EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 January 2018

Overview of comments on 'Points to consider on frailty: Evaluation instruments for baseline characterisation of clinical trial populations' (EMA/CHMP/778709/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder number	Name of organisation or individual
1	United States Food and Drug Administration (FDA)
2	Aging In Motion (AIM) Coalition
3	Mark Stemmler (Institute of Psychology, University of Erlangen-Nuremberg)
4	European Federation of Pharmaceutical Industries and Associations (EFPIA)
5	Abbott Nutrition
6	NDA Regulatory Science Ltd.
7	Medicine Evaluation Board, Netherlands
8	Regeneron Pharmaceuticals, Inc.
9	Dr Roman Romero-Ortuno (Dpt. Medicine for the Elderly, Addenbrooke's Hospital, Cambridge University Hospitals NHS)
10	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)
11	SPRINTT Consortium (Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies)
12	Giovanni Guaraldi (Dpt. Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia)
13	Matteo Cesari (Gérontopôle, Centre Hospitalier Universitaire de Toulouse)

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	The focus on frailty is a critical parameter as we advance our understanding of the impact of co-morbidities and the organ changes associated with the aging process. The document well articulates these considerations, including challenges due to cognitive change/decline. The document focuses on the "frailty" assessment for baseline categorization of elderly patients. Although it successfully highlights the need to include elderly in clinical trials for which we agree, "frailty", as the document points out, is a concept for which there is no expert consensus definition. <u>Strengths and Weaknesses of Selected Instruments</u> Notable strengths of the document are inclusion of other domains of frailty beyond physical and acknowledgement of the impracticality of incorporating the Comprehensive Geriatric Assessment into clinical investigations. Another strength is the document's allowance for different scales for specific frailty domains to be selected based on specific characteristics of the clinical development program. Also, the document encourages development and validation of alternative scales for characterization of specific subpopulations as needed. A shortcoming of the document is the omission of criteria or instruments validated for frailty, e.g., the Fried frailty criteria (1) and its related - FRAIL scale (2). The Fried frailty criteria have been extensively evaluated for validity and are the most widely used criteria in frailty research (3). The 5-item FRAIL scale is a validated screening instrument for identifying frailty (2). In a consensus conference of	Comment noted. Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	frailty consisting of delegates from US, European and 6 major international societies, the FRAIL scale and the Fried frailty criteria (also called the Cardiovascular Health Study Frailty Screening Measure) were among the scales agreed to be used to identify individuals with physical frailty (4). Additionally, two other tests, the Get Up and Go (5) and the Mini Cog (6), routinely used in clinical practice in geriatrics and internal medicine in the U.S, are arguably simpler to perform and considered to be practical and more reliable than some of the alternatives mentioned in the document. Another shortcoming of the document is inclusion of instruments that are not sufficient for identifying frailty and instruments that may be of limited value in most geriatric clinical investigations. The Short Physical Performance Battery (SPPB) has not been validated for identifying frailty, and gait speed is not sufficient for frailty identification in clinical investigations because of its high false positivity when used to screen for frailty. Therefore, for physical frailty screening, the FRAIL instrument and Fried frailty criteria are preferred. The Montreal Cognitive Assessment (MoCA), Mini-Nutritional Status – Short Form (MNA-SF), and Cumulative Illness Rating Scale – Geriatrics (CIRS-G) are acceptable instruments for respectively screening for cognitive dysfunction, malnutrition, and multimorbidity in geriatric clinical investigations. However, routine nutritional screening in geriatric clinical investigations in the absence of potential effects of the investigational product on nutrition should be discouraged. Measurement of baseline multimorbidity with instruments such as CIRS-G will be valuable where exclusion criteria are minimal. Otherwise, the added value of CIRS-G is uncertain if clinical	

Stakeholder number	General comment (if any)	Outcome (if applicable)
	investigations are going to continue to exclude older adults with morbidities as they currently usually do. The document also does not discuss fall risk assessments, which could be a useful measure of frailty. There is limited mention of falls in the document, except in Section 4, where frailty is defined as a term used in geriatric medicine to identify older adults at increased risk of falls. Fall risk assessment is an important part of the clinical assessment of older adults and could be a useful measure of frailty. <u>Discussion of Baseline Frailty Characterization: Implications and Applications to Clinical Investigations</u> Although the document makes recommendations for use of specific instruments, FDA is unclear how those instruments will be used in clinical investigations and what added value they are anticipated to provide. Specifically, consider explaining how frailty will play a role in evaluating products. For example, explain how frailty will impact determining baseline characterizations, efficacy determinations, and safety assessments. Without establishing how the instruments will be used, the frailty assessments might constitute exclusion criteria and could compromise knowledge in patients with frailty. In addition, since frailty screening may not have a high yield in certain geriatric clinical investigations (for example, investigations in which the median age is <70 years), EMA should suggest clinical investigation programs in which frailty screening and inclusion may be particularly valuable. In order to help establish the use of specific frailty measures in clinical investigations, the measures need to	Fall risk assessment is out of scope of the document since fall is an outcome measure and not a frailty domain. Comment noted.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	be prospectively evaluated in a defined context and patient population to adequately identify the outcome we are trying to predict. Additionally, elderly subjects and patients with poor status based on the frailty assessment would need to be included in clinical trials in order to evaluate whether the frailty measure represents added value over age alone. Although frailty is more common in the elderly, frailty is not limited to the geriatric population. Consideration should be given to whether other groups enrolled in a clinical trial should be evaluated by such a measure. Conversely, if trial entry is limited to good performance status individuals, consideration should be given to whether frailty screening adds any information. <u>Increased Burden on Clinical Trial Participants and Investigators</u> Use of instruments to assess frailty will place burdens on subjects and healthcare providers involved in clinical investigations. Subjects and providers will likely need to spend an additional 10-15 minutes for each frailty assessment, a time burden which could become significant depending on the total number of instruments needed to assess frailty. The time burden could be a deterrent to clinical trial participation for both subjects and investigators. Further, additional training likely will be needed for the clinical investigation staff because many of the instruments require specific training to properly perform the assessments. For example, the SPPB is currently only included in geriatric fellowship training, but not other specialties.	Comment noted.

Stakeholder number	General comment (if any)	Outcome (if applicable)
4	▪ The points to consider document does not discuss or recommend a specific Frailty definition. The language used in this draft document at times deviates from the accepted terminology pertaining to the functional impairments and disability in older adults. Especially the term "frailty" is used in the context of, not only the specific geriatric syndrome of frailty, but also functional impairment, cognitive impairment, poor nutritional status and multi-morbidity. The document could be improved if the terminology used was better aligned with the International Classification of Functioning, Disability and Health (ICF) as well as the mainstream geriatrics literature. It would be appreciated if the term frailty would only be used when referring specifically to the geriatric syndrome of frailty per se which has a very specific meaning in geriatric research. Alternatively if the document is only intended to provide industry with some tools that are acceptable to the EMA and can be used to better characterize and describe study populations, this could be more clearly stated.	Comment noted.
	▪ Overall this document provides a good overview of various instruments for the assessment of not only frailty, but also functional impairment, cognitive impairment, nutritional status and multi-morbidity. Our understanding is that the purpose of the document is to highlight instruments that can be employed in development studies to better characterize the enrolled older-adult population, for either risk-stratification or descriptive purposes. As such the instruments outlined in the document are all of value, however it should be noted that many of the proposed instruments would	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	have limitations as outcome measures in a clinical study. Generally it would be highly appreciated if the agency would emphasize that the goal of this document is to provide further guidance on how to better characterise the older adult study population when applicable given that the majority of patients in clinical trials are not frail. For example only 30% of the participants in cancer trials are >65 years of age. The inclusion of these instruments should therefore be indication specific and is not relevant for all trials.	
	▪ Frailty is an emerging concept and there appears to be a lack of consensus in the definition and diagnostic criteria. It might therefore be useful to provide definitions (e.g. in section 4) of different aspects/domains of frailty referred to later in the document, for instance pre-frailty, psychosocial frailty etc.	Comment noted.
	▪ It could be considered to have a wider discussion on the reasons why elderly and frail patients are excluded from clinical trials. One potential reason could be that these patients might not be able to comply with common clinical trial procedures without help of caregivers that might not be allowed for certain assessments. Additional reflection is needed on these broader aspects to provide greater context to the reader.	Comment noted. The discussion on the reasons for exclusion is out of the scope of the document.
	▪ It is welcomed to subdivide patients into more relevant baseline categories as well as the recommendation on specific instruments to assess physical frailty, cognitive function, nutritional status and multimorbidity. It would	Comment noted.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	be appreciated to stress the need for the consistent application of "golden standards" instruments (rather than just providing suggestions of scales that could be selected from) in order to enable the comparison of results between development programmes and within programmes. The document does not provide clarity on the definition nor on the number of subgroups (e.g. fit, pre-frail, frail) that can be derived based on the scales and the relevance of their analysis beyond the analysis of age only. Prior to including these scales as demographic assessments in trials some additional information on the above is needed.	
	▪ Although the guideline seeks to find a definition of frailty status for the purpose of patient enrolment in clinical investigations (which may be used across therapeutic categories), it tends to focus on frailty resulting from the condition that the product intends to treat. A definition that is related to the indication that is being treated may be clouded by the severity of the disease itself and not by the degree of frailty in general. It would be helpful if the guideline better separates the concepts of background frailty from disease-related frailty.	Comment noted.
	▪ There is concern regarding a potential for the emphasis of strength assessments that are isolated from relevant functional assessments in older adults. First, strength is very hard to measure, as it depends on the examiner as well as the participant; requires maximal voluntary effort; is very sensitive to technique; and has high	Comment noted.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	inter-subject variability. Second, there are many different kinds of strength – isometric, isodynamic, isokinetic – and they have different levels of relevance for different tasks. Third, there is no intrinsic meaning to a patient from their level of strength in isolation – what matters is whether they can walk, lift, carry, or do other tasks; which tasks are meaningful depends on the individual and their circumstances. Fourth, there are clear examples of exercise interventions which have improved function without increasing strength. For this reason muscle strength measurement is no longer considered necessary by the FDA, however it remains in vogue in EU. Having a clear statement would support sponsors. Handgrip strength may be an exception because it is easy to measure and relatively reproducible (although affected by the presence of hand arthritis, etc.). Thus it would be highly important to the field if the discussion would shift away from strength and toward the types of functional outcomes that have been nicely described in the document. To do so, further information about what not to do would be extremely helpful.	
	▪ Although the draft document does not intend to define a frail patient in great detail, it would be appreciated if the guidance could provide some background on interpretation of results. For example: if a patient scores between18-23 on the MMSE (mild cognitive impairment), would he be considered frail or would scores between 0-17 (severe cognitive impairment) be required to be considered frail? If it is not possible to provide this level of detailed guidance in this document, reference to other	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	documents for this type of guidance would be appreciated. ▪ A general concern is that this document breaks down the concept of frailty into its individual parts. It should be considered that frailty is an attractive concept because it highlights the idea that the whole is greater than its individual parts. Additionally, it doesn't really matter what caused the frailty (e.g. which comorbidity, lifestyle factor, nutritional status, hormones, etc.), but rather encompasses the accumulation in deficits and is a reflection of the physiologic reserve, which is important to capture for trials. ▪ The numbers of the literature references appear in the titles of some, but not all subsections sections describing the scales. Suggest using a consistent approach throughout the document.	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty. Comment noted.
6	This long-waited guidance document serves as a tool to direct further the development of new medicinal products for use in older, frail adults. However, it is felt that the document is not detailed enough: it is rather general and does not propose how frailty in the different medical disciplines can be evaluated. In other words, should frailty be evaluated in the same way for the purposes of clinical development of a new cardiovascular drug and for a new vaccine? Probably not, but the document does not take this aspect into consideration. It is suggested that a large table be added to propose which frailty index could be used per discipline. Adding such level of detail and concrete therapeutic field-related	Comment noted.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	recommendations in the document would likely improve its intended impact on the development of all medicinal products which will also be used in older adults. The document presents a menu of instruments for use, but the dimensions of frailty will continue to be evaluated separately and no cut-off values are available that could be used for subgroup analyses (severity) based on standardised criteria. This guidance document should ideally go beyond presenting a menu of instruments. It could explain the types of analyses that could be used to anchor benefit and risk endpoints to the presence and level of frailty.	
7	An element that is missing in this guideline is the purpose of identifying and addressing frailty, apart from age, in clinical studies. If e.g. the purpose is for generalisability to this population then it would help to stratify on frailty and to randomise within strata. This in turn would imply a composite measure and not measuring different aspects as suggested in the guideline (otherwise stratification would need to be on many variables, which is hardly feasible). If on the other hand, the purpose is to learn about adequate dosing, then this may be achieved in less demanding designs (i.e. as opposed to randomised clinical trials).	Comment noted.

8	We note the Executive Summary indicates these points to consider outline general principles that *may* be applied. The goals of the Agency in developing this 'Points to Consider' document are clearly described. However, given that "there is still a lack of both a consensus definition and a standardized assessment instrument to be used in clinical practice and in research" for frailty, it would be premature to *mandate* non-routine evaluation instruments to be used for baseline frailty categorisation of older patients. <u>On the practical application of baseline frailty instruments</u> We find the concept and recommendation of applying baseline frailty status, as determined by non-routine clinical measures and evaluation instruments, challenging and not practically applicable in both clinical research and in post-approval safety surveillance programs. As these instruments and assessments are outside routine clinical care, clinical trial coordinators may not be adequately trained in these assessments for the results to have significant clinical implications. For example, sites involved in cardiovascular research would not be familiar with administering neurocognitive scales. In addition, such scales are somewhat subjective and may be open to significant variability, particularly in large multinational studies, that will ultimately impact the usefulness of results. The problems of implementing such assessments in a registry program, as the guidance alludes, should also be acknowledged. The success of a registry typically requires the broad involvement of practitioners who are unlikely to be trained or even familiar with these instruments. Such an instrument could become a hurdle to recruitment or result in inconsistences, and hence bias in the data that would confound the analysis.	Comment noted. Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

	Thus, we believe that baseline categorisation of older patients on the basis of frailty status should not be a *general* requirement or recommendation for drug development programs or post-approval safety surveillance programs, but instead be targeted to situations when such measures may provide meaningful data important to public health. <u>On subgroup analysis</u> Even in the absence of upper age limits in clinical studies, the subgroup analysis of elderly patients is often too small for the results to be clinically meaningful. Additional sub-analyses that take account of baseline frailty status are likely to result in extremely small datasets that do not provide significant clinical meaning. Should such a sub-analysis cover adverse events (AEs), it is difficult to envisage a clear clinical conclusion being supported by such analysis. <u>On the use of baseline frailty assessment in clinical research</u> Currently, the draft guideline does not address how best to apply the frailty evaluation instruments to drug development programs or post-approval studies. For example, if there are cut-points for the validated instruments indicating different degrees of frailty the Agency believes to be clinically relevant, we request that these be provided in the guidance to assist Sponsors in understanding the Agency's thinking and to ensure consistency in how Sponsors utilize and interpret results from frailty evaluation instruments. If there are no such cut-points, then we request that the guideline acknowledge this point.	Comment noted. Comment noted.

	<u>On Conclusion</u> While we acknowledge the goal of recruiting a study population for pivotal studies that is reflective of the target population for a particular product, we also note that these same clinical studies need to ascertain unambiguously the efficacy and safety of the investigational medicinal product. To achieve this, it is sometimes necessary to exclude patients who are unlikely to complete all of the assessments for a study; for example, patients with certain comorbidities. The frail elderly are, in fact, such a population. Within the current framework of the Pharmacovigilance legislation, Sponsors are obliged to detail these potential limitations of the final clinical dataset and very often undertake post-approval activity to address any gaps in knowledge. Where there are gaps in knowledge that will be important for public health, the use of these post-approval activities may form a more appropriate mechanism to consider the impact of frailty status on the product performance. However, it will be important for the EMA to be judicious in applying this guidance. This guidance should not be viewed as creating a new category of patients that every drug development program must evaluate, regardless of the importance of the drug to the care of that patient population. Instead, its use should be targeted to situations when the measures discussed may provide meaningful data important for public health. These instruments, which have generally not been used or developed for the purposes noted in the guidance, should only be considered when there is a specific concern and then only after discussion with EMA.	Comment noted.
9	I would like to express some concern about the choice of the SPPB as the recommended measure for physical frailty. Clinical trials where participants are asked to complete balance tests and chair stands, as well as gait speed, may still fail to recruit a large proportion of vulnerable older	Comment noted.

	adults unable to complete these tests. Indeed, the SPPB was validated in a relatively 'fit', non-disabled population (http://www.ncbi.nlm.nih.gov/pubmed/7838189). For the balance tests, the participant must be able to stand unassisted without the use of a cane or walker, and for the chair stands participants cannot use arms (http://hdcs.fullerton.edu/csa/Research/documents/SPPBInstructions_ScoreSheet.pdf). It has been proven that frailty instruments that are strongly based on performance measures generate a lot of missing data, and this could be a source of potential selection bias. For example, in the African American Health Project, SPPB required imputation for about 50% of scores (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561182/). The Fried's frailty phenotype (http://www.ncbi.nlm.nih.gov/pubmed/11253156) or its European variant SHARE-Frailty Instrument (http://bmcgeriatr.biomedcentral.com/articles/10.1186/1471-2318-10-57) are well validated as measures of physical frailty that still capture a pre-disability state and may be able to include a larger number of frail older adults in clinical trials, because they have less reliance on "difficult" performance measures. For example, the Fried's frailty phenotype only requires preferred gait speed (with walking aid if needed) and handgrip strength (which is done whilst sitting down). SHARE-FI only requires handgrip strength, and its sister instrument SHARE-FI75+ (http://bmjopen.bmj.com/content/4/12/e006645.full) only requires an assessor's observation of gait. The EMA should consider recommending physical frailty instruments that are as inclusive as possible.	

10	The aims of this document are laudable. However, as noted, there is no accepted operational definition of frailty and no one practical tool that captures the multidimensional aspects of frailty. This poses a real problem for sponsors of trials in the choice of instrument(s). In turn, results from the use of selective instruments in one or two domains will limit the interpretation of the general relationship between safety and efficacy of interventions as a function of frailty. I suspect that the sentiment is shared by the Expert Group as judged by their excellent review. In this context, the conclusion of the report jars "In the absence of specific pharmacodynamic parameters of interest but a desire to broadly characterise baseline frailty, then the determination of physical frailty status is the preferred option ….". This statement appears to render evaluation of the other three domains largely redundant. This apparently conflicting position would benefit from clarification.	Comment noted.
11	Frailty (1) is an independent cause of death, primarily leading to progressive or persistent disability and not systematically overlapping with comorbidity (2, 3). Frailty is a predictor of dependence and death (2) not exclusively in high or middle-income countries (4). Sarcopenia, a combination of low muscle mass and weakness in older adults that causes functional problems, is an essential component of physical frailty (5-7). Frailty has been suggested a common final pathway of sarcopenia, although several impaired mechanisms of homeostasis characterize frailty and generate its propensity to negative outcomes (8). Sarcopenia was recently recognized by the Centers for Disease Control and Prevention (CDC) that established an ICD-10-CM code for sarcopenia, M62.84,	Comment noted.

	effective October 1, 2016. We also consider physical frailty and sarcopenia as a specific geriatric condition and an unmet need of older patients deserving innovative therapeutic approaches and adapted pharmacological developments. Because physical frailty in its initial phase is partially reversible, the progressive decline toward physical disability can be slowed or halted. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) project was specifically designed to overcome the existing barriers for an efficient public health intervention against frailty, and promote the implementation of innovative treatment strategies across Europe. The project includes a randomized clinical trial aiming to characterise the frail, sarcopenic older population at risk of mobility disability and adequately describe is clinical history in the presence of non-pharmacological intervention versus standard of care. The SPRINTT CT plans to recruit 1,500 participants aged 70 years and older (750 per treatment arm), distributed across seven regional coordinating site across Europe.	
12	There is the need to make EMA-infectious disease group be involved in this process because the issue of HIV&Ageing has turned to be an epidemic within the HIV epidemic. Last edition of European guidelines on HIV management-EACS has just introduced a sentence which acknowledges the importance of assessing frailty in HIV patients. In this population a higher prevalence of frailty and disability is recognised in comparison of the general population. Nevertheless no data are available regarding specific issue	Comment noted.

	on antiretroviral (ARV) management in HIV patients, regardless the fact that clinicians do consider ageing and frailty as criteria how to choose ARV. I think that EMA should recommend drug companies to perform studies in frail patients. The tools which have been identified in this document including SPPB, MoCA, MNA-SF and CIRS-G have been used in HIV patients. Acknowledge that MoCA has been considered suboptimal to depict NCI in HIV patents where NCI should have some specific HIV issues, nevertheless this test is one of the most widely used in clinical activity. My comment to the document is that it does not mention how to measure frailty improvement during a clinical trial. A good diagnostic tool is not always the best tool how to monitor frailty change. In my clinical experience Frailty Index according to the accumulation of deficit conceptualization by Ken Rockwood is what most effective and easy to use tool is. In the context of a clinical trial many variable are collected and these variables can be used to build a trial frailty index able to capture patients who most benefit from intervention.	
13	All the presented instruments are not assessment tools of frailty, but concur at its characterization. It implies that frailty is assessed elsewhere and otherwise. How? If this is not somehow stated, frailty will result as a mix of low physical performance (SPPB), low cognition (MMSE), risk of malnutrition (MNA), multimorbidity (CIRS)..., whereas it might be something more (e.g. socioeconomic issues, depressive mood, postural modifications...). In other words, I believe the document lacks of a (preliminary) section explaining how to operationally define frailty. After this first section, it will be possible to better	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

	provide details about the questionnaires enriching the identified "frailty" condition with insights on specific aspects. By stating this, I realize the difficulty of providing standards in the operationalization of frailty which is still a topic undergoing a huge debate in the literature (Fried? Rockwood? Others?). However, I think it is important to (at least briefly) mention this for better contextualizing the following recommendations. Talking as a researcher and not as a regulatory agency, I would be perfectly comfortable if instead of the SPPB the Timed-Up-and-Go test is used in a clinical trial to assess physical performance. I would be more concerned if a clinical trial in (frail) older persons would not measure physical function in a standardized and validated way. Similarly, there are a lot of tests for measuring the domains listed in the document that are not considered (probably because considered as not particularly robust by regulatory agencies). And there are also many domains that are equally important for the health status of the individual, but not discussed as well (e.g. quality of life, depressive mood, posture,...). I think it is important to recognize somewhere such limitations because frailty is not only diseases, physical impairment, malnutrition or cognitive decline. And, at the same time, the choice of different tests (other than those listed here) does not potentially affect the quality of the final scientific product.	

2. Specific comments on text

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
11	1	**Comment:** In the Scope section, the authors recognize that concepts about frailty are not exclusive to patients older than age 65. However, line 11 refers only to baseline categorisation of older patients. Concepts about frailty are applicable to persons of all ages. **Proposed change:** Consider replacing "categorisation of older patients" with "categorisation of patients, particularly older patients."	Comment accepted. Text has been reworded for clarity. The final document applies to the population aged ≥ 65 years.
13-15	4	"*A priori* subgroup analysis by baseline frailty parameters may then allow correlation with endpoints including those related to adverse events. Post-authorization risk management could be a further potential area of application of such scales". With respect to the proposed frailty parameters, we would like to caveat that the subgroup definition with respect to each scale has not been well established. Also in the absence of guidance to use the same scales throughout a development plan, it might be difficult to pool data, check consistency across trials. Additionally subgroup analyses from clinical trials could have other issues, e.g. very small subgroups that do not provide meaningful comparisons or subgroups defined by median that may not reveal differences. If implemented, the definition of subgroups should be carefully considered and justified. Some guidance on the groupings to consider for this analysis is considered helpful.	Comment accepted. Text has been revised accordingly.
14-15	1	**Comment:** In line 14, the document states "Post-authorisation risk management could be a further potential area of application of such scales." It is unclear what the EMA definition is for "Post-authorisation risk management."	Comment accepted. The wording is revised.
21-23	1	**Comment:** The only instrument mentioned in the executive summary is the SPPB. Consider explaining why the SPPB is singled out or mentioning the	Comment accepted. Text has been revised.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		recommended scales for all 3 aspects of frailty. **Proposed change:** Consider replacing "However, the Short Physical Performance Battery (SPPB)" with "In the absence of specific pharmacodynamics parameters of interest but a desire to broadly characterise baseline frailty, the Short Physical Performance Battery (SPPB) …"	
21-23	1	**Comment:** The document is about patient selection (not outcomes) for trials. However, several of the measures listed (such as the SPPB) do not have strong predictive value for the baseline characterization of physical frailty. Additionally, with respect to the SPPB in particular, FDA has raised concerns about the use of SPPB as an outcome instrument in various trials. Many of the problems with the tool in those outcomes settings would carry over to the context of this document. **Proposed change:** Recommend that all the scales mentioned in the document be listed in the summary or recommend deleting the following sentence: "However, the Short Physical Performance Battery (SPPB) is identified as the scale providing the overall best predictive value for the baseline characterization of the (physical) frailty of older people enrolled in a clinical trial." Since it is premature to list many of the scales themselves, deletion is the preferred recommendation.	Comment noted. Text has been revised.
26-29	2	**Comment:** To help expand the availability of new treatment options for patients with sarcopenia, AIM is pursuing qualification of the Short Physical Performance Battery (SPPB) and Usual Gait Speed (UGS) by the U.S. Food and Drug Administration (FDA) through FDA's Drug Development Tool Qualification Process. We believe that these two instruments could be valuable performance outcome measures for use in clinical trials for sarcopenia. The executive summary of 'Points to Consider on frailty: Evaluation instruments for baseline characterization of clinical trial population'	Comment accepted.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		acknowledges that the document is not intended to support development programs for sarcopenia. We are not proposing a change to this summary but we express hope that EMA will consider the utility of the SPPB and UGS beyond their ability to assess the frailty status of patient for inclusion in clinical trials.	
105-179 Section 4	6	**Comment:** In this paragraph some of the frailty scales are discussed. E.g. the Frailty Index (reference 29, by Rockwood) however no practical examples are given in which situation the different indexes and scales can or should be used.	Comment noted. Text has been revised.
105-179 Section 4	4	**Comment:** <u>Concept of Frailty, correlation of CGA with individual instruments:</u> The paragraph contains contradictory messages. It is recognized in the document that it is not feasible to obtain a "multidimensional interdisciplinary comprehensive geriatric assessment (CGA)" in all trials including older patients but that it is relevant to document to what degree physical or cognitive frailty is present at baseline. The document appropriately points at preferred instruments in sections 5-8, including recommendations and reasons for the proposed selection. Section 4 however does not give clear guidance. This section states: "In clinical trials, if the correlation between a screening instrument and CGA is acceptable for the desired clinical trial outcome, then screening instruments will at least be able to capture baseline frailty characteristics for a clinical trial population" –however it is unclear what would be "acceptable". To provide guidance it would be better to end this paragraph (or section): "The current guideline proposes a selection of instruments for baseline assessment of frailty, where the correlation with a CGA has been deemed acceptable." **Proposed change:** "…Consideration must also be given to disease-related frailty versus background frailty in the pre-morbid state**.** *The current guideline*	Comment accepted. Text has been revised.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		proposes a selection of instruments for baseline assessment of frailty, where the correlation with a CGA has been deemed acceptable."	
105-179 Section 4	13	**Comment:** I would carefully check the document for correcting some apparent contradictions/ambiguities. If the document is aimed at providing suggestions for evaluating frail older persons, I would consider frailty as the umbrella under which we find the cognitive, functional, nutritional (…) domains. For this reason, I would avoid to talk about physical frailty. I would rather talk about "physical function", mainly for avoiding misunderstandings. In this context, there is no mention of traditional scales/instruments measuring physical function (e.g. ADL, IADL). I realize how obsolete they are, but in the literature there are also alternatives worth to be considered. Other issues here are: 1) To understand why we need to measure frailty (or a specific domain of it). 2) To differentiate the instruments according to their construct and natural objectives. Besides of recommending the use of validated instruments, it is important to consider that the adoption of tools should mainly answer to the specific questions of the investigator. In this context, I think that the easiness-of-use should not be considered as a pivotal factor in the choice of the instrument. Of course, it is important, but simplifying too much sometimes leads to arguable/useless results. Similarly, the predictive value of a tool is a specific property that might not be requested for certain tasks. A wonderful descriptive tool may not necessarily be predictive of certain outcomes.	Comment noted. Text has been revised.
107-114	1	**Comment:** Section 4 discusses the concept of frailty. Frailty is more common in the elderly, but isn't limited to the geriatric population. It is necessary to	Comment noted. Text has been reworded. The final document applies to the population aged ≥ 65 years.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		consider whether other groups enrolled in a clinical trial should be evaluated by such a measure. Conversely, if trial entry is limited to good performance status individuals, it is important to consider whether frailty screening adds any information.	
112-114	13	**Comment:** Not sure about reporting the exact prevalence of frailty because these figures are strongly related to the studied population, the setting, and the adopted instrument for assessing the syndrome. I would simply state that "Frailty is a highly prevalent age-related condition in community-dwelling older persons" (as already done few lines below). Otherwise, I would present the usual/famous data reported by Santos-Eggiman in J Gerontol (from the SHARE study), citing the paper and explaining that the results are closely related to the adopted instrument (a modified version of the frailty phenotype in that case).	Comment accepted. Text has been revised.
128-133	13	**Comment:** This paragraph seems to contradict the exact estimates of frailty prevalence reported above.	Comment accepted. Text has been revised.
135-151	11	**Comment:** Frailty is a specific geriatric condition and represents an unmet need of older patients. Frailty is an independent cause of death. Multimorbidity and polypharmacy are certainly to be taken into account as independent prognostic factors. However, the recommendation to use the CGA seems out of scope. The whole paragraph is actually blurring the frailty concept. Please consider to reformulate the 5th paragraph. **Proposed change:** Please delete "Consideration must also be given to disease-related frailty versus background frailty in the pre-morbid state."	Comment accepted. Text has been revised.
150-151	1	**Comment:** In lines 150 to 151, the document states: "Consideration must also be given to disease-related frailty versus background frailty in the pre-	Comment accepted. Wording has been revised.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		morbid state." It is unclear what is meant by "in the pre-morbid state." Suggest clarifying the difference between disease-related frailty and background frailty. Geriatric frailty may exist with or without disease; this has led to the concept of primary frailty (or premorbid frailty) – occurring in the absence of overt disease, and secondary frailty – occurring with the known disease.	
152-153	1	**Comment:** In lines 152 to 153, the document states: "Several frailty instruments have been tested and validated in epidemiological studies, while their application in clinical settings has been somewhat limited." With respect to the reference to "application in clinical settings," consider, if appropriate, broadening this reference to make it more applicable to this document. **Proposed change:** Consider replacing "while their application in clinical settings has been somewhat limited "with "while their applicability (or generalizability) to other settings has been somewhat limited."	Comment accepted. Text has been revised.
169-171	1	**Comment:** In lines 169 to 171, the document states: "Nevertheless the similar predictive ability among different frailty scales suggest that the choice of an instrument should take into account the purpose of the research, information available and the ease of use, in terms of time and equipment." Suggest clarifying whether the different scales all have similar ability to predict, and if so, consider whether that suggests that all the other factors might be relatively unimportant.	Comment accepted. Text has been revised.
181-245 Section 5	1	**Comment:** Section 5 discusses physical frailty measures. The SPPB and gait speed are acceptable scales for physical performance assessment in older adults who are able to ambulate without significant pain or discomfort. SPPB, however, has not been validated for identifying frailty (3). Gait speed, on the other hand, has undergone an assessment which has shown that the sensitivity, specificity, and predictive values are cut-off dependent (7). Clegg et al. reported that a gait speed of <0.8 m/s has a	Comment noted. Text has been revised.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		99% sensitivity, 64% specificity, and 26% positive predictive value when compared with a reference standard test for frailty. This suggests that although almost all (99%) older adults with frailty will register positive at a gait speed of cut off of <0.8m/s, of those with a gait speed of <0.8 m/s, only 26% will truly be frail on the basis of the reference standard test (in other words, the false positivity rate was high). Hence, the use of gait speed as the only test for identifying frailty may not be sufficient; especially, in a population of older adults in which the baseline prevalence of frailty is low, as may be seen in many clinical trials. Thus, the limitations of SPPB and gait speed outweigh their simplicity for use in clinical investigations.	
181-233	2	**Comment:** We agree that based on their extensive use in the clinical setting, the Short Physical Performance Battery (SPPB) and Usual Gait Speed (UGS) have demonstrated the ability to predict adverse outcomes in older adults and reliably identify those individuals with increased vulnerability. These features make the SPPB and UGS suitable for assessing physical frailty, though they were not originally developed for this purpose. **Proposed change:** In the limitations section of Section 5.1 and 5.2, we encourage the addition of the word "modest" to the instrumentation requirements for the SPPB and UGS. While the instruments necessary to conduct the SPPB and UGS tests are not common every setting where frailty status would be assessed, they do not present a substantially high barrier to access for investigators and healthcare providers.	Comment accepted. Text has been reworded.
183-211 Section 5.1	11	**Comment:** We welcome the introduction of SPPB as the reference tool for operationalising physical frailty. The original Fried's criteria are not satisfactory for clinical trial endpoints. SPPB is increasingly used to operationalise physical frailty in the clinical research in geriatrics, including the SPRINTT CT. SPPB is more comprehensive with respect of Gait Speed, and should be preferred. Overall SPPB can be considered as a good indicator of the physical frailty status and of its changes over	Comment accepted. Text has been revised.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		time. What is not clear from the discussion in the draft document, it is if specific values of SPPB are intended to become a threshold for the selection of older patients expected to be enrolled in "general" phase 3 clinical trials. As stated elsewhere, frailty should not be intended as a justification for excluding older people from participating to clinical trials. Conversely, clinical trials should be adapted to older people participation if older patients are concerned by the condition that is going to be evaluated in the therapeutic trial.	
202-204	13	**Comment:** The SPPB does not identify a "preclinical disability". You may mean "physical impairment".	Comment accepted. Wording has been revised.
210-211	13	**Comment:** It simply requires a 4-meter long corridor and a chronometer. I do not understand what this "strip" is.	Comment accepted.
232-233	13	**Comment:** Same as above. Be aware that the gait speed can be assessed on different distances. 4 meters is usually considered as the standard, but it is very common to find 6 meters, 15 feet, 20 meters, 8 feet,... And it has been demonstrated that gait speed measured on different short-track distances maintains its properties. There are even equations for transforming results obtained on different distances to the 4-meter long standard.	Comment accepted.
246-367 Section 6	1	**Comment:** Section 6 discusses frailty and cognitive dysfunction. Although cognitive dysfunction may increase the risk of frailty in older adults, whether frailty increases the risk of cognitive dysfunction is an issue still under investigation. In a longitudinal study in which older adults without dementia underwent annual assessment for cognition, diagnostic assessment for Alzheimer's Dementia (AD), and frailty, both baseline level of frailty and annual rate of change in frailty level were associated with increased risk of incident AD (8). Such findings make	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		recommendations such as the proposal by EMA for determination of cognitive status of frail older adults reasonable. Indeed, documentation of the cognitive status of older adults participating in clinical investigations regardless of frailty status is also reasonable. This is because the prevalence of cognitive impairment increases with age and cognitive status influences many important aspects of clinical investigations including obtaining proper informed consent, understanding of the research procedures, etc. The EMA document considered MoCA the preferred instrument for baseline screening of the cognitive functions in geriatric clinical investigations. While MoCA has a sensitivity of about 90% for detection of Mild Cognitive Impairment (MCI), Mini-mental State Examination (MMSE) has a low sensitivity (~18%) (9). Also, in patients with mild AD, the sensitivity of MoCA was also appreciably higher than that of MMSE (100% versus 78%). Specificity was excellent for both MoCA and MMSE. Since, the typical older adult who will volunteer to participate in a non-dementia trial is more likely to have MCI than moderate or severe cognitive impairment, the low sensitivity of MMSE for MCI makes it suboptimal for screening of a geriatric clinical investigation population. Therefore, the MoCA preference in the EMA document is acceptable.	
265-266	1	**Comment:** In lines 265 to 266, the document states: "There is however, no direct correlation between depressive status and frailty, or data addressing to what extent depression modulates frailty due to cognitive handicap." It is unclear what is meant by "data addressing." Consider clarifying whether it means there have been insufficient data to allow a direct correlation between frailty and depression. If uncorrelated, consider clarifying whether that would indicate depression does not need to be evaluated.	Comment accepted. Text has been revised.
267	1	**Comment:** In line 267, the document states: "The same holds true for the social impact on frailty." Consider defining "The same" and clarifying whether	Comment accepted. Text has been revised.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		it means there is no direct correlation between social impact and depressive status or that there is insufficient information to know how one influences the other.	
269-277 Section 6.2	1	**Comment:** Certain scales are described in lines 269-277. Other scales exist and it is unclear why they were not included. Suggest clarifying.	Comment accepted. Text has been revised.
269-277 Section 6.2	3	**Comment:** There is another cognitive test that would be useful and feasible to assess cognitive dysfunction in frail elderly subjects, the SKT Short Cognitive Performance Test. Please add a sub-section 6.2.3 describing the SKT Short Cognitive Performance Test. **Proposed change:** Add a third paragraph: 3) SKT Short Cognitive Performance Test (Syndrom-Kurztest, SKT). <u>6.2.3. SKT Short Cognitive Performance Test</u> The SKT Short Cognitive Performance Test (German: Syndrom-Kurztest, SKT) has been published first in 1977 and validated extensively in Germany (Erzigkeit 1986). The SKT consists of 9 subtests and is rated on a linear scale; the total scores range between 0 and 27 with higher scores indicating more severe impairment. The SKT assesses above all memory and attention, but it also taps executive functioning as well as understanding and following instructions. It relies entirely on measurable aspects of performance, there are no subjective ratings. The 9 subtests encompass (I) naming objects, (II) immediate recall, (III) naming numerals, (IV) arranging blocks, (V) replacing blocks, (VI) counting symbols, (VII) reversal naming, (VIII) delayed recall, and (IX) recognition memory. There are normative values for various age groups, the youngest one being 17 to 44 years and the oldest one being 84 years and above. The SKT is most sensitive to assess the severity of cognitive impairment as	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		well as disease- or treatment-related changes from the early beginning of impairment to moderate dementia. Whereas the norms published in 2001 (Erzigkeit 2001) are still valid for late mild cognitive impairment (MCI) and mild to moderate dementia, a new scoring algorithm and new norms for healthy people and those in the earliest stages of cognitive impairment have been published in 2015 (Stemmler et al. 2015; Stemmler et al., in press). At the moment the new norms are suitable for German-speaking countries, but an English validation is in progress which will be available in 2017. SKT total scores correlate well with total scores of the Mini-Mental Status Examination (MMSE). Ihl et al. (1999) and Lehfeld et al. (1999) reported Spearman correlation coefficients (r_s) of -0.79 and -0.84, respectively. The following properties of the SKT render the test particularly feasible for the assessment of cognitive function in clinical trials and in the context of frailty: • The SKT is quick and easy to administer (test duration: 10 to 15 minutes). Due to the game-like procedures, testing is convenient to the tested subjects, which increases and helps maintain their motivation. • Five validated parallel versions are available, reducing training effects with repeated testing, typically seen in clinical trials. • The SKT discriminates well between cognitively healthy persons and those with mild cognitive impairment (MCI), with high sensitivity and moderate specificity, in particular when using the 2015 norms (Stemmler et al. 2015; Stemmler et al., in press). ROC analyses revealed good accuracy of classification with areas under the curve up to 0.88 for the detection of MCI and up to 0.96 for the detection of dementia (Hessler et al., in press). The SKT thereby compares favourably to the MMSE which has lower ROCs for the discrimination of MCI from healthy and demented from non-demented (Hessler et al., in press). The SKT discriminates better than the MMSE between healthy and minimally cognitively impaired persons, as classified by	

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		stages I and II of the Global Deterioration Scale (Lehfeld et al. 1999). It is therefore particularly useful to detect mild or even subtle cognitive deficits that are often present in pre-frail or frail persons (Boyle et al. 2010, Clegg et al. 2013) and to assess cognitive decline in frail persons who are prone to develop MCI and dementia. Likewise, the SKT is feasible for the assessment of treatment effects in clinical trials in patients with MCI or dementia. • SKT total scores and memory sub-scores at a certain point in time have high predictive values for further cognitive decline and for the development of dementia with in the following years (Bickel et al. 2007) • Frailty refers to a pre-morbid physical condition (Fried et al. 2001) that may be associated with mild cognitive impairment (cognitive frailty, Kelaiditi et al. 2013). A patient's abilities to cope with the demands of daily living may be compromised by physical frailty as well as by progressing cognitive impairment. It has been shown that SKT scores correlate well with functional abilities during the stage of MCI and in mild to moderate dementia (Lehfeld et al. 1997, Lehfeld & Erzigkeit 2000, Reisberg et al. 2001, Lehfeld et al. 2014) which seems to indicate that the cognitive functions measured by the SKT are relevant to the activities of daily living. • The SKT is feasible for the assessment of cognitive abilities, impairment and decline in international and worldwide research programs. ○ The test does not use written verbal material and does not require the reading or writing of words or sentences; it is therefore appropriate for use in samples that include pauci-literate subjects. Even many illiterate subjects may be able to read two letters as required by the reversal naming subtest. ○ The SKT does not use word lists for memory testing. Word lists do not only need translation in all languages in which the test is administered, they also need linguistic and	

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		cultural adaptation which usually is a difficult, time-consuming and expensive thing. Only slight modifications of the visual material used for memory subtests of the SKT were found necessary and feasible for certain cultures (Latin America, South East Asia). ○ The SKT has been validated in many countries in different areas of the world: Germany (Erzigkeit 1986, Stemmler et al. 2013), Sweden (Skjerve et al. 2008), the USA (Overall and Schaltenbrand 1992, Kim et al. 1993), Mexico (Ostrosky-Solís et al. 1999), Chile (Fornazzari et al. 2001), Brazil (Flaks et al. 2004), Korea (Choi et al. 2004) as well as in a multinational study carried out in Chile, Greece, Russia and England (Lehfeld et al. 1997). The test proved to be culture fair with a factorial structure remaining stable across cultures and languages (Lehfeld et al. 1997, and 1998).	
271-277	13	**Comment:** The choice of the instruments depends on the objectives of the evaluation. For example, I would say that the ADAS-Cog is more complex than the MMSE, but surely more accurate. In this context, I believe that the ADAS-Cog is even better accepted by regulatory agencies than those listed here.	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
288-289	1	**Comment:** In lines 288-289, the document states: "The MMSE is effective as a screening instrument to separate patients with cognitive impairment from those without it." However, in line 292, the document states: "Further limitations of use [of the MMSE] are inability to detect focal brain dysfunction or mild dementia." These two sentences appear to be in conflict. **Proposed change:** Consider revising the sentence that reads, "The MMSE is effective as a screening instrument to separate patients with cognitive impairment from those without it", to read instead, "The MMSE is effective as a screening instrument to screen for patients with moderate to severe	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		cognitive impairment."	
306-310	1	**Comment:** Section 6.2.1 includes a paragraph that lists the advantages of the MMSE and that ends with the following sentence: "The time of the assessment is short for both instruments." It is not clear which parts of the paragraph apply to the MMSE and which apply to the 3MS test. **Proposed change:** Consider clarifying which parts of the paragraph apply to both instruments and which apply only to the MMSE.	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
314-315 and 358-359	1	**Comment:** Consider if these two sentences are in conflict. In lines 314 to 315, the document states: "Neither the MMSE nor the 3MS have been designed primarily as a screening instrument for dementia." Lines 358-359 state: "Most instruments were either developed for dementia screening or MCI screening,…"	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
323	1	**Comment:** Section 6.2.1 lists the limitations of the MMSE and 3MS test, including "High threshold for illiterate or pauci-literate patients." The term "High threshold" may not be clear to all readers in this context. **Proposed change:** Consider revising to "May be inappropriate for illiterate or pauci-literate patients."	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
327-328	1	**Comment:** Section 6.2.2 begins with the following sentence to describe the MoCA: "Developed to identify early amnestic MCI, but including executive functions particularly important when studying vascular disorders (55), with patients at risk." Consider clarifying this sentence by explaining why executive functions are particularly important when studying vascular diseases and clarifying what patients are at risk for.	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
331-335	1	**Comment:** In lines 331 to 335, the document states: "In patients where cognition impairment is in the near dementia or dementia range, the Alzheimer's	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		Disease Assessment Scale – cognitive subscale (ADAS-cog) or Cognitive Drug Research (CDR) could be used for classification of degree of dementia, although there is evidence that the latter scale is less sensitive to short-term change and may be complicated for use in clinical practice (47, 56-58) (Refer to Guideline on Alzheimer Disease)." It is unclear whether the Alzheimer's Disease Assessment Scale – cognitive subscale and Cognitive Drug Research are components of the MoCA. Consider clarifying this.	frailty.
235-245 Section 5.3	13	**Comment:** I would talk (here and throughout the manuscript) of physical function assessment or physical impairment rather than physical frailty. The question is also: why are we going to assess physical frailty? According to the answer, different instruments can be identified. In this paragraph, there is the risk of mixing measures of physical performance (SPPB), muscle strength (hand grip), vital status/wellbeing (gait speed), and anthropometry (upper arm circumference). Moreover, I do not understand the final part of the statement also considering instruments for assessing sarcopenia (which are them, and why can we consider them as equivalent to the others when this is not true?).	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
347	1	**Comment:** In line 347, the document states that the MoCA "has a low threshold for illiterate or pauci-literate patients." The meaning of "has a low threshold" may not be clear to all readers. **Proposed change:** Consider revising the sentence to state that the MoCA "may be inappropriate for illiterate or pauci-literate patients."	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
351-367 Section 6.3	11	**Comment:** Cognitive impairment is relatively common in older patients and may vary widely in terms of concerned domains, degree, and related disability. We agree that appropriate evaluation of cognitive status, ideally via a multidomain tool like the MoCa, should be implemented in those clinical	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		trials where the pharmacodynamic effects of the investigational drug may affect the Central Nervous System, or if a predefined degree of cognitive impairment could meaningfully limit the actual participation to the clinical trial. Cognitive impairment per se should not be considered automatically an exclusion criterion in all other cases. **Proposed change:** "It is recommended that assessment of cognitive status is made at baseline in clinical trials only in those situations where the pharmacodynamic profile of a product (and the indication) indicates that this is appropriate in order to characterize the cognitive aspects of frailty of the older people included in these trials. Cognitive impairment *per se* should not be considered automatically as an exclusion criterion.	
351-367 Section 6.3	3	**Comment:** The recommendation should be modified to include the SKT Short Cognitive Performance Test. The suggested modifications are set in bold print in the proposed text below. **Proposed change:** (indicated by italic print) 6.3. Recommendation: cognitive function scales in relation to frailty It is recommended that assessment of cognitive status is made at baseline in clinical trials in those situations where the pharmacodynamic profile of a product (and the indication) indicates that this is appropriate in order to characterize the cognitive aspects of frailty of the older people included in these trials. There is no optimal scale for assessment of the cognitive aspects of frailty. Most instruments were either developed for dementia screening or MCI screening, and thus excluding psychosocial frailty. The SKT was developed for assessing cognitive impairment of memory and attention in general. The ease and quickness of assessment should be very important, if the scale is to be recommended for use in elderly clinical trial patients. The SKT, the 3MS and the MoCA are the best positioned instruments. MMSE (SKT and 3MS to a lesser extent) are more widespread in clinical trials. SKT and MoCA identify MCI, include domains not present in MMSE and are well validated. The SKT does not use	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		written verbal material, requiring less linguistic skills, and parallel versions are available. The SKT and the MoCA may be considered to be the preferred instruments for the characterization of the cognitive function in clinical trials. They can be administered quickly and include domains not present in MMSE.	
358	13	**Comment:** I do not believe that a frail person may require specific cognitive function tools (as suggested by this sentence). I would reword it as well as the following sentences. The assessment of cognition (as of any other domain) should be conducted using validated tests independently of the frailty status, as a physical function instrument can be administered independently of the syndrome of interest. Of course, taking into account the strengths and weaknesses of the instrument is important (in order to exclude ceiling/floor effects and guarantee accurate results).	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
365-367	13	**Comment:** Not sure whether it should be mentioned that the MMSE is protected by copyright (and a fee is due for its use).	Comment noted.
369-409 Section 7	1	**Comment:** Section 7 discusses frailty and malnutrition. MNA-SF is a validated instrument with sensitivity between 85.6 to 100% and specificity 37.8 to 100% (10). Therefore, EMA's suggestion of its use for baseline nutritional assessment in clinical investigations where the effects of the investigational product calls for such an assessment is reasonable. The prevalence of malnutrition in community-living older adults in the US is estimated at 5-10% (11); therefore, routine nutritional screening in clinical investigations is likely to be of low yield.	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
378-380	1	**Comment:** In lines 378 to 380, the document states: "The effect of malnutrition is rarely considered in studies on drug dosing or drug use (62) and has ramifications such as the poor precision of renal function estimation by creatinine clearance with low body weight." Consider clarifying this	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		sentence. **Proposed change:** Consider replacing the clause "such as the poor precision of renal function estimation by creatinine clearance with low body weight" with "such as inaccurate estimation of renal function due to reduced muscle mass and/or decreased protein intake."	
389-402 Section 7.2	11	**Comment:** We found very interesting and also very important the point 7, i.e. nutrition, in particular the section 7.2 "nutritional status assessment". Malnutrition is both a risk factor and a marker for mortality. Intensive care unit patients with a low albumin are the ones with the highest risk of dying in the hospital. A recent publication also showed that the quantity of protein ingested has a direct impact on the chair stand up test. So, malnutrition is also intricately interwoven with the assessment of the short physical performance battery. What is important about this is that malnutrition in the elderly is often correlated with a poor dental status. So, old people actually starve in their homes, because they cannot chew adequately, just restricting themselves to the consumption of soups. It should be emphasized that nutritional status has substantial repercussions, not systematically taken into consideration in routine medical practice, and not to be underestimated in clinical research. Therefore, we welcome the use of the MNA-SF as a baseline instrument in all these situations (the majority) where malnutrition in older age may act as a prognostic factor, in order to correct it and make the patient aware of possible quantitative or qualitative deficiencies of nutrients intake.	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
389-402 Section 7.2	5	**Comment:** Abbott Nutrition would like to propose two points to consider for this paper: 1. There are many validated screening and assessment tools available for use in addition to the MNA-SF 2. Nutrition screening and nutrition assessment are often done at	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		different time points, by different clinicians and with different tools. Nutrition screening is the primary mechanism for patients to be referred to a registered dietitian nutritionist (RDN) for further nutrition assessment, diagnosis, and intervention (1). Valid and reliable nutrition screening tools are needed to ensure that referrals and subsequent care is appropriate and targeting the right patients within the hospital setting. However, many hospitals do not utilize readily available valid and reliable screening tools but rather utilize facility-specific, lengthy nutrition screening tools, which have not been tested for reliability, validity or accuracy (2). In 2012, the Academy of Nutrition and Dietetics (AND) conducted an evidence analysis project to identify the most valid and reliable nutrition screening tools for use in acute care and hospital-based ambulatory care settings (3). Only one tool, the NRS-2002, received a grade I (3). Four tools, the Simple Two-Part Tool, the Mini-Nutritional Assessment-Short Form (MNA-SF), the Malnutrition Screening Tool (MST), and the Malnutrition Universal Screening Tool (MUST), received a grade II (3). Further, only the MST was shown to be both valid and reliable for identifying 'undernutrition' in the settings studied (3). Nutrition screening tools that are simple, quick and easily completed by non-professionally trained staff are preferred over tools requiring calculations such as body mass index (3). In 2002, ESPEN published guidelines for nutrition screening and recommended the following various screening tools based on healthcare setting – MUST for community adults, NRS-2002 for hospital patients, and MNA for the elderly (4). Further, according to a 2015 ESPEN consensus statement on malnutrition, the major use of these tools is to screen for malnutrition risk, and the subsequent clinical actions should implemented based on assessment of underlying mechanisms and type of nutritional problems, in order to design personalized nutritional therapies (5).	

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		Nutrition assessment follows nutrition screening for at-risk patients. This step is often completed by a RDN who is skilled in the assessment of an individual's nutritional status. In addition, other tools such as Subjective Global Assessment (SGA) are used for this assessment. The Academy of Nutrition and Dietetics has established the Nutrition Care Process (NCP), which is a systematic approach to providing high-quality nutrition care (6). It provides a framework to individualize care, taking into account the patient/client's needs and values and using the best evidence available to make decisions (6). Other disciplines in healthcare, including nurses, physical therapists and occupational therapists have adopted care processes specific to their discipline. The Nutrition Care Process consists of distinct, interrelated steps including nutrition assessment, diagnosis, intervention, and monitoring/evaluation (6). A similar process is recommended by BAPEN, where it is stated that "nutritional assessment is the systematic process of collecting and interpreting information in order to make decisions about the nature and cause of nutrition-related health issues that affect an individual (British Dietetic Association (BDA), 2012) (7)". BAPEN also states that this differs from nutritional screening which is a brief risk assessment which can be carried out by any healthcare professional and which may lead to a nutritional assessment by a dietician, and that following a structured assessment path enables health professionals to carry out a quality nutritional assessment in order to identify those who need nutritional intervention, and to improve clinical decision making using a person centred approach (7). **Proposed change:** Abbott's recommendation is to include other validated nutrition screening tools such as NRS-2002, MST or MUST as part of the paper's recommendation for screening for nutritional status.	
396-397	1	**Comment:** In lines 396 to 397, the document describes the MNA-SF, stating: "It is accurate to detect under-nutrition, able to detect significant changes, and has the ability to detect risk of malnutrition." Consider defining	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		malnutrition versus under-nutrition (as under-nutrition is used earlier in the sentence).	
399-402	13	**Comment:** The MNA (or MNA-SF) is sometimes considered as a frailty instrument because contains several items that are more related to the health status of the subject rather than on his/her nutritional status. Taking into account the heterogeneity of the populations and the limits of the available instruments, can we indeed exclude the presence of food frequency questionnaires from this paragraph? Even in this case, it is important to understand why we measure the nutritional status. If it is simply to have an idea of the risk of malnutrition presented by the participant, the MNA (or even the MNA-SF) would be fine. Nevertheless, in a trial including an intervention with potential direct or indirect effects on nutrition, I would expect something more than this. Similarly, what about anthropometric data (even mentioned above in the text)?	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.
401-402	1	**Comment:** In lines 401-402, the document states: "A self-MNA that can be filled by the patient/research subject may simplify its use in most settings." It is not clear what is meant by "self-MNA." Consider clarifying.	Comment noted.
406-409 Section 7.3	1	**Comment:** Section 7.3 provides recommendations with respect to nutritional assessment. Although we do not disagree with the recommended preferred tool, the prevalence of malnutrition in community-living older adults in the US is estimated at 5-10%; therefore, routine nutritional screening in clinical investigations is likely to be of low yield. Routine nutritional screening in geriatric clinical investigations, in the absence of potential effects of the investigational product on nutrition, should be discouraged.	Comment noted. To improve the focus of the document, the final Reflection paper only deals with physical frailty.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
411-476 Section 8	1	**Comment:** Section 8 discusses frailty and multimorbidity. CIRS-G is a validated instrument; as a result, the recommendation of the EMA for its use in geriatric clinical investigations is not objectionable. Although CIRS-G may provide a better estimate for the disease burden of an older adult than merely counting their comorbidities, and such accurate measurement of disease burden may be advantageous for control of confounding or achieving balance during randomization, its added value after the typical exclusion criteria are applied is unclear.	Comment noted.
430-431	1	**Comment:** In lines 430-431, the document states: "Two main aspects need to be considered in the relationship between frailty and multimorbidity (also called comorbidity when referred to an index disease)." Consider clarifying the clause "when referred to an index disease." **Proposed change:** Consider replacing "when referred to an index disease" with "in the context of an index disease."	Comment noted.
448-454	13	**Comment:** What about the simple count of diseases?	Comment noted.
469	13	**Comment:** The Geriatric Index of Comorbidity is not widely known (in particular if compared to the CIRD or the Charlson). It seems weird to have it recommended here.	Comment noted.
473-476	1	**Comment:** Section 8.3 provides recommendations with respect to multimorbidity assessment. Measurement of baseline multimorbidity with instruments such as CIRS-G will be valuable where exclusion criteria are minimal. Otherwise, the added value of CIRS-G is uncertain if clinical investigations continue to exclude older adults with morbidities.	Comment noted.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
478-489	13	**Comment:** This is arguable. Physical frailty seems more important simply because it is more studied and there are more interests around it (e.g. sarcopenia, nutrition). I think that social, behavioural, or cognitive aspects of frailty are equally predictive of negative outcomes. Again, the focus on an instrument or a specific aspect of frailty is related to the research question. I do not believe that it is possible (at least to date) to definitively state that one aspect (or instrument) is more relevant than others.	Comment noted.
488-489 and 148-149	1	**Comment:** In lines 488-489, the document states "where appropriate, to consider post-authorization studies to include a frail population characterized at baseline." Additionally, in lines 148-149, the document states that "the screening instruments will at least be able to capture baseline frailty characteristics for a clinical trial population." However, it would be ideal to continue to focus on the functioning of the frail throughout a clinical trial, to look beyond static trial outcomes that might be related to aging and frailty, and to look at the dynamic relationship between functional status and the morbidity and mortality seen in older patients. In other words, in addition to studying primary outcomes for frail individuals who happen to be enrolled in clinical trials, it would be worthwhile to study the effect of an intervention on frailty itself. It follows that it would be important to look at so-called "pre-frail" older individuals, one consideration being that a particular intervention may have the effect of preventing the development of frailty. The elderly transition between frailty states, which can be related to an acute medical event or a psychosocial stressor. It would be of interest to see whether a given intervention, no matter the intended disease target, is able to reduce the impact of potential stressors, and thus reduce the risk of becoming frail—or more frail. **Proposed change:**	Comment accepted. Text has been revised.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		We recommend that the EMA study (and maybe define) the degrees of frailty, as this might allow for a more precise determination of the effects of medical intervention on the elderly, and the elderly frail.	

3. References

FDA (Stakeholder number 1)

1. Fried LP et al. (2004): Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J. Gerontol. A Biol. Sci. Med. Sci., 59 (2004), pp. 255–263
2. Morley JE et al. (2012): A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012 Jul;16 (7):601-8.
3. Bouillon K et al. (2013): Measures of frailty in population-based studies: an overview. BMC Geriatrics, 13:64
4. Morley JE et al. (2013): Frailty Consensus: A Call to Action. J Am Med Dir Assoc. 14 (6): 392–397
5. J Am Geriatr Soc. 1991 Feb;39(2):142-8.The timed "Up & Go": a test of basic functional mobility for frail elderly persons. Podsiadlo D1, Richardson S.
6. Ann Intern Med. 2012 Oct 16;157(8):JC4-8. doi: 10.7326/0003-4819-157-8-201210160-02008. ACP Journal Club. Hirsch C.
7. Clegg A, Rogers L, and Young J (2015): Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review. Age and Ageing. 44:148-152
8. Buchman AS et al. (2007): Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosomatic Medicine 69:483-489
9. Nasreddine Z et al. (2005): The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. JAGS 53: 695-699
10. Secher et al. (2007): The Mini Nutritional Assessment (MNA) after 20 years of research and clinical practice. Reviews in Clinical Gerontology; 17:293-310
11. Maher D, Eliadi C (2013): Malnutrition in the elderly: An unrecognized health issue. Journal of Nursing.

Mark Stemmler (Stakeholder number 3)

1. Erzigkeit H. SKT: Kurztest zur Erfassung von Gedächtnis- und Aufmerksamkeitsstörungen. Manual. Erlangen: Geromed, 2001.
2. Hessler JB, Stemmler M, Bickel H. Cross-validation of the SKT for the detection of MCI and dementia. Journal of Gerontopsychology and Geriatric Psychiatry, (in press).
1. Ihl R, Grass-Kapanke B, Jänner M, Weyer G.
2. Neuropsychometric tests in cross sectional and longitudinal studies – a regression analysis of ADAS-cog, SKT and MMSE. Pharmacopsychiatry 1999;32:248-254.
3. Lehfeld H, Rudinger G, Rietz C, Heinrich C, Wied V, Fornazzari L, Pittas J, Hindmarch I, Erzigkeit, H. Evidence of the cross-cultural stability of the factor structure of the SKT short test for assessing deficits of memory and attention. International Psychogeriatrics1997;9:139-153.
4. Overall JE, Schaltenbrand R. The SKT neuropsychological test battery. Journal of Geriatric Psychiatry and Neurology 1992;5:220-227.

5. Stemmler M, Lehfeld H, Horn R. SKT nach Erzigkeit. SKT Manual Edition 2015. Spardorf: Geromed, 2015.
6. Stemmler, M., Lehfeld, H., Siebert, J.,, Horn, R. Ein kurzer Leistungstest zur Erfassung von Störungen des Gedächtnisse und der Aufmerksamkeit - SKT Manual Edition 2015 - und der regressionsbasierte Ansatz [A short performance test for the assessment of impairments in cognitive performance and information processing - SKT Manual Edition 2015 - and the continuous norming approach]. Diagnostica, (in press).

Further references (mentioned above, but not necessarily for inclusion into the points to consider):

7. Bickel H, Mösch E, Förstl H. Prediction of dementia. A prospective longitudinal study with the SKT short test [Vorhersage von Demenzerkrankungen mit dem Syndrom-Kurztest (SKT)]. Zeitschrift für Gerontopsychologie & -psychiatrie 2007;20:7-16.
8. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. Journal of the American Geriatrics Society 2010;58:248-255.
9. Choi SH, Lee BH, Hahm DS, Jeong JH, Ha CK, Han SH, Erzigkeit H, Na DL. Validation of the Korean version of the Syndrom Kurztest (SKT): a short test for the assessment of memory and attention. Human Psychopharmacology Clinical and Experimental 2004;19:495-501.
10. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in older people. Lancet 2013;381:752-762.
11. Erzigkeit H. Manual zum SKT Formen A-E. Ein Kurztest zur Erfassung von Aufmerksamkeits- und Gedächtnisstörungen. Ebersberg: Vless-Verlag, 1986.
12. Flaks MK, Regina ACB, Cid CG, Yassuda MS, Camargo CHP, Forlenza OV. The Short Cognitive Test (SKT) – a transcultural test for early detection and discrimination of dementia: a preliminary study in Brazil. Neurobiology of Aging 2004;25(Suppl 2):113.
13. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, for the Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. Journal of Gerontology 2001;56A;M146-M156.
14. Fornazzari L, Cumsille F, Quevedo F, Quiroga P, Rioseco P, Klaasen G, Martinez CG, Rhode G, Sacks C, Rivera E, Gassic I, Hammersley F, Hoppe A, Arriagada P, Flaskamp, R. Spanish validation of the Syndrom Kurztest (SKT). Alzheimer Disease and Associated Disorders 2001;15:211-215.
15. Kelaiditi E, Cesari M, Canevelli M, Abellan van Kan G, Ousset PJ, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salva A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten JL, Vellas B. Cognitive frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. Journal of Nutrition, Health & Aging 2013;17:726-734.
16. Kim YS, Nibbelink DW, Overall JE. Factor structure and scoring of the SKT test battery. Journal of Clinical Psychology 1993;49:61-71.
17. Lehfeld H, Reisberg B, Finkel S, Kanowski S, Wied V, Pittas J, Tsolaki M, Robert PH, Hulla F, Heininger K, Erzigkeit H. Informant-rated Activities-of-Daily-Living (ADL) assessments: Results of a study of 141 items in the U.S.A., Germany, Russia, and Greece from the International ADL Scale Development Project. Alzheimer Disease and Associated Disorders 1997;11(Suppl 4):S39-S44.
18. Lehfeld H, Wied V, Heinrich C, Kabanov M, Moesler T, Erzigkeit H. On the international validity of the SKT: A comparison of German and Russian test results in elderly patients with cognitive impairment [Zur internationalen Validität des SKT: Ein Vergleich von deutschen und russischen Untersuchungsergebnissen bei älteren Patienten mit kognitiven Beeinträchtigungen]. In: Gegenwärtige Probleme der russischen Psychiatrie. Ministerium für Gesundheitswesen und Medizinische Industrie Russlands / Psychoneurologisches Wissenschaftliches Forschungsinstitut W. M. Bechterew, St. Petersburg, 1998.
19. Lehfeld H, Ihl R, Schweizer A, Steinwachs K, Frölich L, Gutzmann H, Blaha L, et al. Psychometrische Schweregradbeurteilung bei dementiellen Erkrankungen: ein Vergleich von MMST, ADAS, BCRS und SKT. [Psychometric assessment of dementia severity: a comparison between MMSE, ADAS, BCRS and SKT.] Zeitschrift für Neuropsychologie 1999;10:187-202.

20. Lehfeld H, Erzigkeit H. Loss of activities of daily living function (ADL) and cognitive impairment in various stages of dementia. A comparison of ADL informant ratings, ADL self ratings and psychometric test results [Beeinträchtigungen der Alltagsaktivitäten (ADL) und der kognitiven Leistungsfähigkeit in unterschiedlichen Demenzstadien]. Fortschritte der Neurologie - Psychiatrie 2000;69:262-269.
21. Lehfeld H, Schläfke S, Hoerr R, Stemmler M. SKT Short Cognitive Performance Test and activities of daily living in dementia. GeroPsych 2014;27:75-80.
22. Ostrosky-Solís F, Dávila G, Ortiz X, Vega F, Ramos GG, de Celis M, Dávila L, Gómez C, Jiménez S, Juárez S, Corte G, Molina B. Determination of normative criteria and validation of the SKT for use in Spanish-speaking populations. International Psychogeriatrics 1999;11:171-180.
23. Reisberg B, Finkel S, Overall J, Schmidt-Gollas N, Kanowski S, Lehfeld H, Hulla F, Sclan SG, Wilms HU, Heininger K, Hindmarch I, Stemmler M, Poon L, Kluger A, Cooler C, Bergener M, Hugonot-Diener L, Robert PH, Erzigkeit H. The Alzheimer's Disease Activities of Daily Living International Scale (ADL-IS). International Psychogeriatrics 2001;13:163-181.
24. Skjerve A, Nordhus IH, Engedal K, Braekhus A, Nygaard HA, , Pallesen S, Haugen PK. Validation of the Seven Minute Screen and Syndrom Kurztest among elderly Norwegian outpatients. International Psychogeriatrics 2008;20:807-814.

Abbott Nutrition (Stakeholder number 5)

1. Writing Group of the Nutrition Care Process/Standardized Language Committee. Nutrition care process and model part I: the 2008 update. J Am Diet Assoc 2008; 108: 1113-1118.
2. Chima CS et al. Nutrition risk screening in acute care: a survey of practice. Nutr Clin Pract 2008; 23: 417-423.
3. Skipper A et al. Nutrition screening tools: An analysis of the evidence. JPEN J Parenter Enteral Nutr 2012; 36: 292-298.
4. Kondrup J et al. ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003; 22: 415-421.
5. Cederholm T et al. Diagnostic criteria for malnutrition: an ESPEN consensus statement. Clin Nutr 2015; 34: 335-340.
6. The Academy of Nutrition and Dietetics. http://www.eatrightpro.org/resources/practice/nutrition-care-process; accessed May 31, 2016.
7. The British Association for Parenteral and Enteral Nutrition. http://www.bapen.org.uk/nutrition-support/assessment-and-planning/nutritional-assessment; accessed May 31, 2016.

SPRINTT Consortium (Stakeholder number 11)

1. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56: M146-M156.
2. Gill TM, Gahbauer EA, Han L, and Allore HG. Trajectories of Disability in the Last Year of Life. N Engl J Med 2010; 362:1173-1180 April 1, 2010 DOI: 10.1056/NEJMoa0909087
3. Macklai NS, Spagnoli J, Junod J, Santos-Eggimann B. Prospective association of the SHARE-operationalized frailty phenotype with adverse health outcomes: evidence from 60+ community-dwelling Europeans living in 11 countries. BMC Geriatrics. 2013;13:3. doi:10.1186/1471-2318-13-3.
4. AT J, Bryce R, Prina M, et al. Frailty and the prediction of dependence and mortality in low- and middle-income countries: a 10/66 population-based cohort study. BMC Medicine. 2015;13:138. doi:10.1186/s12916-015-0378-
5. Roubenoff R. Sarcopenia: a major modifiable cause of frailty in the elderly. J Nutr Health Aging. 2000;4(3):140-2.
6. Evans W. Functional and metabolic consequences of sarcopenia. J Nutr. 1997 May;127(5 Suppl):998S-1003S.

7. Chumlea WC, Cesari M, Evans WJ, et al. Sarcopenia: Designing Phase IIB trials: International working group on Sarcopenia. The journal of nutrition, health & aging. 2011;15(6):450-455.
8. Clegg A1, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in Elderly People. Lancet. 2013;381(9868):752-762. doi:10.1016/S0140-6736(12)62167-9.
9. Del Signore S, Guillet P. Clinical trials in older Adults: a point of view from the industry. In the book Clinical Trials in Older Adults, First Edition edited by A. Cherubini, R. Bernabei, L. Ferrucci, N. Marchionni, S. Studenski and B. Vellas. 2015 John Wiley and Sons Ltd (P 23-43)