inform how to approach sicker populations as well

Theoretical model of PF&S treatment

Possible future perspectives

SPRINT-T