

Growing the Silver Economy in Europe

Brussels, 23 September 2014

Clinical Development for Older Patients

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Scene setter - Keynotes

the potential of the silver economy

- **Clinical trials for the Ageing Population: Approaches to Ensure Safety and Efficacy of Medicines**
 - The example of Diabetes
 - The example of Vaccines
- **Unmet Medical Needs of Older Patients**
 - The example of Physical Frailty&Sarcopenia (PF&S)
- **Next Steps**

Confirmatory **Clinical Trials** in Older Adults : the **ICH E7 guidance**

- ❑ Older subjects can be included in the same phase3 confirmatory trials than younger adults, this in order to allow direct comparison of age groups within the same protocol.
- ❑ In 2009, a Q&A update partly lift this recommendation saying that the same phase 3 or a dedicated clinical trial are both acceptable options.
- ❑ **Adapting clinical trial methodology to geriatric patients** can provide the most effective means for collecting and documenting the clinical information that is relevant for the geriatric population:
 - in terms of efficacy by adding functional endpoints and quality of life
 - in terms of safety by establishing tailored detection of pre-identified events.

Ad hoc geriatric CTs can be appropriately integrate specific validated geriatric assessment tools. The CT design can be built around the older patient medical needs, driven by high comorbidity and loss of function.

This approach will decrease the risk of missing relevant characteristics of a product when administered to geriatric populations.

Ad Hoc geriatric Clinical Trials: the example of Diabetes type2

The first case is the conduction of a **dedicated clinical trial in 340 older patients suffering from Type2 diabetes** and receiving treatment with a GLP-1 receptor agonist.

- Hypoglycemia is a major treatment limiting factor in older patients with T2DM and that the risk of developing more severe symptoms associated with hypoglycemia (e.g., transient hemiparesis, coma, and falls), increases exponentially with aging.
- Nocturnal hypoglycemia seems also to be associated with increased dementia/decrease in cognition in this population.
- New types of anti-diabetic medicines, such as GLP-1 receptor agonists, may offer a valuable new therapeutic option in older patients. They provide a physiological blood glucose-insulin response associated with a low risk of hypoglycemia. GLP-1 receptor agonists have beneficial effects, such as delay of gastric emptying, reduction of appetite, and weight loss.

Ad Hoc geriatric Clinical Trials: 70 years and older T2DM patients



ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"

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Ad Hoc geriatric Clinical Trials: 70 years and older T2DM patients



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Primary Outcome Measures: Change from baseline in HbA1c [Time Frame: week 24]

Secondary Outcome Measures: Change from baseline in fasting Plasma Glucose (FPG)
Change in 2-hour PPG and plasma glucose excursions (2-hour postprandial plasma glucose - FPG) during the liquid standardized breakfast meal test from baseline

Change in 7-point Self-Monitored plasma glucose (SMPG) profile from baseline

Change in body weight from baseline

Change in total daily basal insulin dose from baseline for patients taking basal insulin

Percentage of patients requiring rescue therapy during the 24-week double-blind treatment period

Documented (PG <60 mg/dl) symptomatic hypoglycemia (percentage of subjects with at least one episode, number of events per patient-year) [Time Frame: week 24]

[Designated as safety issue: Yes]

Severe hypoglycemia [Time Frame: week 24] [Designated as safety issue: Yes]

Gastrointestinal side effects [Time Frame: week 24] [Designated as safety issue: Yes]

Ad Hoc geriatric formulations: the example of High Dose Influenza vaccine

A second case of **adapted clinical development** is the recent completion of a large clinical trial testing a high-dose vaccine for the prevention of seasonal influenza in older subjects.

- *The authors conducted a randomized, controlled, multicenter, phase II study to evaluate the immunogenicity and safety of an investigational intradermal (ID) trivalent influenza vaccine (TIV) and a high-dose (HD) intramuscular (IM) TIV in older adults (≥ 65 years of age).*
- **This project was based on the evidence that older adults are not only more susceptible to infections, but also less responsive to vaccination.** When infected with the influenza virus, in general they are less able to mount an effective immune response. Compared to younger adults they suffer disproportionately from seasonal influenza disease and its complications, including severe illness leading to hospitalization and death.
- This randomized CT has recruited and followed **more than 30 000 older persons (mean age 73.3 ± 5.8) suffering from common comorbidities.**



ORIGINAL ARTICLE

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., Avi Collins, B.Sc.N., Richard Pollak, D.P.M., Janet Christoff, R.N., John Earl, M.D., Victoria Landolfi, M.Sc., M.B.A., Earl Martin, D.O., Sanjay Gurunathan, M.D., Richard Nathan, D.O., David P. Greenberg, M.D., Nadia G. Tornieporth, M.D., Michael D. Decker, M.D., M.P.H., and H. Keipp Talbot, M.D., M.P.H.

Conclusions

- Among persons 65 years of age or older, IIV3-HD induced significantly higher antibody responses and provided better protection against laboratory-confirmed influenza illness than did IIV3-SD. (Funded by **Sanofi Pasteur**; ClinicalTrials.gov number, [NCT01427309](https://clinicaltrials.gov/ct2/show/study/NCT01427309).)

Ad Hoc geriatric formulations: the example of High Dose Influenza vaccine

Table 1. Baseline Demographic and Clinical Characteristics of the High-Dose and Standard-Dose Vaccine Groups.*

Characteristic	IIV3-HD (N = 15,990)	IIV3-SD (N = 15,993)
Female sex — no. (%)	9,131 (57.1)	8,963 (56.0)
Mean age — yr	73.3±5.8	73.3±5.8
Racial background — no. (%)†		
White	15,103 (94.4)	15,167 (94.8)
Asian	118 (0.7)	105 (0.7)
Black	670 (4.2)	612 (3.8)
Other	97 (0.6)	106 (0.7)
Hispanic ethnic group — no. (%)‡	958 (6.0)	982 (6.1)
At least one prespecified chronic coexisting condition — no. (%)‡	10,750 (67.2)	10,752 (67.2)
At least two prespecified chronic coexisting conditions — no. (%)	5,385 (33.7)	5,403 (33.8)
Cardiac and respiratory disorders — no. (%)		
Coronary artery disease	2,735 (17.1)	2,732 (17.1)
Atrial fibrillation	1,103 (6.9)	1,112 (7.0)
Valvular heart disease	744 (4.6)	741 (4.6)
Congestive heart failure	451 (2.8)	446 (2.8)
Chronic obstructive lung disease	1,500 (9.4)	1,495 (9.4)
Asthma	1,415 (8.8)	1,408 (8.8)
Received influenza vaccine the previous season — no. (%)	11,758 (73.5)	11,773 (73.6)

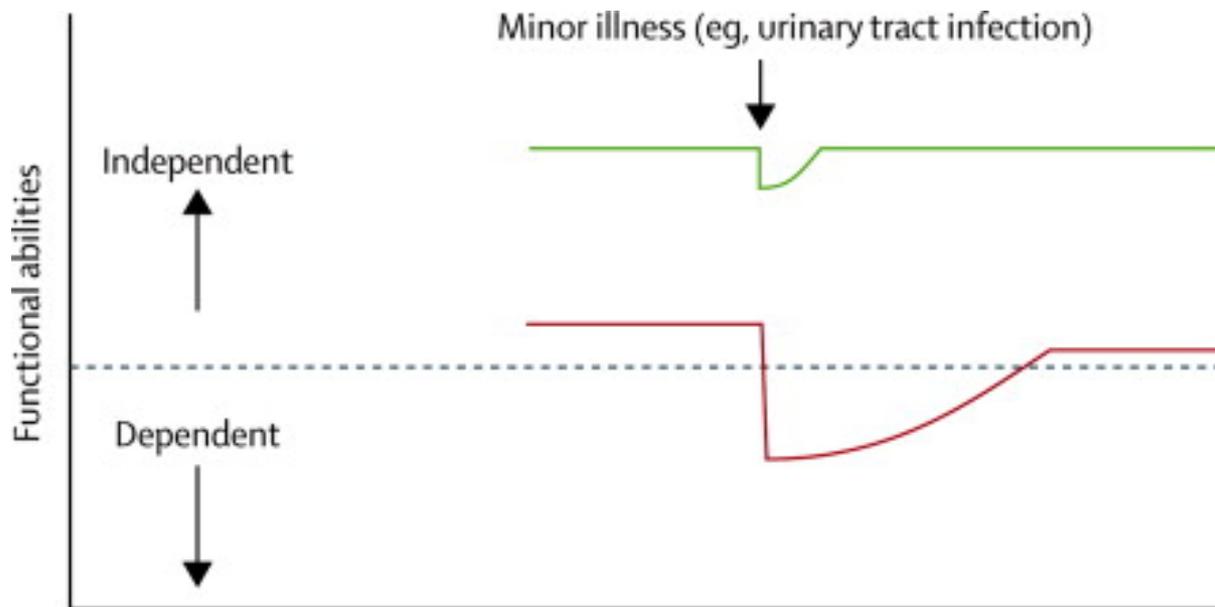
Scene setter - Keynotes

the potential of the silver economy

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Frailty is an **Unmet Medical Need** of Older Citizens

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



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%

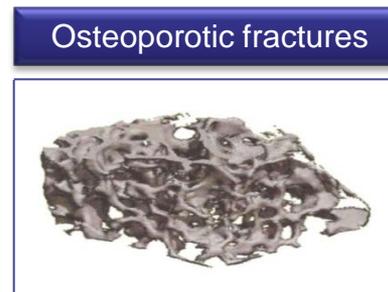
A potentially reversible condition

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

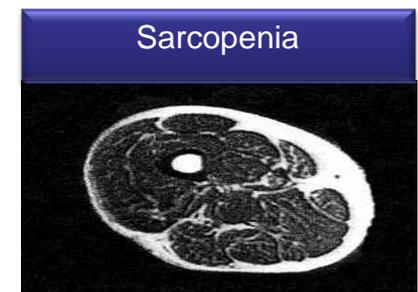
Baseline Frail status predicts outcome

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

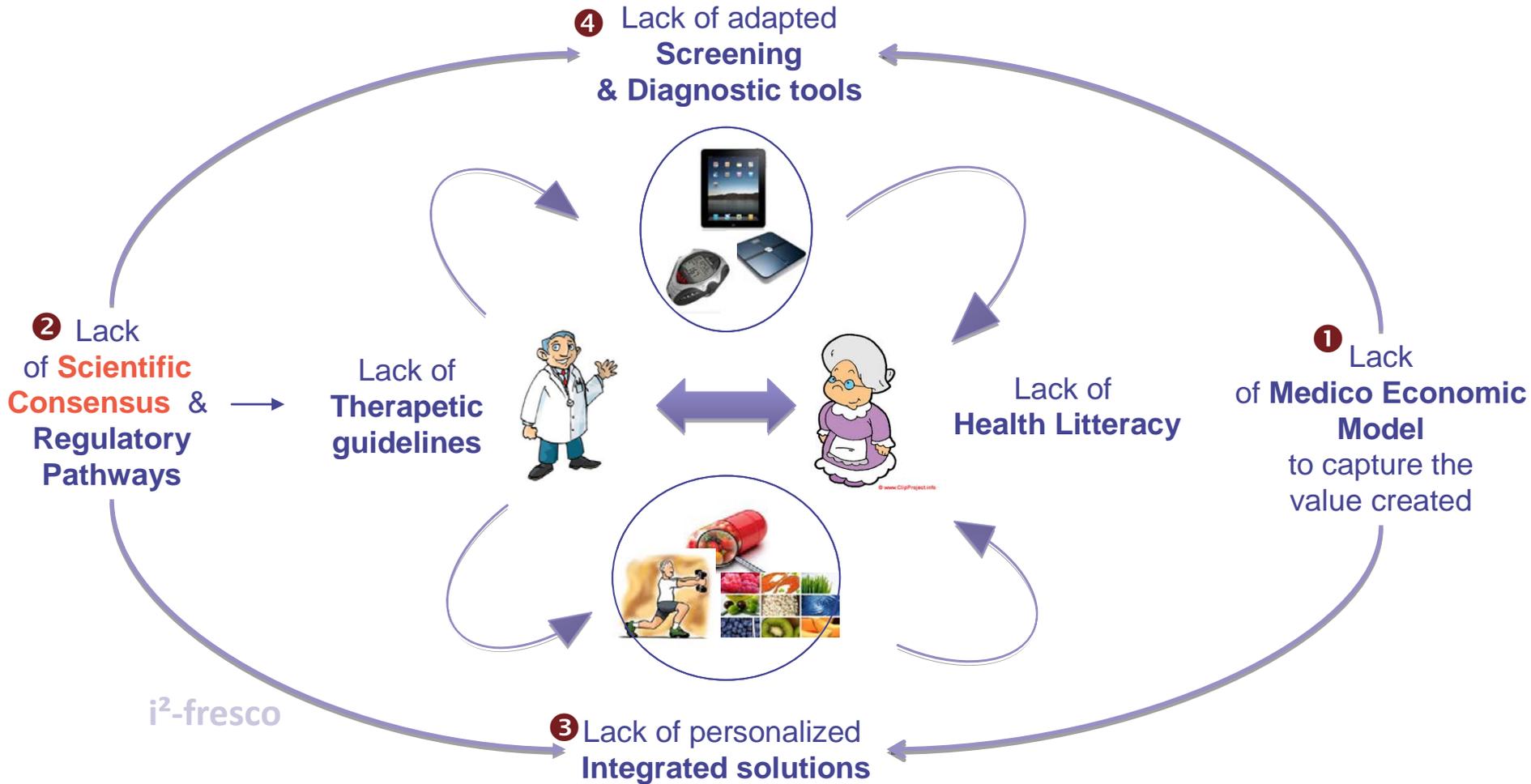


\$16.3 billion



\$18.5 billion

Gaps exist in the current management of frailty





SPRINTT

Sarcopenia & Physical Frailty in older people:
multi-component Treatment strategies

Objectives & Deliverables

Roberto Bernabei, Managing Entity (Catholic University Rome)
Susanna Del Signore, Coordinator (Sanofi)

Kick-off Meeting
Sanofi R&D Campus
9-10 July, 2014



Frailty is an **Opportunity for Innovation**

- Studying and developing novel treatments for a specific geriatric condition like physical frailty&sarcopenia can contribute shifting our current model of **reactive** healthcare focused on the resolution of acute events, towards a **proactive** care model aimed at maintaining higher health level in at-risk citizens
 - Metrics of intervention will be linked to the **postponement of physical disability** (as a proxy for healthy life extension), or decrease of index events like hospitalisations
-

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



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



Innovative Medicines Initiative



GlaxoSmithKline



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



Innovative Medicines Initiative

Consortium Partners



- 5 EFPIA partners: Sanofi (lead), GSK (co-lead), Novartis, Servier and Eli Lilly
- 12 Academia institutions and 3 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 Madrilenio de Salud - Spain
 - Universitaetsmedizin Goettingen, Georg-August-Universitaet, - Germany
 - Université Paris Descartes (UPD) - France
 - Università degli Studi di Firenze - Italy
 - Friedrich- Alexander- Universität 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)
 - NICHE Science&Technology (UK)



Clinical Study implementation and Operations

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

9 backup sites

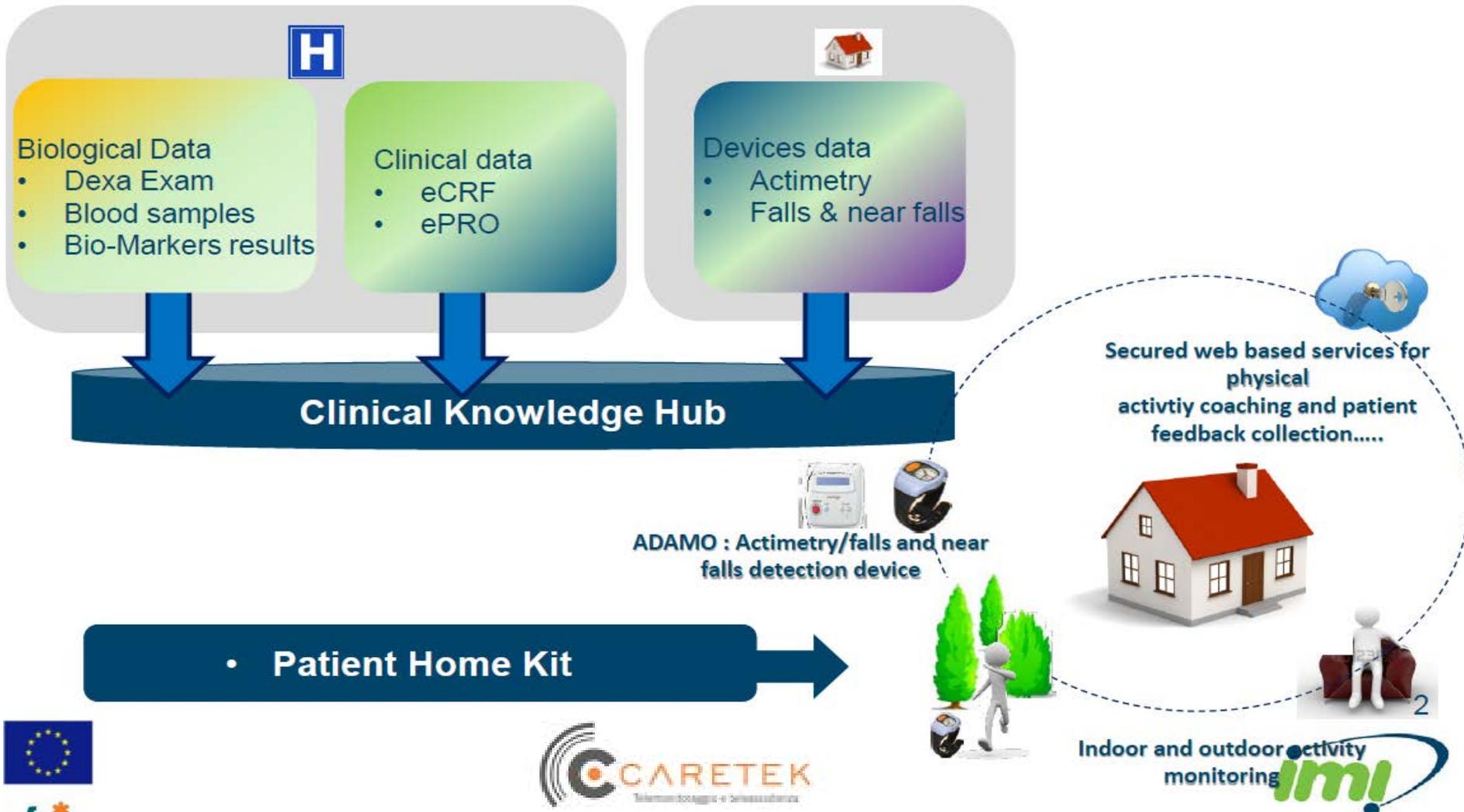
 Pre-selected study site

 Backup study sites



ICT as a key enabler

Several type of electronic data will be collected:



Patient centricity and innovative CT methodologies

- Older person's awareness and effective participation to an integrated intervention
- Capturing data in the older person's normal environment: home
- Coaching remotely
- Monitoring physical activity
- Detecting falls
- Administering PROs
- Monitoring food intake

- Etc.



Take the most from innovative ICT methodologies to keep the patient at the centre of therapeutic/preventative Interventions against PF&S

Clinical Study implementation and Operations

- IMI public-private partnership is a suitable model of collaborative research
- We want to operationalize PF&S and generate prospective data to be shared in view of further development
- European countries diversity and their older population specificities, need to be adequately captured in the clinical trial
- Early regulatory dialogue is integrated in our project as key objective
- Finally, taking advantage of evolving ICTs, we will put frail older subjects at the center of this initiative and give them a voice in our work

More information can be found [here](#)



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FAQ



Why an innovative study in Geriatrics ?



-
- Sanofi group is proactively working over the last few years to provide building blocks to the “silver economy” in the pharmaceutical area, by identifying obstacles (including regulatory ones) and implementing solutions – in view of **optimizing the treatment of chronic conditions that characterize older people life.**
 - **Private-public partnerships, like IMI Consortia, are key enablers for complex undertakings, as the case of Physical Frailty&Sarcopenia, that need tight collaboration of multiple competences, Industry, Academia and SMEs.**
 - **New methodologies, including ICT, have the potential to substantially improve the efficiency of clinical development and of healthcare**
 - Next steps point to integrated therapeutic solutions (medicines plus devices). These are today an established trend expected to grow further in the context of m-health novel opportunities.
 - Adequate EU and MS policies should sustain this promising landscape.
-

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THANK YOU!

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