Developing Innovative Therapeutic Interventions against Physical Frailty and Sarcopenia (ITI-PF&S) as a Prototype Geriatric Indication

Webinar

July 1, 2013

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My today presentation:

- Why do we need innovation in Geriatrics?
- Key Objectives of the IMI Physical Frailty&Sarcopenia project
- Workpackages and Requirements to the candidate Consortia
- Questions&Answers

Acknowledgements:

Ram Miller and Bill Evans

Ronenn Roubenoff

Frailty is an Unmet Medical Need of Older Patients

An opportunity for Innovation

Background

- Ageing societies are an emerging and seemingly irrevocable trend in Europe, but also in the US, Japan and China. The number of Europeans aged 65+ will almost double over the next 50 years, from 85 million in 2008 to 151 million in 2060.
- This trend represents a challenge for public authorities, policy makers, healthcare providers and payers by increasing the demand of healthcare products and services. Optimal use of resources is an issue, as we lack today of an efficient model of care for this segment of the general population, to contain raising costs and inappropriate use of resources.
- However, the existence of **regulatory gaps** hampering innovative development in geriatric medicine has been acknowledged in the frame of the Active & Healthy Aging pilot project launched by the European Commission in 2011.
- In that frame, a Workshop on **Frailty in Old Age: a public health concern at EU level** was held in Brussels on April 18, 2013.

Regulators' point of view

Frailty is a predictor of clinical outcomes, and the reduction of frailty has benefits for individuals and society.

The EMA is exploring the possibility of reaching a consensus on an operational definition of frailty and tools for evaluating it that could be used for clinical research and to guide therapeutic decisions.

NEJM perspective 2012_EMA.pdf

N Engl J Med. 2012 Nov 22;367(21):1972-4.

European Innovation Partnership (EIP) on Healthy & Active Ageing

- **EU2020**
  - **Smart, sustainable**, inclusive growth
    - 75% of the **20-64 year-olds to be employed**
    - **3% of the EU's GDP to be invested in R&D**
- **INNOVATION UNION**
  - **Refocusing** R&D and innovation policy on major challenges for our society **& launch of new European Innovative partnerships (e.g. health and demographic change)**
  - **Strengthening every link in the innovation chain**, from research to commercialization

To add 2 Healthy Life Years (*EU average of HLY at birth)*

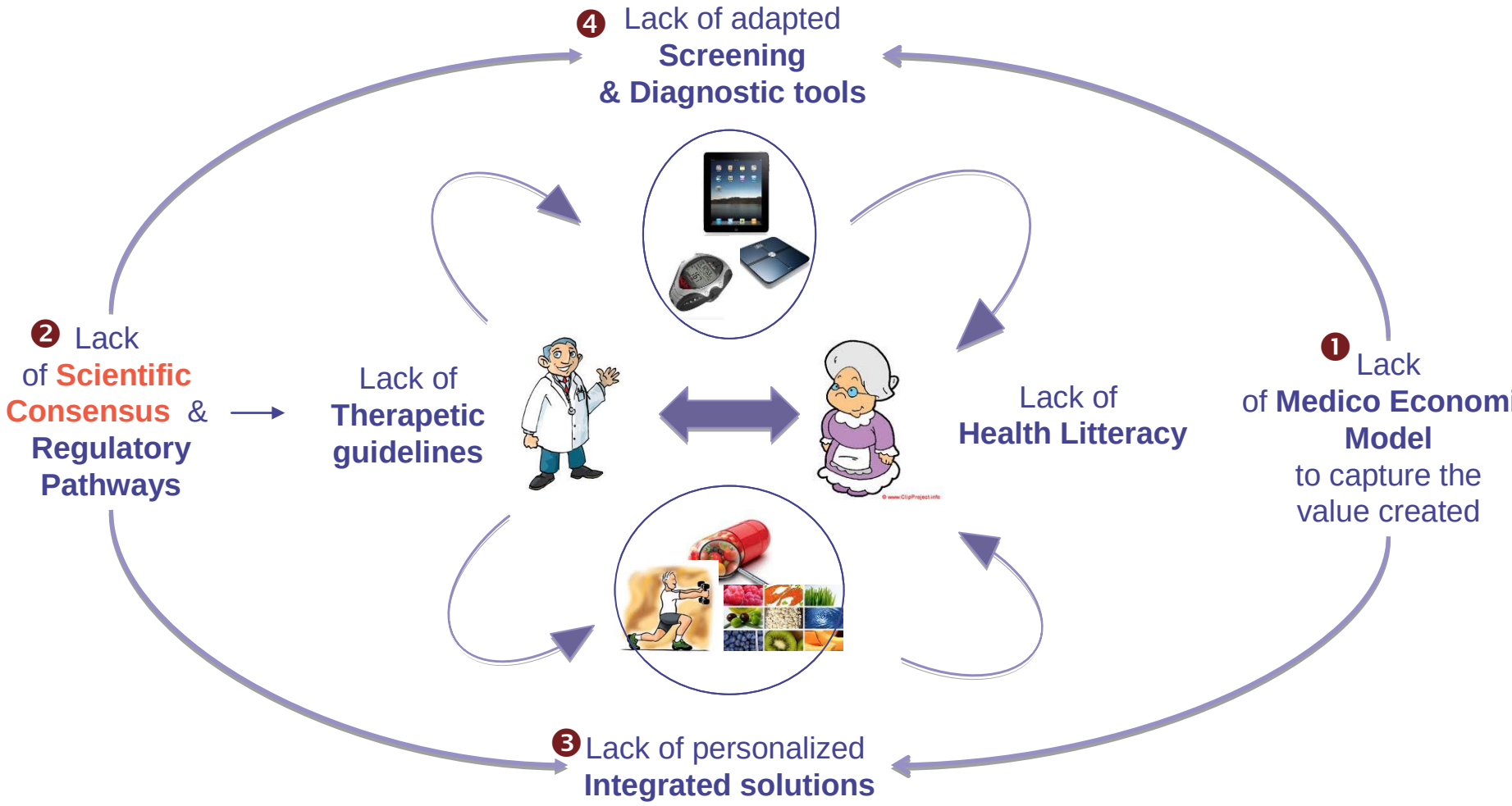
3 targets

- EU citizens **healthier, more active & independent until old age**
- Social & health care systems **more sustainable, dynamic & efficient**
- Competitiveness & market growth **of innovations in ageing sector fostered**

3 areas of actions

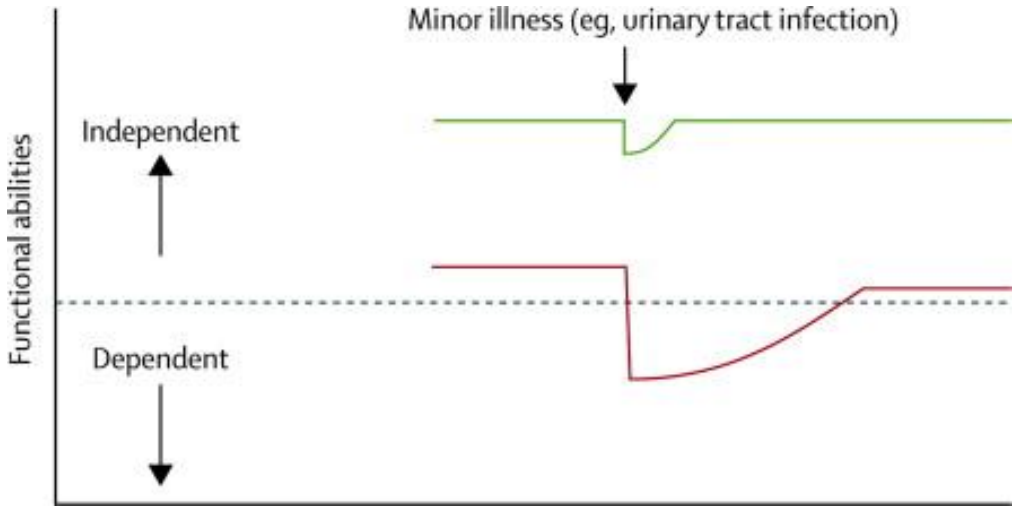
- **Prevention & early diagnosis (includes Frailty)**
- **Cure & Care**
- **Independent living & Ageing**

Gaps exist in the current management of Frailty



Frailty in older persons

- Frailty is a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability.



Andrew Clegg et al, Lancet 2013; 381:752-62

Frequent clinical presentations of Frailty (1)

Non-specific

- Extreme fatigue, unexplained weight loss, and frequent infections.

Falls

- Balance and gait impairment are major features of frailty, and are important risk factors for falls. A so-called hot fall is related to a minor illness that reduces postural balance below a crucial threshold necessary to maintain gait integrity. Spontaneous falls occur in more severe frailty when vital postural systems (vision, balance, and strength) are no longer consistent with safe navigation through undemanding environments. Spontaneous falls are typically repeated and are closely associated with the psychological reaction of fear of further falls that causes the patient to develop severely impaired mobility.

Andrew Clegg et al, Lancet 2013; 381:752-62

Frequent clinical presentations of Frailty (2)

Delirium

- Delirium (sometimes called acute confusion) is characterised by the rapid onset of fluctuating confusion and impaired awareness. Delirium is related to reduced integrity of brain function and is independently associated with adverse outcomes. Roughly 30% of elderly people admitted to hospital will develop delirium, and the point prevalence estimate for delirium for patients in long-term care is 15%.

Fluctuating disability

- Fluctuating disability is day-to-day instability, resulting in patients with ”good”, independent days, and ”bad” days on which (professional) care is often needed.

Andrew Clegg et al, Lancet 2013; 381:752-62

The five phenotype model indicators of Frailty and their associated measures

Weight loss

- Self-reported weight loss of more than 4.5 kg or recorded weight loss of ≥5% per year

Self-reported exhaustion

- Self-reported exhaustion on US Center for Epidemiological Studies depression scale (3–4 days per week or most of the time)

Low energy expenditure

- Energy expenditure <383 kcal/week (men) or <270 kcal/week (women)

Slow gait speed

- Standardised cutoff times to walk 4.57 m, stratified by sex and height

Weak grip strength

- Grip strength, stratified by sex and body-mass index

Frailty models lead to a unified construct

- Reliable frailty models should be assessed by their success in predicting both natural history and response to therapeutic interventions and should be underpinned by biological principles of causality.
- The two main emerging models of frailty are the **phenotype model** described by Linda Fried in 2001 and the **cumulative deficit model**, which forms the basis of the Canadian Study of Health and Aging (CSHA)frailty index.
- Both models show overlap in their identification of frailty and have notable statistical convergence.
- The demonstration of **convergent predictive validity for adverse health outcomes** between two conceptually different models of frailty could help to advance the debate about whether frailty is best defined as a syndrome or a state by providing support for recognition of **the condition as a unified construct.**

Sarcopenia

- **Frail skeletal muscle (sarcopenia)** has been defined as progressive loss of skeletal muscle mass, strength, and power, **and is regarded as a key component of frailty.**
  - **Loss of muscle strength and power could be more important than changes in muscle mass.**
  - **Under normal circumstances, muscle homoeostasis is maintained in a delicate balance between new muscle cell formation, hypertrophy, and protein loss.**
  - **This balance is coordinated by the brain, endocrine system, and immune system, and is affected by nutritional factors and amount of physical activity.**

Lancet. 2013 Mar 2;381(9868):752-62.

Next step should be prevention

- More recent work suggests that the overlap is more frequent and increases with greater frailty.
- The contribution of subclinical disease might be especially important, and physiological measurements to identify elderly people at risk of frailty could help to guide the **development of early preventive interventions**.

Arch Gerontol Geriatr, 55 (2012), pp. e1–e8
J Am Geriatr Soc, *59* ***(2011), pp. 1581–1588***

Frailty, an area of unmet needs

Increased vulnerability to stress

- Accumulation of deficits
- Associated decreased physiological reserve
- In multiple, interacting complex systems

Increased incidence of adverse outcomes

- Falls & Fractures
- Delirium
- Hospitalizations & Institutionalization
- Disability & Death
- Greater use of health care services

Prevalence in the EU (SHARE)

Age 50-64 : Pre-frailty: 37.4% , Frailty: 4.1%

Age 65+ : Pre-frailty: 42.3% , Frailty: 17.0%

A potentially reversible condition

- **Recovery to relatively fittest state common at younger ages**
- **Chance of complete recovery declines with age**

Baseline Frail status predicts outcome

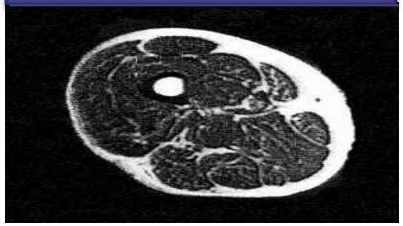
Outcome	Hazard Ratio
Incident Fall	1.29
Worsening Mobility	1.50
Worsening ADL Disability	1.98
Hospitalizations	1.29
Death	2.24

Estimated yearly cost of Sarcopenia

Osteoporotic fractures

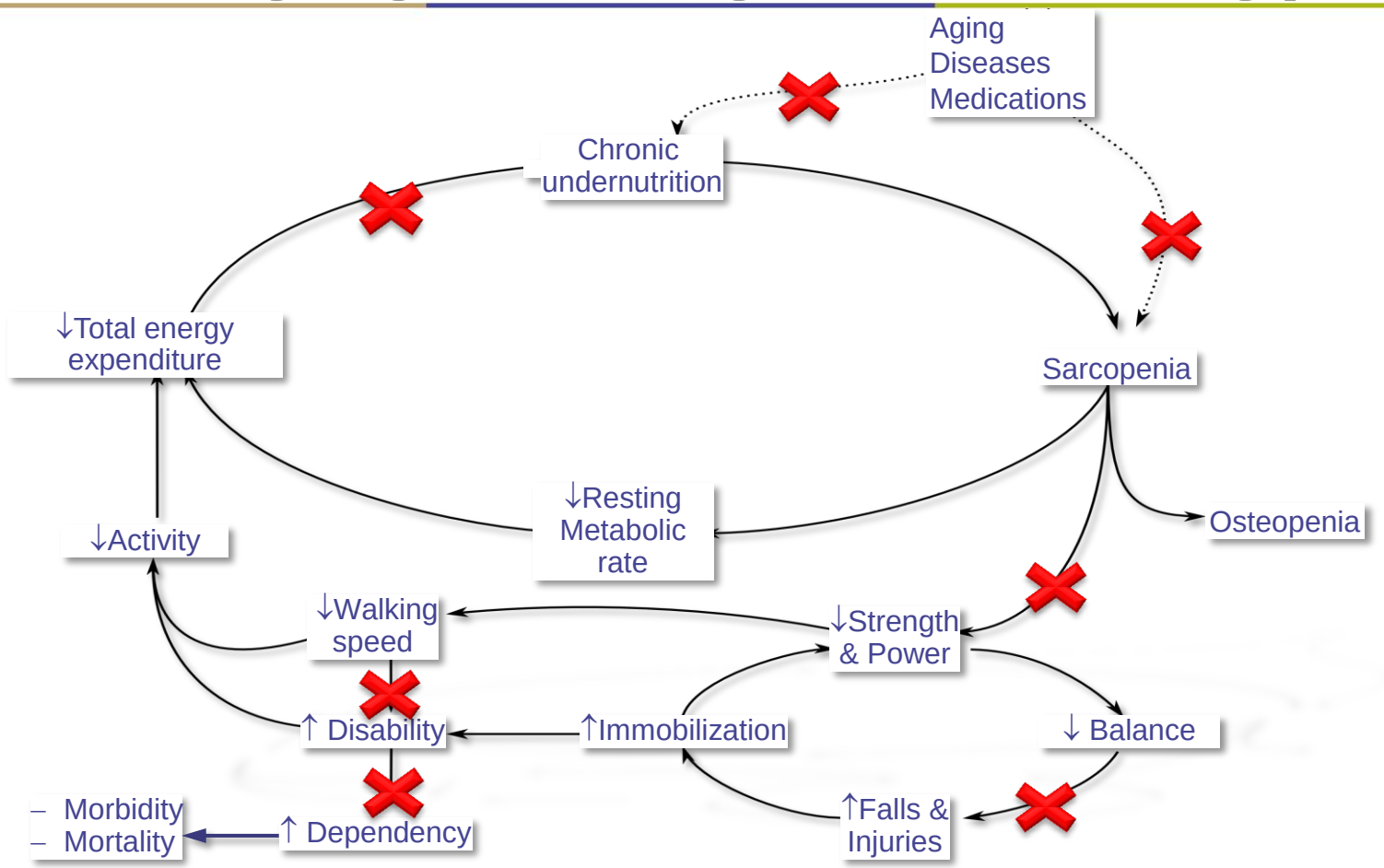
$16.3 billion

Sarcopenia



$18.5 billion

The Frailty Cycle – Physical Phenotype



Modified from Fried LP et al. J of Gerontol 56:M146; 2001

Topics under consideration for IMI's 9TH CALL FOR PROPOSALS are (as of June 25, 2013):

Innovative Medicines Initiative

- *Leveraging technologies for pharmacovigilance*
- ***Physical frailty and sarcopenia****
- *Developing drug-drug combinations*
- *Antimicrobial resistance*

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

Innovative Medicines Initiative

SANOFI

GlaxoSmithKline

NOVARTIS

Lilly

ITI-PF&S
OUTLINES and KEY OBJECTIVES

Qualification of biomarkers and adapted clinical methodologies for the regulatory development of innovative interventions against Physical Frailty and Sarcopenia (PF&S) in at-risk Older Persons, to prevent or delay mobility disability and its consequences, is the overarching objective of this IMI project, including:

- Development of an **operational definition of at-risk subpopulations (1)** with undisputable therapeutic need;
- **Qualification of biomarkers (2)** of muscle **anabolism and catabolism** and indicators of **muscle function** in at-risk sub-populations and their correlation with major outcomes;
- Development of advanced therapeutic approaches in preclinical settings
- **Implementation of innovative clinical development methodologies (3)** for testing integrated interventions for the prevention of PF&S and consequent mobility disability;
- **Scientific and Regulatory Consensus** on these three elements.

Expected key deliverables

- **Delineate and agree with regulators the regulatory framework for a sustainable development of innovative geriatric indications that will respond to specific unmet therapeutic needs**

ITI-PF&S In Practice

Generate longitudinal data in older persons at-risk of frailty and sarcopenia in order to determine/qualify:

- **Specific population**, specific therapeutic/preventative **targets** suitable for regulatory appraisal
- Adapted **clinical trial methodologies**, including **biomarkers**, functional endpoints, **ICT** based data capture paradigms and applied biostatistics
- Economic savings in terms of public health costs
- Adapted, innovative & sustainable R&D development models

Work Package 1

Project Management and Oversight

- This Work Package will address the strategy and implementation of the project management. This will encourage regular meetings and interaction between sub-groups and teams, to coordinate and follow up on the work effort.
- EFPIA contribution: Project Management including planning, budgeting, follow up and tracking, and consolidation of Work Package reports. Project risk management and comprehensive communication and dissemination of its progress and its milestones are important additional elements of EFPIA contribution.
- Expected Applicant consortium contribution: providing detailed follow up and tracking, via regular Work Package reports, early report of any unexpected organisational or structural issue or delay with respect to the project deployment and intermediate objectives.

Work Package 2

Clinical Consensus over Indication, Target Population and Clinical Trial Design for Data Generation

- Academia, EFPIA, Patients & Carers Representatives and Health Care Professionals will jointly contribute to the overall evaluation of currently available evidence **to set up the scientific consensus necessary to support sound operational definitions**
- EFPIA contribution: providing a reliable and feasible operational setting for implementation, in keeping with member companies consolidated expertise and preliminary data made available
- Expected Applicant consortium contribution: build up and consolidation of the scientific consensus necessary to support sound operational definitions in term of sought indication, population and clinical trial designing for longitudinal data generation.

Work Package 3

Regulatory Consensus over operational definitions

- Regulators, EFPIA, Academia, and Patients Representatives will jointly contribute to the overall evaluation of evidence and results from WP 2.
- EFPIA contribution: planning, hosting and organizing workshop(s) with regulators, contributing to discussion of available evidence (including unpublished data), literature analysis, publication support, (co-)authoring of reviews and white paper(s).
- Expected Applicant consortium contribution: participate, actively contribute to **constructive discussion with regulators to promote and achieve regulatory consensus over operational definitions**. (Co)-authoring of reviews and white paper(s).

Work Package 4

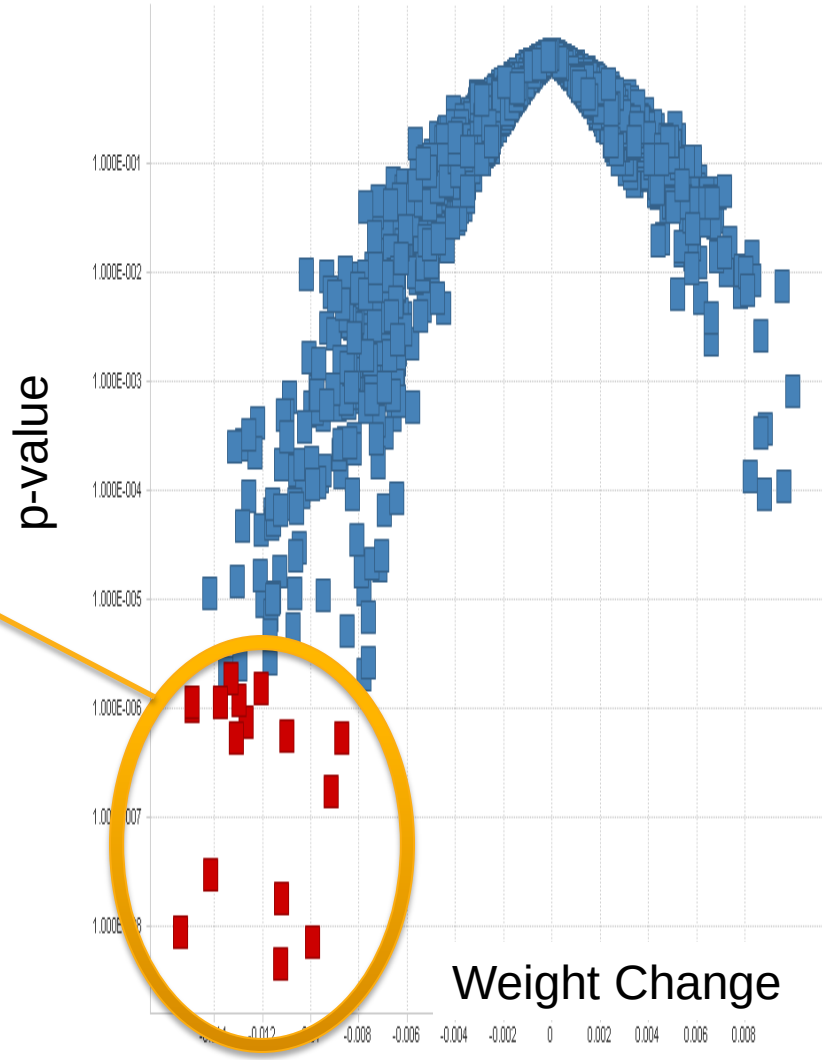
Biomarkers qualification

- Regulators and Academia will be invited to jointly contribute to the **qualification pathway definition and requirements** during the initial consultation phase of the project, in order to allow preliminary agreement on the protocol design.
- EFPIA: biomarkers operational deployment; member companies will provide specific expertise, investigational/diagnostic products, related centralised bioanalytical facilities, will set up operations, deliver results and reports.
- Expected Applicant consortium contribution: scientific clinical expertise and biomarkers pathway per protocol implementation in the predefined population.

Biomarkers of weight loss in elderly adults with cancer

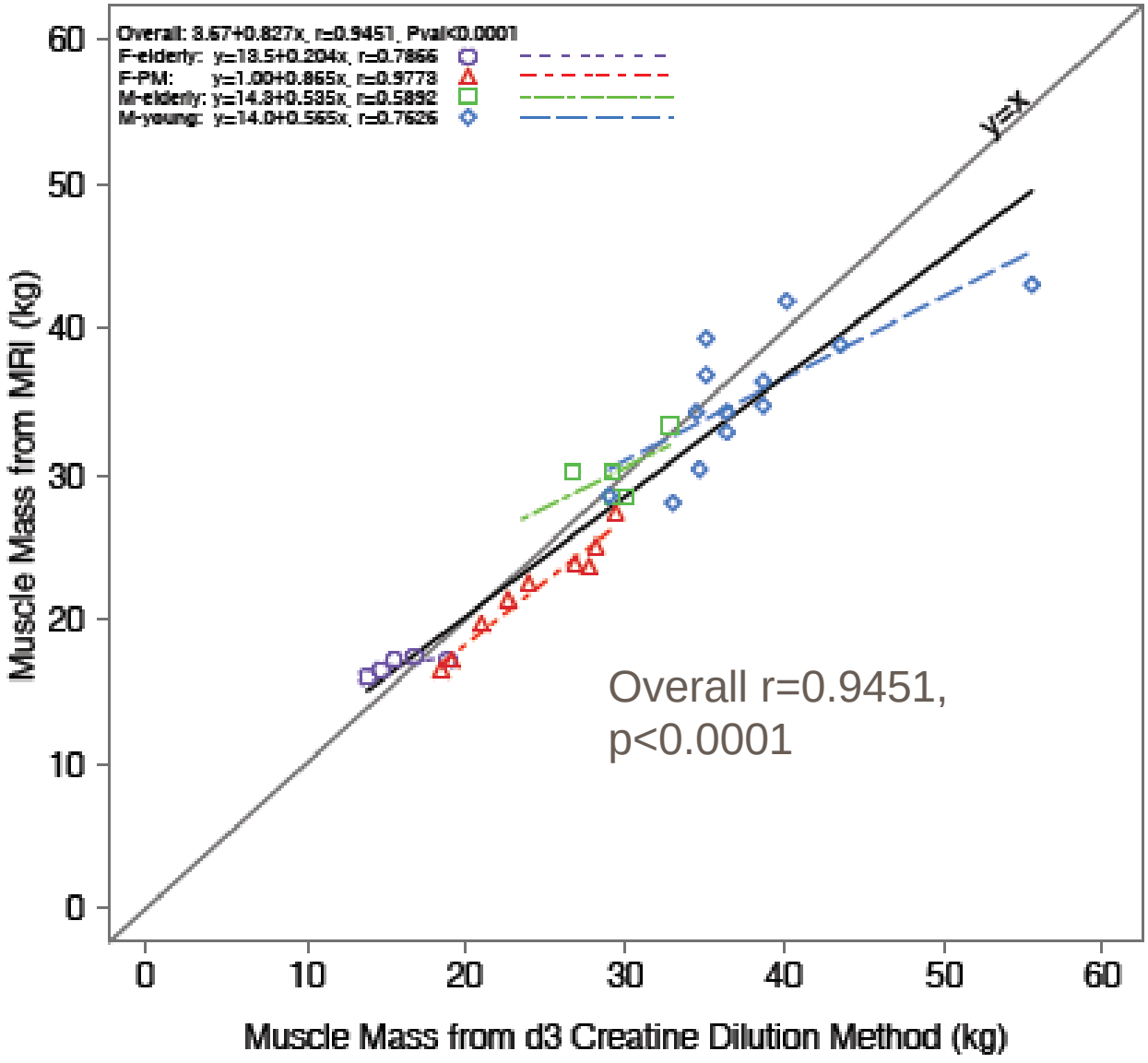
Assessment of utility for frailty and sarcopenia

- Discovery data set: Patient samples
  - 23 > 10% weight loss (8 GI cancers, 13 pancreas, 1 duodenum, 1 small bowel);
  - 32 < 10% weight loss (22 GI, 9 pancreas, 1 pancreas/duodenum);
  - 8 healthy controls
- Analysis
  - LC-MS/MS
  - Identification of peaks present in weight loss patients but not in patients without weight loss
- Preliminary results – autoantibody, proteases, inflammation markers were identified as potential markers. Verification/validation is required to firm up the results.
- Validation –
  - In additional patients with cancer cachexia – now in progress
  - In other indications – COPD (with COPD MAP consortium), sarcopenia (with IMI) planned



NOVARTIS

Scatterplot of MRI Total Muscle Mass vs Muscle Mass from d3 Creatine Dilution Method
Overall Regression Line with P-Value



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Measurement of Protein Synthesis in vivo with ^2H_2O

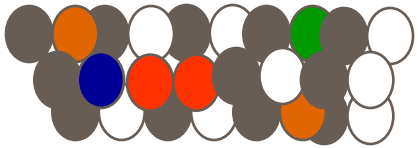
1) ^2H_2O drinking water given to animals or humans

^2H_2O

^{2}H-Alanine:
^{2}H-Cysteine
^{2}H-Cystine
^{2}H-Glutamine
^{2}H-Glutathione
^{2}H-Glycine
^{2}H-Histidine:
^{2}H-Serine:
^{2}H-Taurine:
^{2}H-Threonine:
^{2}H-Asparagine:
^{2}H-Apartic acid:
^{2}H-Proline:

2) ^{2}H labels non essential amino acids during normal metabolism

3) ^{2}H-amino acids are incorporated into proteins during synthesis



4) % of ^{2}H label in proteins is proportional to the % of new protein

- The amount of labeling of each AA depends on the number (n) of C-H bonds which exchange with body water
- Total label incorporated into a peptide is the sum of the individual AA n's
- **Synthetic rate can be determined for many individual, specific proteins in a single study**

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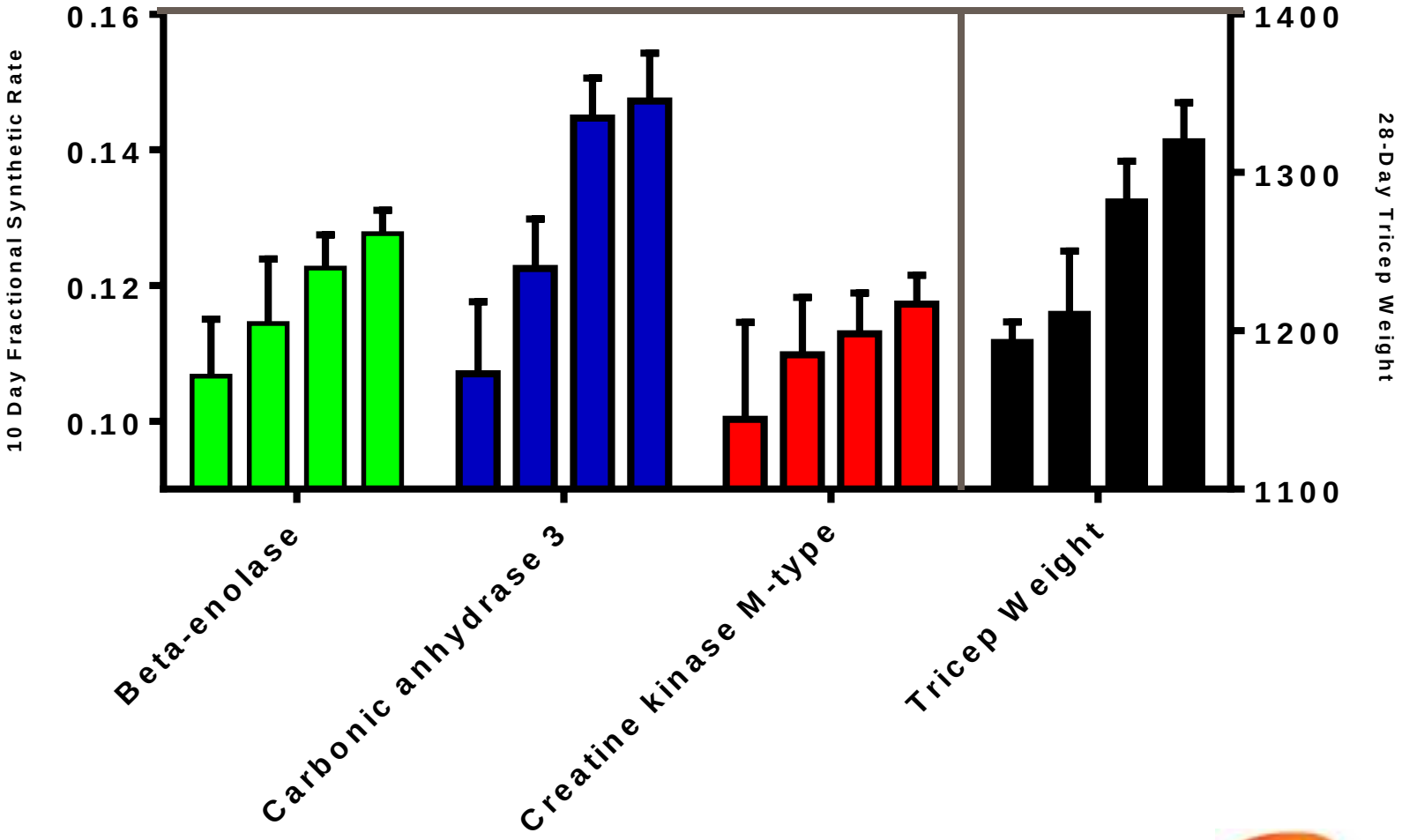
10-day Fractional Synthesis Rates predict 28 day triceps weights



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Work Package 5

Health Technology Assessment

- HTA Representatives will jointly contribute to the **definition of relevant outcomes during the methodology consolidation phase**, and to the overall evaluation of collected evidence and results at the end of the study.
- EFPIA contribution: Literature analysis, publication support, (co-)authoring of review and white paper(s), hosting and organizing workshop(s).
- Expected Applicant consortium contribution: participate, actively contribute to constructive discussion with HTA representatives to achieve consensus over operational definitions. (Co)-authoring of reviews and white paper(s).

Work Package 6

ICT enabling infrastructure and operations

To provide the operational definition and implementation of **a state-of-the-art ICT platform,** enabling optimal data capture in conditions adapted and customized to older persons living in the community. This should include integrated sensing/telemonitoring systems complementing standard clinical data collection and data management.

- The participation in the Applicant Consortium of an Information and Communication Technologies (ICT) established SME with proven expertise in the field of geriatric applications and large database management seems appropriately required.
- EFPIA: definition of ICT, data capture and data warehouse requirements adapted to the clinical trial final design;

Work Package 7

Work Package 7: Clinical Study implementation and operations

- EFPIA and Academia Experts have identified during an *ad hoc* preparatory workshop a set of operational objectives to be met by a randomized controlled clinical trial. The rationale for the clinical trial is aligned with the scientific community, state of the art knowledge of frailty in older persons and takes also into consideration elements that emerged from the public debate currently underway in the frame of Active and Healthy Aging, European Commission initiative. Outlines are presented and should be considered as indicative.
- The final design of the randomized Clinical Trial will be agreed with EFPIA partners at the Full Project Proposal stage.

Work Package 8

Evaluation of results (includes Data Analyses and Hypothesis generation)

Academia, Regulatory Authorities and specifically the European Medicines Agency and its Experts, EFPIA via the member companies Experts **will collaboratively review the clinical trial results in order to draw the necessary clinical and regulatory conclusions.**

- EFPIA: planning, hosting and organizing workshop(s) with regulators; contributing to results discussion via its Experts (including biostatisticians); providing technical support (translations, etc.); (co-)authoring of reviews and white paper(s).
- Expected Applicant consortium contribution: participate, actively contribute to **constructive discussion with regulators to achieve scientific and regulatory agreement us over the interpretation of study results.**

Work Package 9

Stakeholder information and results dissemination

- Academia, Regulatory Authorities, EFPIA, Healthcare professionals, Patients representatives will contribute over the 5- year project duration **to health literacy planned actions**, project awareness, project milestones presentation to stakeholders and media as appropriate.
- EFPIA: logistics and organisational support, contribution of experts as appropriate; providing technical support (translations, etc.); this will include a dedicated website and organisation of milestone workshops for stakeholders (and the general public as appropriate).
- Expected Applicant consortium: provide the scientific and medical content for health literacy elements building, consolidation and update over the project duration; provide personal and collegial contribution to the dissemination program implementation; authoring main papers in peer reviewed scientific journals.

The Randomized Clinical Trial

Innovative **T**herapeutic **I**ntervention against physical **F**railty and **S**arcopenia, a European Study in Older Persons living in the Community as a Prototype Geriatric Indication:

ITI-PF&S

A multi-center*, randomized clinical trial.

**each center corresponding to a catchment area in the community in 5-6 participating EU Member States, and in one US comparative catching area*

ITI F&S: Operational (primary) objectives

- To evaluate and compare health changes in the study groups over 2-year intervention in order **to correlate chosen biomarkers with physical frailty&sarcopenia major outcomes**
- The incidence of Physical Frailty status defined according to Fried phenotype criteria (or a predefined Short Physical Performance Battery cut-off)

ITI PF&S: Secondary objectives (1)

- The incidence of major mobility disability (defined as inability to walk 400m or usual gait speed < 0.8 m/s)
- The incidence of falls, “near falls”, and of serious fall injuries (non-vertebral fractures)
- Changes in nutritional status (measured by Body Mass Index, anthropometric measures, and body composition parameters [estimated by dual energy X-ray absorptiometry]
- Changes of physical performance (measured by the Short Physical Performance Battery score and gait speed)
- Validation of novel biomarkers for changes in skeletal muscle mass, and functional capacity in older men and women.
- Ability of biomarkers to predict rate of change in muscle mass and functional capacity
- Modifications of sarcopenia (defined according to the European criteria)

ITI PF&S: Secondary objectives (2)

- Changes in physical function (measured using the Pepper questionnaire, including ADL, IADL and mobility tasks)
- Changes in cognitive function (measured by the Mini Mental State Examination score) and mood (measured by means of the Geriatric Depression Scale)
- Health care utilization (emergency room admissions, hospitalizations, institutionalizations)
- Changes of quality of life, PRO specific for sarcopenia

ITI PF&S: Study design

- **Randomized comparative clinical trial** with a two arm intervention
  - **Under this Initiative, clinical longitudinal data will be generated by comparing two groups of older persons who will be randomized to a state-of-the-art integrated intervention against muscular function loss, centered on the administration of a standardized physical activity program, versus an integrated healthy aging counselling program without regular physical activity.**
  - **The Consortium will consider the opportunity for an add-on design with an investigational drug within the same investigational setting.**
- Duration of the study: 4 years
- Follow-up of participants: **2-year integrated intervention**; follow-up until operations are closed
- Sample size: to be calculated based on the estimated incidence of the finally selected major events in the chosen at-risk population

ITI PF&S: Inclusion criteria

- Age ≥70 years
- Summary score <8 on the Short Physical Performance Battery
- Sedentary lifestyle, defined by ≤125 min/week of activity on the CHAMPS-18 questionnaire
- Able to complete the 400-m walk test within 15 minutes at baseline without sitting, leaning, using a walker, or the help of another person
- Willingness to be randomized to either intervention group
- Living in the community with no project to relocate or moving to a nursing home

ITI PF&S: Exclusion criteria

- Unable or unwilling to give informed consent
- Acute or rapidly evolving conditions implying a life expectancy less than 6 months or necessitating heavy chronic treatment(e.g. dialysis, COPD, others)
- Temporary exclusion criteria:
- Planned surgical intervention or acute benign condition

NB: **Diabetes , hypertension, common cardiovascular conditions (except valvulopaties), cancer in clinical remission, etc. are not exclusion criteria**

ITI PF&S: Study interventions

Physical activity (PA) program

The PA intervention includes **structured exercise and PA**, includes aerobic, strength, flexibility, and balance training

Health Literacy (HL)

Addressed mainly to the older person but involves the General Practitioner and carers

Nutritional Intervention (NI)

Includes anthropometric measurements, nutritional risk assessment, body composition, and dietary assessment

ICT intervention

Includes data capture and sensoring devices based at patient's home, integrated with more traditional data collection by the study personnel.

Expected contribution of the applicant Consortium (1)

- State-of-the-art expertise in the field of geriatrics, physical frailty and sarcopenia ; capacity to provide specific expertise and supporting objective elements to the clinical, regulatory and HTA table of discussions;
- Geographic capacity to implement the project and specifically the Clinical Trial in at least 5 EU Member States;
- Capacity to establish for all the investigational centres an efficient, representative territorial network to reach older patients living in the community and eligible to the clinical trial, also in collaboration with General Practitioners, Orthopaedists, other Health Care Professionals as appropriate, and informal carers/family;
- Capacity and availability of clinical and care facilities, adequate trained physicians and specialised personnel to implement the clinical trial protocol;

Expected contribution of the applicant Consortium (2)

- Functional capacity for effective interfacing with ICT specialists in order to speed all enabling operations;
- Provide the contribution of an Information and Communication Technologies (ICT) established SME with proven expertise in the field of geriatric applications and large database management;
- Provide and effectively inject scientific and medical knowledge throughout the project, including health literacy content;
- For the Consortium Experts to adequately populate in person and via validated content and regular reporting the tracking of project implementation and the progress of the randomized clinical trial and of its confluent work streams;
- Provide a risk management plan for the RCT and its results;
- Populate in person and via validated content the dissemination work stream as appropriate.

Questions&Answers

Gaps identified*

From the **regulatory** point of view:

- **no current consensus over the operational definition of Physical Frailty/Sarcopenia**.
- **insufficient definition of the target population(s) for clinical development**, spanning from at-risk population to meaningfully impaired subgroups of older patients,
- uncertain regulatory status **functional end-points**, **and biomarkers,** for designing confirmatory clinical trials.
- to utilize tests and techniques that will be replicable in the standard clinical practice and in real life conditions.

**hampering clinical development of innovative indications for older patients*

Are frailty, comorbidity and disability overlapping?

The CHS study population was used to investigate the overlap between frailty, comorbidity, and disability.

- Frailty and comorbidity (defined as two or more of the following nine diseases: myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, and chronic obstructive pulmonary disease) was present in 46·2% of the population;
- Frailty, and disability (defined as the presence of restriction in at least one activity of daily living) was present in 5·7%;
- The combination of frailty, disability, and comorbidity in 21·5% of the study group.
- Importantly, **frailty was present without comorbidity or disability in 26·6% of the study group**, which provides support for frailty as an independent factor that is distinct from comorbidity and disability.

Prevalence of frailty

- According to a recent systematic review (21 community-based cohort of 61 500 elderly people) in studies that used the phenotype model the weighted average prevalence rate was:

  9·9% (95% CI 9·6–10·2) for frailty

  and 44·2% (44·2–44·7) for pre-frailty.

- In 11 studies, frailty was statistically more prevalent in women:

  (9·6%; 9·2–10·0) than in men (5·2%; 4·9–5·5).

- Frailty increased steadily with age:

  65–69 years 4%;

  70–74 years 7%;

  75–79 years 9% ;

  80–84 years 16%;

  older than 85 years 26%.

Lancet 2010; **375:** 773–75..

A **prototype** innovative geriatric indication

- Physical Frailty/Sarcopenia (PF/S) in Older persons is an unmet therapeutic need and represents as well a powerful model of a geriatric condition with measurable impact on healthcare expenses. In facts (PF/S) often progress to mobility disability, which is a common cause of increased morbidity (including falls and fractures), loss of autonomy, frequent/inappropriate healthcare use, and nursing home admission.

- Interestingly, **some key components of physical frailty like the loss of muscular mass and muscular function can be reversed**, e.g. through physical activity and nutritional supplementation and secondary mobility disability avoided or postponed, generating important savings.

- Therefore **treating or preventing this geriatric condition** offers an opportunity to the pharmaceutical industry and all stakeholders to develop **innovative therapeutic approaches**:

Frailty as a leading cause of death

- Evidence for the importance of frailty as a leading cause of death in elderly people comes from a 10-year prospective cohort study of community-dwelling elderly people (n=754).
- Cause of death was based on clinical home-based assessments done at 18-month intervals and on death certificates. **The most common disorder leading to death was frailty (27·9%);** the others were organ failure (21·4%), cancer (19·3%), dementia (13·8%), and other causes (14·9%).

TM Gill et al, Trajectories of disability in the last year of life; N Engl J Med, 362 (2010), pp. 1173–1180