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**advantAGE**  
MANAGING FRAILTY

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## EXECUTIVE SUMMARY

### Background:

- A common understanding of a conceptual definition of frailty, as well as the identification of tools to screen and diagnose this condition, is needed as a basis for a practical management approach. Chronic diseases, disability and frailty are used interchangeably to identify vulnerable older adults. However, they are distinct clinical entities that are causally related; they are often associated and overlap. There is a need to distinguish between them because frailty offers higher predictive value than chronic disease for adverse outcomes.

### Objectives:

- To review the concept of frailty and available tools to screen and diagnose this condition.
- To assess of the interaction of chronic diseases and multimorbidity with the development and progression of frailty.

### Methods:

- We searched three databases for relevant articles: 1) PubMed 2) Web of Science, and 3) Embase. Two assessors independently screened the titles and abstracts of the selected studies, and independently extracted the data.
- A survey on good clinical practices on frailty was performed to identify the screening and diagnosis tools used across the European Union Member States and another one was done to collect good practices and grey literature among projects on frailty funded by the European Union (EU).

### Results:

- A meaningful and comprehensive definition of frailty should be based on five components: phenotype, characteristics, pathogenesis, vulnerability/triggers and adverse outcomes.
- Multiple definitions of frailty are available. The one recently provided by World Health Organization (WHO) incorporates all the five components mentioned above.
- Several validated tools are available to screen and diagnose frailty in older people. There is a wide range in the applicability of these frailty measurements: from short, fast, and crude frailty screening instruments to the more sophisticated, time-consuming measurements.

- Chronic disease and multimorbidity are associated with frailty, but these represent different concepts. The presence of frailty in association with chronic diseases should modify the approach to care and disease treatment.

Recommendations for ADVANTAGE JA:

1. The adoption of the WHO definition to identify frailty.
2. The creation by WHO of an International Classification of Diseases (ICD) code for frailty in order to improve the awareness and diagnosis of this condition among medical doctors and public health providers.
3. The use of one of the available validated tools to screen and diagnose frailty. The choice of the tool should be contextualized to practice priorities and characteristics.
4. The adoption of the Comprehensive Geriatric Assessment (CGA) approach to provide a global assessment of frail persons.
5. The adoption of a personalized/individualized approach to the treatment of chronic diseases in the presence of frailty.

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## ACRONYMS

CGA = Comprehensive Geriatric Assessment.

CHS = Cardiovascular Health Study (Frailty phenotype).

EIP-AHA: European Innovation Partnership on Active and Healthy Ageing

EU = European Union.

FRAIL Index = Fatigue, Resistance, Ambulance, Illness, Loss of Weight.

FTS = Frailty Trait Scale.

ICD = International Classification of Diseases.

JA = Joint Action.

SOF = Study of Osteoporotic Fractures Index.

SPPB = Short Physical Performance Battery.

UCSC = Università Cattolica del Sacro Cuore.

WHO = World Health Organization.

WP4 = work package 4.

## INTRODUCTION

Frailty is considered to be a clinical state in a person that increases his/her vulnerability to develop adverse outcomes such as dependency and mortality when exposed to a stressor, but specific definitions of frailty differ depending on the criteria used. Indeed, frailty does not yet have an internationally recognized standard definition, although the general premise is that frailty may be considered to be a geriatric syndrome. The two most known definitions are probably the frailty phenotypic model proposed by Fried and colleagues (Fried et al., 2001), which focuses on physical components such as weight loss and weak grip strength and the deficit accumulation one developed by Rockwood which includes a more multidimensional concept including social, psychological, and physical elements (Rockwood et al., 2005). Multiple tools have been developed in the past to screen and diagnose this condition. Therefore, so far, despite a growing body of knowledge, there is no widely accepted definition/screening/assessment tool on frailty.

A common understanding of the concept of frailty, together with the identification of standardized tools for its screening and diagnosis will form the basis for a common effort to alleviate the growing older populations from its burden and adverse outcomes. In the first instance, a common understanding will provide the basis for a unified effort of the ADVANTAGE Joint Action (JA) initiative to develop a common management approach of older people who are frail or at risk for developing frailty in the European Union (EU). Therefore, the first aim of work package four (WP4) is to come to an accepted definition of frailty and the second aim is to identify available screening and diagnostic tools to assess this condition. The scientific literature (systematic review) and opportunist review of grey literature and good practices were analyzed to complete these tasks.

In addition, it is becoming increasingly evident that frailty may play a role in the development of certain chronic diseases, and conversely that chronic diseases may increase the risk of frailty in older individuals. Further, multimorbidity, defined as the co-occurrence of multiple chronic diseases or conditions in a single individual, is a prevalent condition in older ages (Tinetti et al., 2012) and is associated with adverse events such as mortality and disability (Onder et al., 2015). Emerging evidence suggests also a link between frailty and multimorbidity, but until now no systematic review of the evidence is available. Therefore, the third aim of WP4 is to review the scientific literature to identify clinical aspects of frailty, assess patterns of multimorbidity and their interactions in the development and progression of frailty, and assess the impact of frailty on the outcomes of multimorbidity. More specifically, in the present report, we explored the following questions:

1. What is the definition of frailty?
2. Which tools can be used to screen and diagnose frailty at an individual level?
3. What is the relationship between frailty and multimorbidity?

To answer these questions we performed: a) a review of the scientific literature; b) a survey of good clinical practices focused on frailty in Member States participating in the ADVANTAGE JA.

## METHODS

### Review of the Scientific Literature

A systematic search of the peer-reviewed medical literature published from 2002 to 2017 was undertaken to:

1. Identify available definitions of frailty
2. Identify tools used to screen and diagnose frailty
3. Assess the relationship between frailty and chronic diseases

Three databases were searched for relevant articles: 1) PubMed electronic database of the National Library of Medicine; 2) Web of Science and; 3) Embase. Strategies used for search and inclusion and exclusion criteria are available in Annex 1.

In order to systematically retrieve only relevant text data from the diverse publications on frailty concept and definition, concept analysis was adopted (Bergman et al., 2007). Using this approach concepts and their characteristics and relation to other concepts are defined. For each of the identified definitions of frailty the following main categories were assessed: phenomena of frailty, (phenotype), characteristics, pathogenesis, vulnerability/triggers and adverse outcomes.

For each of the identified screening and diagnosis tools the following data were collected: original reference, tool description, time to complete the assessment, number of items, use for screening and/or diagnosis, use of special equipment, presence of validation data, areas assessed (including nutrition, performance/disability, cognition, diagnoses, drugs, mood, continence, and social aspects).

For the review on multimorbidity and frailty, a meta-analysis was performed when at least three studies used the definition of frailty based on frailty phenotype and a common definition of multimorbidity to assess the association of the two conditions.

For review processes, two assessors independently screened the titles and abstracts of the selected studies. Two assessors read the full texts and independently extracted the information from the selected studies. A third assessor reviewed the data extraction, and any disagreement was resolved through consensus. Articles that were written in another European language than English were sent for translation by a native speaker who conducted the data extraction.

Reviews were performed between February and May 2017 and results summarized in tables and figures presented in the Annexes in June 2017.

### Survey among good clinical practices and grey literature

One email survey was developed to assess how frailty was screened and diagnosed in good practices. It was carried out on the ADVANTAGE JA partners and to practices listed in the European Innovation Partnership on Active and Healthy Ageing (EIP-AHA) document on Prevention and Early Diagnosis of Frailty – Action Group A3. Recipients of the questionnaire were invited to share it with other persons in charge of practices assessing persons with frailty.

A large part of the questions could be answered by ticking one box or all boxes that applied. To keep the questionnaire as simple as possible, the answers did not include a "do not know/no option" and few descriptive questions were included (e.g. name of the practice, location, etc.).

The questionnaire covered different aspects relevant for practices focused on frailty, including main target population, setting, selection criteria for admission, number of frail persons cared for, use of screening and diagnostic tools to assess frailty, and use of comprehensive assessment instruments.

The second email survey was sent to other European Projects on Frailty to collect grey literature and good practices in relation to the screening and diagnosis of frailty.

### Limitations

The methodology adopted for the review and survey have some limitations:

1. We followed a standardized methodology for literature search, but all publications within the scope of the research may not have been identified correctly.
2. We explored 3 datasets for the literature search (PubMed, Web of Science, and Embase) and we excluded others (e.g. Google Scholar). This might have led to an underestimation of the number of available publications.
3. The articles used different definition of frailty, and this might make difficult to extract general conclusions.

## RESULTS

The number of articles initially found and finally selected are presented in the table below.



Task	Definition	Screening	Diagnosis	Chronic Diseases
Number of articles found	494	6611		2282
Number of articles selected	74	52		25

Table. Number of articles found and selected in the overall search.

### Frailty definition

Overall 31 out of 74 publications offered their own definition of frailty or of a frailty subtype (e.g. physical frailty) and 68 included at least one approximate citation of a definition. Sixty publications explained relevant aspects of the definition or concept of frailty or of a frailty subtype.

*Different approaches to defining frailty.* Three different perspectives were taken when describing the phenotype of frailty (see Table 1 in Annex 2):

- *Clinical*: it is depicted as a “definable clinical state involving multiple signs and symptoms” (Xue, 2011). Using the clinical approach the syndromal character is emphasized. It allows for a certain heterogeneity of expressions. However, uncertainty exists about whether heterogeneous phenotypic expressions in frailty share common, or different, pathways. Consequently it remains unclear whether frailty is a syndrome or several syndromes. The prototype of a clinical definition is the frailty phenotype definition with five phenotypic components (Fried et al., 2001). Others authors also adhere to this clinical perspective.
- *Multidimensional*: it is defined as a “heterogeneous...(state) that includes physical, cognitive, and psychosocial domains or phenotypes” (Ruan et al., 2017). Another author states: “Frailty cannot be limited to a physical domain; psychological, cognitive, emotional, social, and spiritual factors contribute to frailty and need to be taken into account in its definition”(Fougère, et al., 2015). An example of this approach is Rockwood et al.’s frailty approach based on the theory of risk accumulation (Rockwood et al., 2005). Health deficits are physical and functional impairments that accumulate until the increasingly precarious homeostasis is disturbed. Rockwood et al. emphasize that the whole health is affected. Thus, disability is part of a later frailty stage and should not be excluded from the definition. Clegg’s definition (Clegg, et al., 2013) avoids a certain perspective and concentrates on pathogenesis and outcomes.
- *Functional*: frailty is presented in terms of losses in human functioning, alterations in several domains of function and reduction of activities. It is stated that “the total functioning of the person lies at the heart of the conceptual definition”(Gobbens, et al., 2010). It is understood to be “a diminished ability to carry out life functions, both of personal and of a social nature” and highlighted as the “hallmark of frailty”(Cooper et al., 2012).

*Main categories of frailty* - For the defining statements of frailty the following main categories were found: phenomena of frailty (phenotype), characteristics, pathogenesis, vulnerability/triggers and adverse outcomes (see Figure 1 in Annex 2).

*Frailty as a phenomenon* – Frailty cannot be easily recognized because of its complexity, heterogeneity, its fluctuating nature and difficulties in staging the progressive pathway. Frailty phenotype's criteria are often used to depict core features (weakness, shrinking-meaning weight loss-), slowness, poor endurance and energy, low physical activity). However, frailty may also affect cognition, mood and behavior. It interacts with co-morbidities and facilitates the occurrence of geriatric syndromes. An overshooting health response to stresses is characteristic (Clegg et al., 2013). As mentioned above, three different perspectives can be taken, when describing the phenotype of frailty: the clinical, the functional and the holistic perspective. Frailty from the clinical perspective is depicted as a clinical state or geriatric syndrome. Using the functional perspective, frailty is presented in terms of losses in human functioning, alterations in several domains of function and reduction of activities. This perspective includes a multidimensional approach, where frailty covers different domains (physical, cognitive and psychosocial) (Cesari et al., 2016).

*Characteristics of frailty* - The following properties are considered to be defining attributes of frailty: multiple affections, complexity, relation to old age and a specific trajectory. Frailty has multiple simultaneous affections and is not restricted to one body system or one area of human functioning. The trajectory of frailty is also characteristic as it is a progressive process of declining health that accumulates "health deficits" over the lifetime stretching from early stages that cannot be clinically identified and progressing into disability; thus frailty is seen as a pre-disability state. However, this decline is dynamic and non-linear, allowing for potential reversibility "not an inevitable trajectory to death" (Gobbens et al., 2010).

*Pathogenesis* - Frailty develops on the basis of multiple causal relations. Several systems seem to play a major role, especially the nervous, endocrine, immunological and musculoskeletal systems. It is driven by intrinsic (such as the genetic disposition and the ageing process) and extrinsic factors (such as the environment, lifestyle and nutrition). Morbidities contribute to a further malfunction. Physiological functions decline and alter progressively so that the functional resources diminish. The result is a loss of reserve and redundancy or - in other terms - a loss of adaptive capacity with difficulties maintaining homeostasis. In the face of increased demands on the system, the precarious balance tips over. A threshold is exceeded and the interrelated physiological systems start to fail. "Frailty results from reaching a threshold of decline across multiple organ systems" (Gielen et al., 2012).

*Vulnerability and triggers* – Situations that trigger frailty expressions or progressions are called stressors. Stressors impinge on the reduced physiological functions and reserves and induce "pathophysiological responses", thereby contributing to vulnerability and adverse outcomes. Vulnerability is referred to as a health state ("state of increased vulnerability" or "susceptible individual") that occurs due to reduced physiological functions and leads to adverse health outcomes, e.g. "vulnerability to adverse events" (Rodríguez-Mañas et al., 2012). Vulnerability implies that there is a high "likelihood of being affected by small changes in biomedical, psychosocial or environmental factors" when exposed to stressors. The vulnerable state raises the risk of adverse health outcomes (Clegg et al., 2013).

*Adverse outcomes* foremost affect health in a multidimensional, functional and person-centered way. Adverse functional outcomes are mobility and balance impairments, falls, functional decline and disability. Subsequently it promotes dependency. Adverse outcomes are also described in a person-centred way as affecting quality of life. There is the propensity of worsening comorbidity and of complications (e.g. surgical). Frailty is related to a greater health care use such as emergency visits, hospitalization, institutionalization and a higher mortality risk than non-frailty (Clegg et al., 2013).

Definitions were evaluated further according to the occurrence of the five core categories: (see *Table 2 in Annex 2*). There are only one that fully incorporate the six categories:

- WHO, 2015 (functional): Frailty is a progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes.

### Screening and diagnostic tools

Overall, 21 tools were identified. A summary of their main characteristics is presented in Table 3 in Annex 3; most of them appear in a meta-analysis of recent publication (Dent et al., 2016). There was a wide range in the applicability of these frailty measurements: from short, fast, and crude frailty screening instruments to sophisticated, time-consuming measurements. Overall 17/21 frailty tools have been validated in the literature. Moreover, many frailty measurements were modified somewhat from their original, validated version, which in turn, can have a striking impact on frailty classification. This concern was underlined in a recent meta-analysis by Theou and colleagues, which found 262 different versions of frailty phenotype's definition (Theou et al., 2015).

In our results, on the one hand as screening tools we selected those that are faster to administrate (they take 10 minutes or less), do not require special equipment and are validated and used for screening: Clinical Frailty Scale; Edmonton Frailty Scale; Fatigue, Resistance, Ambulance, Illness, Loss of Weight Index (FRAIL Index); Inter-Frail; Prisma-7; Sherbrooke Postal Questionnaire; Short Physical performance Battery (SPPB); Study of Osteoporotic Fractures Index (SOF); and gait speed. Frailty criteria from Cardiovascular Health Study (CHS – frailty phenotype) have never been used as screening tools and require the use of a dynamometer. However, given their wide use and the short time needed for the assessment (<10 minutes), we believe this tool might be used for screening purposes.

An international consensus group recommended all persons older than 70 years should be screened for frailty (Morley et al, 2013). In addition the Health Ministry of Spain proposes screening of frailty in all people 70 years or older with the SPPB or other tests as the gait speed (Ministry of Health of Spain, 2014). In spite of gait speed not being a scale, it has been demonstrated to be a good predictor of frailty (Cesari et al., 2005). For this reasons, we add it to our recommendation.

On the other hand, the gold standard for diagnosing the functional status of the person (that includes frailty status) is the comprehensive geriatric assessment (CGA) (Clegg et al., 2013). It is therefore important, when screening is positive, to perform a CGA and to diagnose frailty by the use of validated scales, derived from the CGA. In our results, we selected tools that were used for diagnosis, were validated and were used with CGA: Frailty Index of accumulative deficits and Frailty Trait Scale (FTS). In spite of not meeting these requirements, the most used and validated scale for the diagnostic of frailty is the frailty phenotype. Nevertheless, a wide use alone is not sufficient for an unconditional recommendation (Buta et al., 2016). These scales appear in a recent review (Dent et al., 2016).

In a meta-analysis, (Bouillon et al., 2013) analyzed the tools more used in articles. In 69% of publications, the frailty phenotype developed by Fried and colleagues was utilized; 12% used the Frailty Index developed by Mitnitski and colleagues; 4% the Edmonton Frail Scale; and  $\leq 2\%$  used the remaining instruments.

In the first of our surveys, there were a total of 47 responses received by the end of June 2017. Countries provided the following number of questionnaires: Bulgaria (n=7), Cyprus (n=4), Finland (n=1), France (n=3), Italy (n=10), Lithuania (n=1), Poland (n=1), Portugal (n=2), Romania (n=1), Slovenia (n=1), Spain (n=12), United Kingdom (n=4). Most practices were operating in acute care hospitals (38%), primary care (26%) or nursing homes (18%). Other settings included Day Hospitals (10%) and home care. In 6% of cases settings were not declared. Overall 30% of practices performed a screening for frailty before, or at, admission, 30% did not perform a screening, and 40% did not report this information. 21% used the same instrument to screen (*see Figure 1, Annex 3*) and diagnose frailty (*see Figure 2, Annex 3*). A huge variety of instruments was used, including the CGA, frailty phenotype, Edmonton frailty scale, Frail Trait Scale, Gerontopole Frailty Scening Tool, VES-13, or a combination of instruments. The CGA was used in 26% of cases.

In the second survey we identified one good practice and one piece of grey literature related to frailty screening and diagnosis. As an example of good practice, Frailclinic is an EU funded project (<http://frailclinic.eu/index.htm>) in the Second Health Programme call aimed to systematically evaluate tools used for screening and diagnosis of frailty applied to the same sample of patients in different clinical settings (n= 735). A number of results achieved in this project are of great interest to ADVANTAGE JA, namely: A) Among all the scales used for screening of frailty, the frailty phenotype is the least feasible one. The main cause of non-fulfillment of the test is the patient's bad condition at the time of evaluation. In fact, this scale is not viable for the characteristic of the patient in the Urgent Surgery Department or the Emergency Department, due to his/her clinical status. B) The best scale for evaluating frailty at the Urgent Surgery Department is the FRAIL Index due to its high feasibility, its high level of agreement in different clinical entities, and its similarity with the frailty phenotype in the classification of frailty. C) The degree of concordance among the frailty scales evaluated in the project is low, thus suggesting that they measure different clinical entities.

## Frailty and multimorbidity

Various definitions of frailty were used in the studies, with the majority of studies using frailty phenotype definition (Fried et al., 2001). Methods for defining disease within the samples differed, with some studies using extensive diagnostic procedures and others relying on self-report. The quality of studies differed, with only some conducting extensive multivariate analyses to account for potential confounders.

The majority of studies on multimorbidity found an increased odds of frailty. Analysing more in depth the association between multimorbidity and frailty, we found 9 studies, all of them involving community-dwelling persons, reporting data on the overlap between frailty defined based on frailty phenotype definition (Fried et al., 2001) and multimorbidity (2+ diseases), for a total of 14,704 individuals. According to these data, 868 (6%) persons presented contemporary multimorbidity and frailty, 403 (3%) presented only frailty and 6213 (42%) only multimorbidity (*see Figure 1 in Annex 4*). Overall, we found that 7 out of 10 frail adults present with multimorbidity and that almost 2 out of 10 adults with multimorbidity also present a condition of frailty.

In addition, the review performed suggested that intensive treatment of multimorbidity may increase negative health outcomes in frail persons. In particular, if treatment of symptoms related to chronic diseases (i.e. pain in osteoarthritis, dyspnea in respiratory disease, motor symptoms in Parkinson disease) might potentially reverse frailty, the benefits related to preventive pharmacological treatment of chronic diseases (i.e. antihypertensive treatment) in patients with prevalent frailty is not certain. In particular, several factors might alter the risk/benefit ratio of a given treatment in persons with frailty. These include: exclusion of frail persons from clinical studies, reduced life expectancy in frail persons, increased susceptibility to iatrogenic events and poor adherence (Onder et al., *in press*).

## CONCLUSION

This report summarizes the state of the art on available definitions of frailty, and tools used to measure this condition, and assesses the association between chronic diseases and frailty.

### Question 1. What is the definition of frailty?

A common definition of frailty is not available. However, based on the review it seems clear that a comprehensive definition of frailty should cover five domains, which include phenotype, characteristics, pathogenesis, vulnerability/triggers, and adverse outcomes. It has become apparent that no theme can be missed in building a full understanding on the concept and definition of frailty.

There seems to be an agreement on the content of the some components of the frailty concept, but the components phenotype and adverse outcomes find little consensus. There are groups of

experts who promote a typical cluster of phenotypic expressions; best known are the five factors from frailty phenotype (Fried et al, 2001). There are also broader clusters, such as the ones from Strawbridge et al. (1998) and Bergman et al., (2007). In contrast there is the Rockwood's definition, which emphasizes that the type of health deficit is not essential. As explained above, the phenotype of frailty is partly expressed through adverse outcomes – meaning, for example, that a clinician may think of frailty for the first time in an older person with a fall. Because of this overlap between adverse outcome and phenotypic expression, there is uncertainty whether certain phenotypes are a component of frailty or a consequence of frailty.

Among available definitions, the one provided by WHO seems to better cover the five domains. WHO (2015) defines frailty as ‘... a progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes.’ It is the opinion of the partners of the present JA that the recognition and endorsement of the present definition should be followed by the creation by the WHO of an ICD code for frailty. This action might lead to improvement in the awareness and diagnosis of this condition among medical doctors and public health providers.

## Question 2. Which tools can be used to screen for and diagnose frailty at an individual level?

The review showed that there are multiple measurements used to screen and diagnose frailty. Few studies comparing these measurements are available and the applicability range is wide. This large heterogeneity is confirmed by both the literature review and the survey performed among good clinical practices on frailty in Europe. Also, there is little distinction about tools used to screen and diagnose frailty, since in most cases the same instrument is used for both aims. Many frailty measurements had been robustly validated in the literature. Noticeably, many frailty measurements were modified somewhat from their original, validated version, which in turn, can have a striking impact on frailty classification.

As pointed out by Dent et al (Dent et al, 2016) in a recent review ‘... *there are three potential future options for frailty measurement. Firstly, as part of a consensus, we can decide on one frailty measurement from the multitude of already existing measurements. Having just one measurement would be advantageous given that it would allow comparison of frailty prevalence worldwide. However, having one frailty measurement may not be best route forward. Frailty measurements can be likened to ‘horses for courses’, wherein different frailty measurements are suited to different populations. Some are better for population-level frailty screening, whereas others are best suited for clinical screening, or for clinical assessment. ... Secondly, a new gold frailty standard measurement could be developed. However, countless research groups have done exactly this, which partially explains why there are so many frailty measurements in existence today. Thirdly, we could use one frailty measurement for screening and a second one for a full assessment....*

As recently underlined by Cesari et al. (Cesari et al., 2016) in the absence of a “gold standard”, the instrument to screen and diagnose frailty should be chosen according to the characteristics of the

studied population, the aims of the assessment and the clinical context. The choice of instrument and thresholds of risk should be based on the available resources allocated to the entire planned action. We agree with Dent's first and third potential future options and Cesarí's proposal. We recommend that all persons older than 70 years should be screened for frailty. Therefore we propose a range of instruments to pick first in a screening phase and secondly in a diagnostic one. According to the criteria we have considered the most relevant, the recommended tools for screening of frailty would be: Clinical Frailty Scale; Edmonton Frailty Scale; FRAIL Index); frailty phenotype; Inter-Frail; Prisma-7; Sherbrooke Postal Questionnaire; Short Physical performance Battery (SPPB); Study of Osteoporotic Fractures Index (SOF); and gait speed.

When screening is positive we recommend performing a CGA to have a global assessment of persons and to diagnose frailty by the use of validated scales, derived from the CGA (Frailty Index of accumulative deficits and Frailty Trait Scale).

### Question 3. What is the relationship between frailty and multimorbidity?

The review shows that frailty and chronic multimorbidity are two different concepts. Overall there appears to be more evidence suggesting that multimorbidity is associated with frailty than not, but the lack of longitudinal studies makes it difficult to draw any firm conclusions.

If chronic diseases have a role in determining frailty, as hypothesized by some theoretical models of frailty, it could be hypothesized that treating these conditions may, in turn, counteract the development of frailty, eventually reducing any associated negative consequences. However, this hypothesis is poorly supported by existing studies. In contrast, some evidence suggests that intensive treatment of chronic diseases may increase negative health outcomes in frail older adults (Palmer et al., 2016).

Alternatively it can be suggested that presence of frailty in association with chronic diseases should modify the approach to care and disease treatment (Onder et al., 2017). For example, it has been shown that frailty may act as an effect modifier, by modifying the risks and benefits of chronic disease treatments. This may have relevant implications. So far, clinical guidelines have provided specific recommendations for the treatment of chronic diseases in older people generally speaking. For the above mentioned reason, clinical guidelines should provide specific recommendations for the treatment of frail people, underlining the pros and the cons of drug treatment and possible targets for therapy in this population. Also the approach to care of chronic diseases might differ according to presence of frailty. The traditional disease-oriented approach might be considered appropriate for persons with chronic diseases not experiencing frailty, while a more comprehensive and integrated approach is necessary for treatment of persons in which chronic diseases and frailty coexist.

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## ANNEXES

### Annex 1: Strategies for literature review and questionnaires

#### *Definitions of frailty*

Pretests with possible search terms and filters were undertaken to understand their coverage and selective properties. Entry terms were frail\*, vulnerab\* and definition\*, mean\*, understand\*, concept\*, character\*, phenomen\*, construct\*, syndrome. The MeSH subheading “Frail elderly” was tested as well. As we did not want to include any trials, exclusion terms were tested: clinical trial, observatory study, cohort study and the MeSH term “epidemiologic methods”. Finally the efficiency of filters were tested using a combination of publication type filters, time frames and publication components. On the basis of the pretests a full search was carried out using the following search strategy: Frail\* [Title] AND (concept\* [Title/Abstract] OR construct\* [Title/Abstract] OR definition\* [Title/Abstract]).

#### *Tools to screen and diagnose frailty*

The following keywords were used: (“frail elderly”[MeSH Terms] OR “frail\*”[Title/Abstract] OR “frailty”[Title/Abstract]) AND (“assessment”[Title/Abstract] OR “asses\*”[Title/Abstract] OR “instrument”[Title/Abstract] OR “instrum\*”[Title/Abstract] OR “tool”[Title/Abstract] OR “tools”[Title/Abstract] OR “evaluation”[Title/Abstract] OR “screening”[Title/Abstract] OR “screen\*”[Title/Abstract] OR “questionnaire”[Title/Abstract] OR “measure”[Title/Abstract] OR “institu\*”[Title/Abstract] OR “scale”[Title/Abstract] OR “index”[Title/Abstract]).

Exclusion criteria: Articles involving paediatric samples; articles written not in English or in languages covered by the consortium countries; reviews, editorials, letters to the editor, perspective papers, position papers, guidelines, conference proceedings; articles that do not propose, develop or test instruments for the screening/assessment of frailty.

#### *Frailty and multimorbidity*

The following keywords were used:

(multimorbidity OR, comorbidity OR, chronic diseases), AND (frail elderly OR, frail OR, frailty).

Exclusion criteria: articles that did not assess the association between frailty and chronic diseases, included persons younger than 18 years; reviews, editorials, letters to the editor, perspective papers, position papers, guidelines, conference proceedings; articles that did not provide an explicit definition of frailty or assessed only with a single symptom/measure; articles not in English or in languages covered by the consortium countries.

### *Questionnaires*

The complete form of the questionnaires can be accessed in the following links:

<https://www.cemiricerca.org/redcap/surveys/?s=77TPMDHMXR>

<https://www.cemiricerca.org/redcap/surveys/?s=NKNKRFJHEY>

## Annex 2. Definition.

Table 1. Definitions of frailty

Author	Conceptual definition
<b>Frailty as a clinical/geriatric syndrome</b>	
<b>Fried (2001)</b>	<p>There is a growing consensus that markers of frailty include age-associated declines in lean body mass, strength, endurance, balance, walking performance, and low activity and that multiple components must be present clinically to constitute frailty. Many of these factors are related and can be unified, theoretically, into a cycle of frailty associated with declining energetics and reserve.</p> <p>Operational definition: Fried frailty phenotype</p>
<b>Strawbridge (1998)</b>	<p>Deficiencies in the following domains:</p> <ul style="list-style-type: none"> <li>- physical health (sudden loss of balance, weakness in arms, weakness in legs, and orthostatic dizziness)</li> <li>- nutritional (loss of appetite and un- explained weight loss)</li> <li>- cognitive (attention deficit, trouble finding words, and memory difficulties)</li> <li>- sensory (visual and hearing problems)</li> </ul> <p>Frailty can thus be conceived as a grouping of problems and losses of capability which make the individual more vulnerable to environmental challenge</p> <p>Operational definition: Strawbridge</p>
<b>Roschelle, Heuberger (2011)</b>	<p>“Frailty in older adults is a complex syndrome, characterized by loss of lean body mass, weakness, exhaustion, and decrements in physical function and activity. The frailty syndrome results in an increased vulnerability to stressors, which may propel the progression to disability, comorbidity, and mortality. Mechanistically, the syndrome is mediated through inflammatory and coagulative dysregulation, with alterations in a variety of hormones, peptides, and other homeostatic controls.”</p>
<b>Kuzuya (2012)</b>	<p>Frailty may now be regarded as a geriatric syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and leading to adverse health outcomes including physical disability, falls, hospitalization, institutionalization and mortality.</p>

Frailty is multidimensional – perspective predominately clinical	
<b>Kelaiditi (2013)</b>	Frailty is a multidimensional geriatric syndrome characterized by increased vulnerability to stressors as a result of reduced capacity of different physiological systems.
<b>Rodriguez-Manas (2013)</b>	The experts clearly agreed that frailty is a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors.
<b>Villacampa-Ferna (2017)</b>	The term frailty refers to a dynamic and multidimensional clinical condition of increased vulnerability to poor resolution of homeostasis when facing a stressor event.
<b>Walston (2006)</b>	<p>Frailty is evident over time through an excess vulnerability to stressors, with reduced ability to maintain or regain homeostasis after a destabilizing event.</p> <p>Frailty is currently identified through characteristics that are directly related to physical function and that at the same time are consequences of the accumulation of subclinical conditions, acute and chronic disease, and behavioral and social risk factors.</p>
<b>Bergmann (2007)</b>	<p>(shown in a figure: no original text)</p> <p>Life-course determinants of frailty are biological, psychological, social societal and environmental. They can induce disease and a decline in physiologic reserve. The phenotypic candidate domains of frailty are: nutrition, mobility, physical activity, strength, endurance, cognition, mood. In the face of modifiers adverse outcomes occur, which are disability, morbidity, death, institutionalization and hospitalization.</p>
<b>Rockwood (2005)</b>	<p>“Frailty is defined as the cumulative effect of individual deficits—the more individuals have wrong with them, the more likely they are to be frail. As ‘wrong’ we consider symptoms, signs, disabilities, diseases, and laboratory measurements, which we term deficits”.</p> <p>Operational definition: Frailty index</p>
Frailty – perspective left open	
<b>Clegg (2013)</b>	<p>It is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiological systems during a lifetime. This cumulative decline depletes homoeostatic reserves until minor stressor events trigger disproportionate changes in health status.</p> <p>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.</p>

Frailty – functional perspective	
<b>WHO definition (2015)</b>	a progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes
<b>Gobbens (2010)</b>	Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social) that are caused by the influence of a range of variables and which increases the risk of adverse outcomes
<b>Schuurmans (2004)</b>	Frailty is a loss of resources in several domains of functioning, which leads to a declining reserve capacity for dealing with stressors. Frailty, the risk for adverse outcomes due to losses in different domains of functioning, relates directly to these adverse processes.
<b>Boers (2015)</b>	Frailty is the weakening of health; (health is defined as the resilience or capacity to cope, and to maintain and restore one's integrity, equilibrium, and sense of wellbeing in three domains: physical, mental, and social).

Table 2. Comprehensiveness of definitions

Author	Phenotypic description	Characteristics	Pathogenesis	Trigger	Vulnerability	Adverse Outcomes
Fried (2001)	Biological syndrome	+,+	+	+	-	Unspecified
Roschelle, Heuberger (2011)	Syndrome	+,+	+	+	-	Specified
Kuzuya (2012)	Geriatric syndrome	+	+	+	-	Specified
Kelaiditi (2013)	Geriatric syndrome	+	+	+	+	-
Villacampa-Fernandez (2017)	Clinical condition	+,+	+	+	+	-

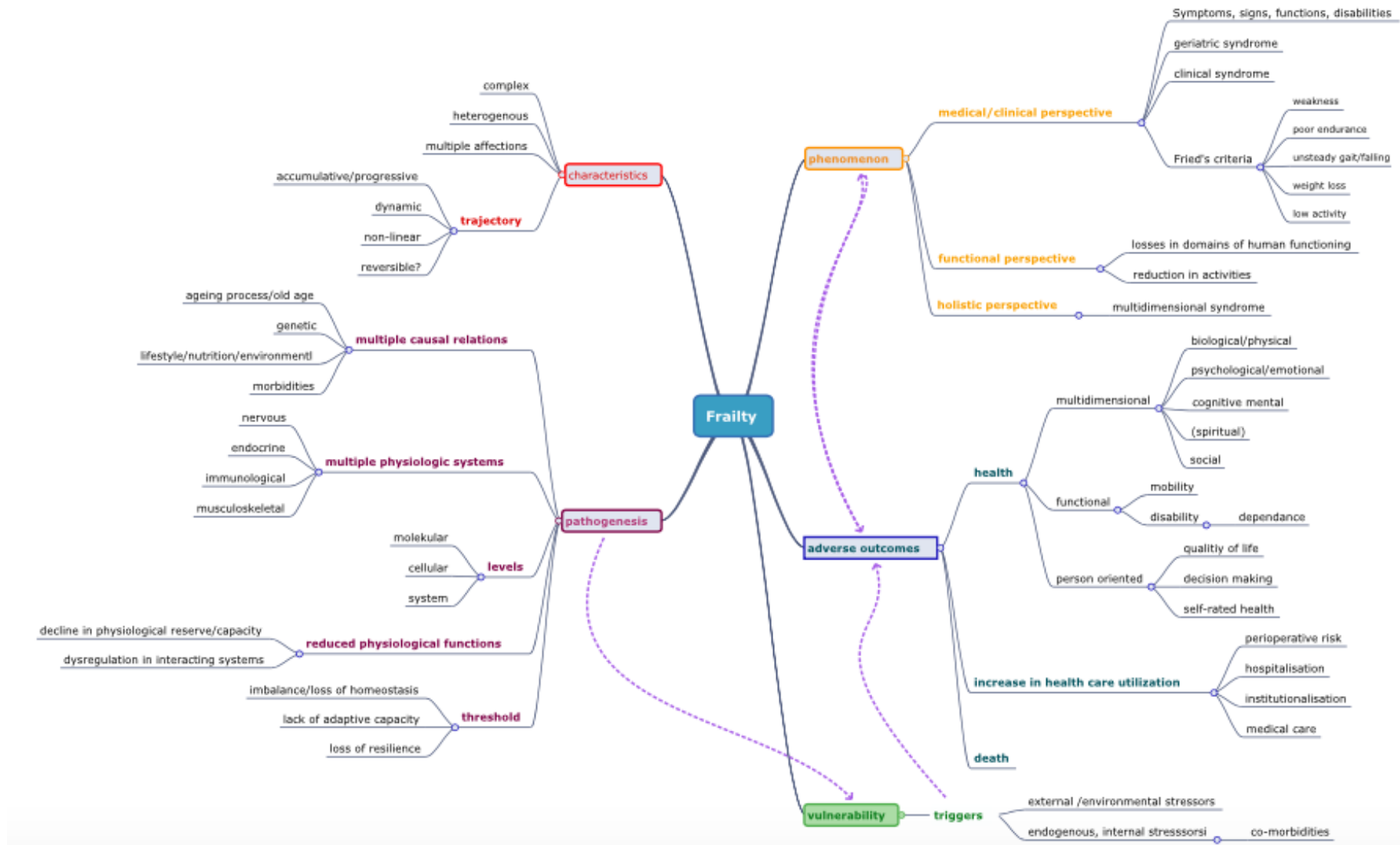
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Rodriguez-Mañas (2013)	Syndrome	+	+	-	-	-
Walston (2006)	Syndrome(s)	+	also social , behavioural risks	+	+	Unspecified
Clegg (2013)	A state	+,+	+	+	+	-
Strawbridge (1998)	Physical, nutritive, cognitive and sensory domains	+	-	-	-	See phenotypic description
Rockwood (2007)	Symptoms, signs, disabilities, diseases, laboratory measurement (health deficits)	+,+	+	-	-	See phenotypic description
WHO 2015	A decline	+,+	+	+	+	Unspecified
Gobbens * (2010)	State	+,+	(-)	-	-	Unspecified
Schuurmans (2004)	A loss of resources	-	+	+	-	-
Boers* (2015)	Weakening of health	-	+	-	-	See phenotypic description

\* explicitly stated are physical psychological or mental and social domains



Figure 1. Main categories of frailty



## Annex 3. Tools for screening and diagnosis of frailty

Table 1. Tools of frailty.

Tool	Original reference	Tool description	Time	N of items	Used for screening	Used for diagnosis	CGA data	Special equipment	Validated	Nutrition	Performance/disability	Cognition	Diagnoses	Drugs	Mood	Continence	Social
<b>CHS/Frailty criteria</b>	Fried et al. Gerontol A Biol Sci Med Sci 2001	5 items: weight loss, low physical activity, exhaustion, slowness, weakness	< 10 min	5	No	Yes	No	Yes (dynamometer)	Yes	No	Yes	No	No	No	No	No	No
<b>Frailty Index of accumulative deficits</b>	Mitnitsky et al. Sci World J. 2001	number of health deficits present / number of health deficits measured	20-30 min	>30	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b>Frailty Index derived from comprehensive geriatric assessment</b>	Jones DM et al, J Am Geriatric Soc, 2004.	14 items: ADL, IADL, comorbidities, mood, cognition, weakness, falls, dental problem.	< 20 min	14	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	
<b>Study of Osteoporotic Fractures Index (SOF)</b>	Ensrud et al. Arch Intern Med. 2008	3 items: weight loss, reduced energy level, inability to rise from a chair, and reduced energy level.	< 5 min	3	Yes	No	No	No	Yes	No	Yes	No	No	No	No	No	No
<b>Edmonton Frail Scale</b>	Rolfson et al, Age Ageing. 2006	Timed up and Go Test, Clock draw test, 7 Questions exploring frailty domains	<5 min min	9	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
<b>FRAIL Index (Fatigue, Resistance, Ambulance, Illness, Loss of Weight)</b>	Morley et al. J Am Med Dir Assoc. 2008	5 items: fatigue, resistance, ambulation, illnesses, loss of weight	< 10 min	5	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No	No	No
<b>Clinical Frailty Scale</b>	Roockwood et al. Can Med Assoc J 2005	Single descriptor of a person's state of frailty (fitness)	5 min	NA	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No	No	No
<b>Multidimensional Prognostic Instrument</b>	Pilotto et al. Rejuvenation Res, 2009.	Comorbidity, cognition, polypharmacy, nutrition, ADL, IADL, Living status.	<15 min	8	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	

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<b>Tilburg Frailty Index</b>	Gobbens et al. J Am Med Dir Assoc 2010	Part A 10 Determinants of frailty, Part B 15 Components of frailty	<15 min	25	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes
<b>Prisma-7</b>	Raiche et al. Arch Gerontol Geriatr 2007	Self-reported. 7 questions on demographics and performance	5 min	7	Yes	No	No	No	Yes	No	Yes	No	Yes	No	No	No	Yes
<b>Groningen Frailty Indicator</b>	Peters et al. Gerontologist. 2001	Self-reported. 15-point questionnaire exploring physical, cognitive, social and psychological components	<15 min	15	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
<b>Sherbrooke Postal Questionnaire</b>	Hebert et al. Age Ageing 1996	6 item questionnaire	< 5 min	6	Yes	No	No	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes
<b>Gerontopole Frailty Screening tool</b>	Vellas et al. J Nutr Health Aging. 2013	6 items: living alone, involuntary weight loss, fatigue, mobility difficulties, memory problems and gait speed	< 5 min	6	Yes	No	No	No	No	Yes	Yes	Yes	No	No	No	No	Yes
<b>Kihon Check list</b>	Fukutomi et al. Geriatr Gerontol Int. 2013.	25 items in areas of daily life, physical ability, nutrition, oral condition, memory	<20 min	25	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
<b>Inter-Frail</b>	Bari et al. J Am Geriatr Soc 2014	1 disability and 10 frailty items (yes-or-no questions)	10 min	11	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
<b>FIND</b>	Cesari et al. PLoS ONE 2014	2 items on mobility disability + 3 items on weight loss, exhaustion, and sedentary behavior.	< 5 min	5	Yes	No	No	No	No	Yes	Yes	No	No	No	Yes	No	Yes
<b>Physical Frailty and Sarcopenia</b>	Stoever et al. J Frailty Aging. 2015	Low muscle mass according + SPPB from 3 to 9	30 min	2	Yes	Yes	No	Yes (DXA)	No	No	Yes	No	No	No	No	No	No
<b>FRAIL-NH</b>	Kaehr et al. J Am Med Dir Assoc. 2015	7 items: fatigue, resistance, ambulation, incontinence, loss of weight, nutritional approach, help with dressing.	5 min	7	No	Yes	No	No	No	Yes	Yes	No	No	No	No	Yes	Yes

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<b>Frailty Trait Scale</b>	García-García et al. J Am Med Dir Assoc. 2014	7 dimensions: energy balance and nutrition, activity, nervous system, vascular system, weakness, endurance, and slowness	20 min	12	No	Yes	Yes	Yes (albumin dynamometer)	Yes	Yes	Yes	Yes	Yes	No	No	No	No
<b>Short Physical Performance Battery (SPPB)</b>	Guralnik et al. J Gerontol 1994	3 dimensions: balance, gait and weakness.	<10 min	12	Yes	Yes	No	No	Yes	No	Yes	No	No	No	No	No	No
<b>Gait Speed</b>	Guralnik et al. J Gerontol 1994	1 dimension: gait speed measured over a 4 m course	1 min	1	Yes	Yes	No	No	Yes	No	Yes	No	No	No	No	No	No

Figure 1. Survey results: screening tools (n=47)

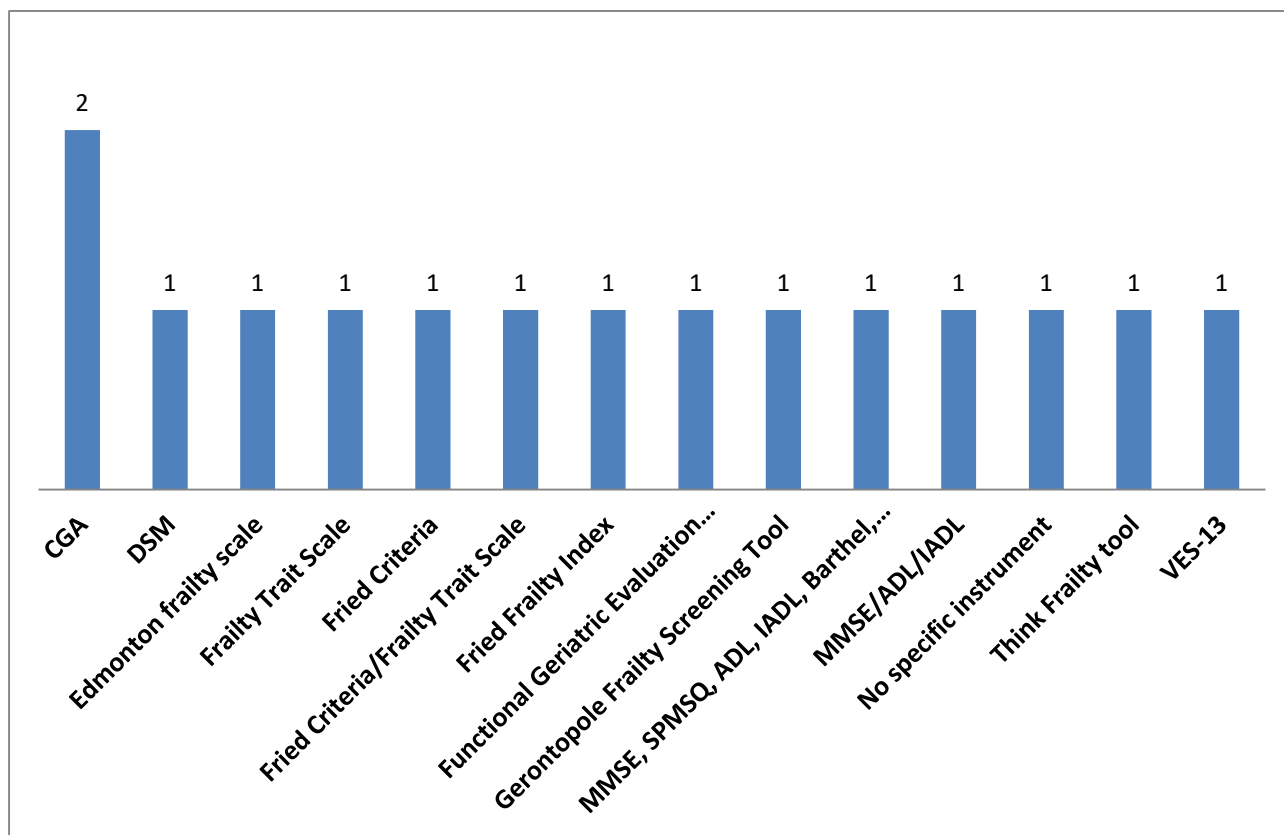
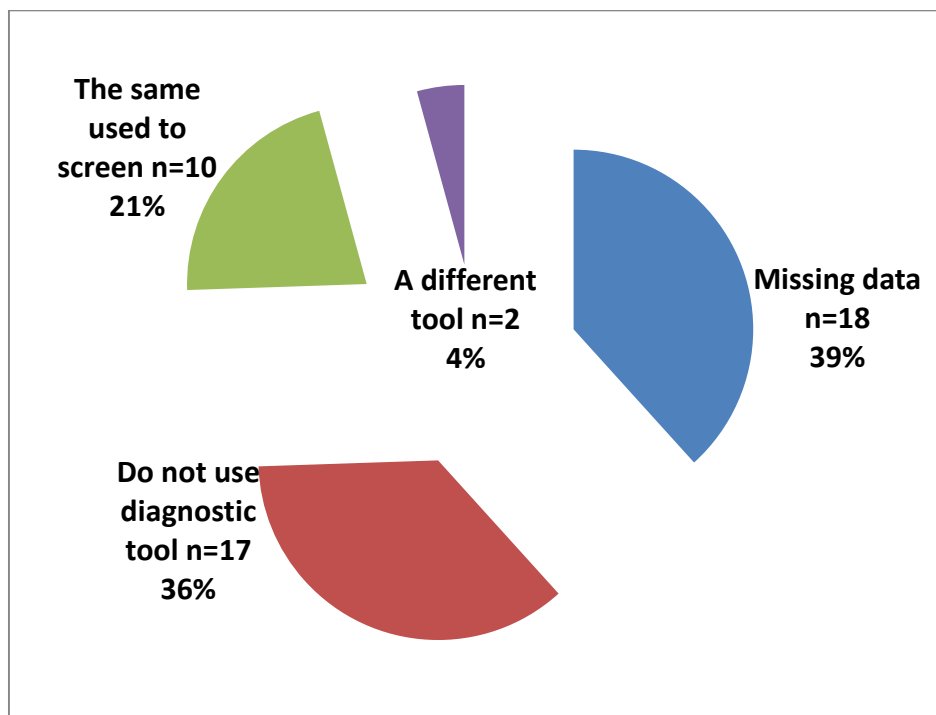


Figure 2. Survey results: diagnostic tools (n=47)



#### Annex 4. Frailty and multimorbidity overlap

Figure 1. Pooled data from 9 studies; n=14,704. Frailty was defined according to the CHS criteria and multimorbidity defined as 2 or more diseases.

