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# Points to consider on frailty: Evaluation instruments for baseline characterisation of clinical trial populations

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**List of Abbreviations**

3MS: Modified Mini-Mental State Test

6MWD: Six-Minute Walk Distance

AD: Alzheimer disease

ADAS-cog: Alzheimer's Disease Assessment Scale – cognitive subscale

ADL: Activities of Daily Living

CDR: Cognitive Drug Research assessment system

CGA: Comprehensive Geriatric Assessment

CHMP: Committee for Medicinal Products for Human Use

CIRS-G: Cumulative Illness Rating Scale-Geriatrics

ESPEN: European Society for Clinical Nutrition and Metabolism

GEG: Geriatric Expert Group

GIC: Geriatric Index of Comorbidity

ICH: International Conference on Harmonisation

MCI: Mild Cognitive Impairment

MMSE: Mini Mental State Examination

MNA-SF: Mini-Nutritional Status - Short Form

MoCA: Montreal Cognitive Assessment

PD: Pharmacodynamic

PK: Pharmacokinetics

SPPB: Short Physical Performance Battery

# Executive summary

Older persons are large drugs consumers for a number of chronic diseases, but despite this they have often been excluded from clinical trials. The ICH E7 Question and Answers advocates that *it is very important to ensure, to the extent possible, that the population included in the clinical development program is representative of the target patient population* and that *in the marketing application, depending on the numbers of patients, data should be presented for various age groups (for example <65, 65-74, 75-84 and > 85) to assess the consistency of the treatment effect and safety profile in these patients with the non-geriatric patient population*. It is recognised, however, that chronological age alone is a suboptimal predictor of susceptibility to adverse outcomes. These Points to Consider outline the general principles that may be applied for the baseline categorisation of older patients enrolled in a clinical trial or other clinical investigation (e.g. registry) on the basis of their frailty status. *A priori* subgroup analysis by baseline frailty parameters may then allow correlation with endpoints including those related to adverse events. Post-authorisation risk management could be a further potential area of application of such scales.

The following aspects of frailty are considered; physical frailty, cognitive dysfunction, malnutrition and multi-morbidity, with scales recommended categorising patients in these domains on the basis of their frailty status. Different scales focusing on specific aspects may be selected for a clinical development program to investigate the frailty status, according to the therapeutic area and the Pharmacodynamic (PD) profile of the medicinal product under investigation. 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. This document provides an overview of validated and therefore recommended instruments for characterisation of patient profiles for frailty and related states including cognitive impairment, malnutrition and multimorbidity. Those most relevant instruments can be selected to best match the product in development and the patient population to be studied. The development and validation of alternative / additional scales to better characterise specific populations is encouraged.

This document should be read in conjunction with other EMA and ICH (International Conference on Harmonisation) guidelines, which may apply to this patient population. This document is not intended to define a frail patient, or to support development programmes for indications such as sarcopenia and cachexia.

# 1. Introduction

Article 6 of the Clinical Trials Regulation ((EU) No 536/2014) requires a *justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria.*

Reasons for exclusion often have been poorly justifiable, and have included predefined arbitrary upper age limits, lists of different comorbidities or polypharmacy. Such frequent exclusion has generated a situation of "evidence biased", as opposed to evidence based medicine for older adults. This selection bias is even more evident for the frail elderly, who account for a large proportion of older persons at risk. Important elements to be considered in the development of a new medicine for use in the older population include the recruitment of sufficient numbers of elderly in appropriate age ranges (particularly the very elderly) for Pharmacokinetics (PK) as well as PK/PD analyses, the use of an age-appropriate measure of renal function, and awareness of and openness to testing covariates reflecting biological rather than chronological age. The very elderly often exhibit enhanced PD sensitivity and

thus exploration of the minimum effective dose is key to improving tolerability. Better characterisation of this growing segment of the population, following a standardized approach, might also help the evaluation of efficacy and safety of drugs in the post authorisation phase, and perhaps in defining enrolment criteria for future studies in the pre authorisation phase(1, 2).

To try to address this point, the EMA Geriatric Medicines Strategy included the following action:

*The Agency should perform a search among available documentation and other scientific data to identify available and validated instruments/methods (e.g. scales) which can be used to examine effect and safety in "frail" patients.*

In August 2011 the Committee for Medicinal Products for Human Use (CHMP) requested the GEG (Geriatric Expert Group) to perform such a search, and this Points to Consider document is the result of that work.

A standardized characterisation of frailty is potentially useful for risk stratification and to improve the description of the characteristics of older populations involved in clinical trials. If such frailty scales could be routinely introduced to characterise the baseline demographics of the population enrolled in a clinical trial for a drug with highly prevalent use in the older population, this would enhance the knowledge of the benefit/risk balance of the product in the target population.

# 2. Scope

These Points to Consider are intended to provide guidance only for the evaluation of the baseline frailty status of patients (typically, but not exclusively aged > 65 yrs.) enrolled in a clinical trial or other clinical investigation (e.g. registry), and to supplement the requirements of ICH E7 Questions and Answers.

# 3. Legal basis and relevant guidelines

The legal basis for the inclusion of older people in a clinical development program can be found in the Annex to the Clinical Trials Regulation (EC) No 536/2014.

The data requirements are found in Part II, Section 4 of the Annex I of Directive 2001/83/EC, as amended.

In addition, the following guidelines should be taken into account:

These Guidelines have to be read in conjunction with the introduction and general principles and Part I and II of the Annex I to Directive 2001/83/EC as amended. Applicants should also refer to other relevant adopted European and ICH guidelines.

- Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E7) and the Questions and Answers - EMEA/CHMP/ICH/604661/2009;
- Note for Guidance on Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4);
- Note for Guidance on Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9);
- Guideline on Missing Data in Confirmatory Clinical Trials - CPMP/EWP/1776/99 Rev.1-;
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety - CHMP/ICH/375/95 (ICH E1);
- Pharmacokinetic Studies in Man- EudraLex vol. 3C C3A;
- Note for Guidance on the Investigation of Drug Interactions - CPMP/EWP/560/95;

- Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 1) - EMA/838713/2011 Rev 1

# 4. The concept of Frailty

Frailty is a term used in Geriatric Medicine to identify older adults who are at increased risk of poor clinical outcomes, such as incident disability, cognitive decline, falls, hospitalization, institutionalization, or increased mortality. Frailty represents a reduction in resistance to stressors leading to increased clinical vulnerability and adverse health outcomes. Frail older persons are also vulnerable to clinically important adverse drug reactions. Hospital admissions related to medicines are especially seen in these patients and are often preventable (3-5). Cross-sectional studies suggest that about 7% of persons older than 65 years are frail, and that the prevalence of frailty increases with age and may exceed 45% after age 85.

Frailty is a dynamic process with several phases and in older persons can be preceded by multimorbidity and followed by the development of disability. However multimorbidity and disability often co-exist and overlap at least in part with frailty, therefore contributing to increasing the heterogeneity of the old population. Frailty prevalence increases with age, with a non-linear pattern, is higher in women than in men, but frail women have a better survival than frail men (6).

Although there is a general agreement on the necessity and usefulness of the concept of frailty, there is still a lack of both a consensus definition and a standardized assessment instrument to be used in clinical practice and in research. Thresholds based on chronological age, which are the prevailing indicators, are not sufficient, as they do not offer a good estimate of their biological age. Frailty develops as a continuum, from fit to pre-frail, and then frail older people.

The main controversy arises around the precise identification of frailty, as different models have included the exploration of either physical, functional, cognitive, social functioning measures or any combination of them (7-25). Different frailty models lead to identification of subgroups of frail older subjects which may not directly overlap in comparisons between the instruments (26). Multimorbidity, polypharmacy and nutritional status are clearly correlated with frailty but may exist independently from a frailty phenotype.

Although this document is focussed on the measurement of frailty, the experts of the GEG strongly recommend that frailty is not evaluated outside the framework of a multidimensional interdisciplinary comprehensive geriatric assessment (CGA) and thus this remains the 'gold standard'. Domains assessed in a typical CGA include multimorbidity, polypharmacy, socio-economic factors, nutritional status, plus physical and cognitive function. The reason underlying this recommendation is that the complexity of older subjects' health status cannot be characterised by a single frailty instrument. The advantages of CGA are its comprehensive nature, making it the optimal instrument for patient management in clinical practice. However its limitations include the time required for the assessment, lack of standardisation and the operator experience required for good reproducibility. These limitations render incorporation of CGA into clinical trials largely impractical. As such, attention has turned to the development of screening instruments which may correlate well with CGA. In clinical practice, identification of the 'fit' elderly who do not require subsequent CGA is desirable. 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. As such, the optimal screening instruments may be system or disease dependent and one size will not fit all. Consideration must also be given to disease-related frailty versus background frailty in the pre-morbid state.

Several frailty instruments have been tested and validated in epidemiological studies, while their application in clinical settings has been somewhat limited. The problems arising when using them in clinical settings are shown by a Dutch study, in which four often-used frailty instruments were investigated for their feasibility and effect on the selection of frail older patients among those consecutively admitted to an acute geriatric or old age psychiatry ward (27). The prevalence of frailty was different using different criteria and the patient populations identified by these criteria only partially overlapped. The author's conclusions were that "the choice of the most appropriate frailty criterion should be based on the purpose, the outcome on which the criterion was originally validated, the quality of the validation process carried out so far, and the similarity of the current population to the validation group".

Several studies compared the ability of different frailty scales to predict adverse outcomes in older subjects, in particular disability and mortality. A common finding is that different frailty scales capture different but overlapping groups of older adults (28). In general, the different scales can all predict these adverse outcomes, although the psychometric properties might be slightly different, in terms of sensitivity, specificity and area under the curve. In several studies the Frailty index showed the highest capacity to predict adverse outcomes, possibly related to its reliance on a larger set of information (29). 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. A major limitation of all these studies is the fact that frailty scales were usually adapted from the original definitions to use data available in each specific study (30).

Several specific instruments to measure physical frailty, cognitive function, nutritional status and multimorbidity can be considered. Parameters to be taken into account when making the choice are: validation status, predictive value, and ease of use. It is acknowledged that other instruments (e.g. G8 in geriatric oncology) may be used in clinical practice to identify patients for whom a comprehensive geriatric assessment is indicated to assist treatment decisions, but their scope is different.

# 5. Physical frailty

## *5.1. Short Physical performance battery (SPPB)*

The Short Physical Performance Battery (SPPB) assesses lower-extremity function by measures of three separate tests, i.e. standing balance, walking speed, and ability to rise from a chair (31, 32). A summary performance score was created by adding the scores for the tests of standing balance, walking, and repeatedly rising from a chair. The summary scores range between 0 and 12, with higher scores indicating better performance. The SPPB assessment takes 10-15 minutes (31).

Advantages:

Performance measures, such as the short physical performance battery and the gait speed at usual pace, are an attractive alternative to more complex measures. They can reliably identify the increased vulnerability that is the hallmark of frailty, being predictive of adverse outcomes in older subjects and have been extensively used in clinical settings (33-37).

Physical performance measures in general, appear to integrate the effects of multiple facets of health and aging, including disease processes nutritional status, fitness, and emotional state. Physical performance measures may offer advantages over self-report measures of functional limitation in terms of validity, reproducibility, sensitivity to change, applicability to cross national and cross-cultural

studies, and the ability to identify a "preclinical disability" in subjects who, because of high levels of function, are considered "normal" as a consequence of the ceiling effect that is a limitation to the scales currently used to assess disability (31).

Limitations:

The test was not originally developed to identify frailty. Moreover, it can have a floor effect, particularly in very sick patients or those with Activities of Daily Living (ADL) disability, who might be unable to do the performance test (21, 37). It requires some instrumentation (e.g.: a chronometer; a 4-meter strip and adequate space to position it, to measure gait speed).

## *5.2. Gait/walking speed*

Gait speed at usual pace is one of the tests of the SPPB, and in studies it has shown the same predictive ability as the whole battery (38-40). It is a good predictor of disability and survival in older adults (38, 41), and proved to add meaningful information to the assessment of prognosis of older individuals undergoing cardiac surgery (42, 43). Walking requires strength, coordination and balance, and thereby places demands on multiple organ systems, including the heart, lungs, circulatory, nervous, and musculoskeletal systems. Slowed gait may reflect both damaged systems and a high-energy cost of walking.

Advantages:

It is a simpler test than the whole battery of SPPB, and in some studies it has shown the same predictive ability, principally for mortality but also for incident disability. Gait speed could be considered a simple and accessible summary indicator of vitality because it integrates both known and unrecognised impairment of multiple organ systems, many of which affect survival. In addition, decreasing mobility may induce a vicious circle of reduced physical activity and de-conditioning that has a direct effect on health and survival (41).

Limitations: As mentioned for the SPPB, it requires some instrumentation (e.g.: a chronometer; a 4-meter strip and adequate space to position it, to measure gait speed), and training to personnel.

## *5.3. Recommendation: physical frailty assessment*

While all the criteria and scales presented in this section have advantages and disadvantages, the ones identified in this document may offer the best balance in terms of validation status, predictive value, ease and frequency of use, for the baseline characterization of the physical frailty level of older people enrolled in a clinical trial. The SPPB has many advantages and may be the preferred scale in many instances. Should it not be practical to assess physical frailty by SPPB then Gait Speed is an alternative instrument, though not as well validated, nor as multifaceted as SPPB. In patients with lower limb disorders, there are no instruments available with validation comparable to SPPB but Hand Grip Strength, upper arm circumference (44), or selected instruments used to assess sarcopenia (45) would be alternative options.

# 6. Frailty and Cognitive dysfunction

## *6.1. General considerations on frailty and cognitive dysfunction*

Frailty in the context of cognitive dysfunction is poorly studied compared to physical frailty, and therefore the most suitable instruments for assessment are less well validated. A number of epidemiological studies have reported that frailty increases the risk of future cognitive decline and that cognitive impairment increases the risk of physical frailty suggesting that cognition and frailty interact mutually (46, 47). The probability of delirium is increased in cognitively impaired individuals demonstrating increased vulnerability in this population (48). The elderly as a group may be more vulnerable to drugs that can reduce their cognition such as anticholinergic drugs (49). Drugs with certain actions such as dopamine agonists can cause more confusion and visual hallucinations. Several acute or systemic disorders may be associated with frailty and cognitive decline, without being related to CNS degeneration (adverse drug reactions, electrolytic imbalance, food deprivation, and hypothyroidism).

Cognition is not only influenced by physical frailty but also by psychosocial parameters. Therefore, factors that can influence cognitive function such as depression and educational level should be carefully evaluated in all individuals included in clinical trials, where the evaluation of the impact of frailty on cognitive function is considered important. There is however, no direct correlation between depressive status and frailty, or to what extent depression modulates frailty due to cognitive handicap. The same holds true for the social impact on frailty.

## *6.2. Proposed scales*

The following scales are suggested to be used in clinical trials for cognitive function:

*1) Mini Mental State Examination (MMSE)* - or the abridged version Modified Mini-Mental State Examination (3 MS) score (50). The 3 MS is an expanded version of the MMSE to yield better psychometric properties (51).

*2) Montreal Cognitive Assessment (MoCA)*

### 6.2.1. Mini-mental state Examination (MMSE)(52) and Modified Mini-mental State Exam (MMS, or 3MS)(53)

The MMSE was developed in 1975 as a bedside instrument to evaluate the cognitive status of elderly people in clinical settings and has been validated and extensively used in clinical practice and research. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The MMSE takes only 5-10 minutes to administer and is therefore practical to use repeatedly and routinely.

The MMSE is effective as a screening instrument to separate patients with cognitive impairment from those without it. The instrument relies heavily on verbal response and competence of reading and writing. Therefore, patients that are hearing and visually impaired, intubated, have low literacy or those with other communication disorders may perform poorly even when cognitively intact. Further limitations of use are inability to detect focal brain dysfunction or mild dementia. There is no administration manual so that scoring and interpretation varies between users.

In 1987, a modified version of the MMSE was introduced. Four additional items (on long-term memory, abstract thinking, category fluency, delayed recall) were introduced to assess a broader range of cognitive capacity and difficulty levels. More uniform administration and a refined scoring were incorporated to enhance the reliability and validity of the test scores.

The 3MS test has a score range of 1–100 and takes 8-15 minutes to administer. It can provide an estimated score of the MMSE, and can also be used to monitor cognitive change over time. It is more sensitive than the MMSE in detecting within-individual changes over time. By now a large body of literature has shown the usefulness of the 3MS test in both research and clinical studies.

*Advantages*:

The MMSE is an ubiquitous scale, used as a screening instrument for dementia in CNS and non CNS trials. It is easy to compare among trials. It has been in use for almost 40 years, it is easy to use by psychologists, clinicians, study nurses and other clinical trial staff. It explores several domains: orientation, calculus, memory, delayed recall, language, praxis. The time of the assessment is short for both instruments.

*Limitations:*

- Neither the MMSE nor the 3MS have been designed primarily as a screening instrument for dementia.
- Not formally validated in most languages
- Does not quantify the response time
- Is less sensitive to executive functions (which may be significant in frail persons)
- High threshold for illiterate or pauci-literate patients

### 6.2.2. Montreal Cognitive Assessment (MoCA)(54)

Developed to identify early amnestic MCI, but including executive functions particularly important when studying vascular disorders (55), with patients at risk. Also, in research projects where periodic cognition frailty assessment or if repetition of evaluation within 3 months is needed, the learning effect should be considered. MoCA is a rapid cognitive test, available in multiple languages and easy to apply, encompassing all of these aspects. In patients where cognition impairment is in the near dementia or dementia range, the Alzheimer's 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 recognized that a psychological component of the condition is evident and increases the vulnerability of the individuals. Specific tests for assessment of depression and / or social role are not being proposed, as their relation to cognitive frailty is variable as signalled above. Also their assessment usually depends upon experienced clinicians.

MoCA is an easy to fill in, intuitive scale designed as a screening instrument for early detection of mild cognitive impairment (MCI), it can be administered in about 10 – 15 minutes (including patient intervention) by psychologists, clinicians, study nurses and other clinical trial staff. MoCA has been in use for almost 10 years and is formally validated in more than 60 languages and for the blind. It

explores several domains: orientation, calculus, abstraction, delayed recall, memory, language, praxis, visuospatial / executive and attention, and has a low threshold for illiterate or pauci-literate patients.

A limitation of MoCA is that it is less well known, particularly in non-neurological / psychiatric trials.

### *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 ease and quickness of assessment should be very important, if the scale is to be recommended for use in elderly clinical trial patients. The 3MS and the MoCA are the best positioned instruments. MMSE (and 3MS to a lesser extent) are more widespread in clinical trials. MoCA identifies MCI, includes domains not present in MMSE and is also well validated.

The MoCA may be considered to be the preferred instrument for the baseline characterization of the cognitive function in clinical trials. It can be administered quickly and includes domains not present in MMSE. Alternatively, 3MS or MMSE could be used.

## 7. Frailty and malnutrition

### *7.1. General considerations on malnutrition*

Malnutrition is more common in older persons as a consequence of many age associated physical, mental and social conditions, and may result in cachexia/sarcopenia. Malnutrition is associated with a reduced overall survival and is an independent risk factor for morbidity and mortality (59) both in general geriatric patients and in those with different chronic diseases (60, 61). Awareness of this problem is therefore important. However, malnutrition is not usually measured or considered in clinical trials of most chronic diseases. 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.

Malnutrition has a dramatic influence on both older individuals and health and social care systems. In one study, at least 20% of care home residents were malnourished, and one out of four patients in hospitals is undernourished, leading to increased length of hospital stay and costs of care (63). Many countries are considering the implementation of universal malnutrition screening for adults at hospital admission. Malnutrition can change the effects of drugs, and polypharmacy increases the risk of malnutrition (64).

### *7.2. Nutritional status assessment: Mini-Nutritional Status - Short Form (MNA-SF)*

The European Society for Clinical Nutrition and Metabolism (ESPEN) suggested some time ago the use of the 30 points Mini-Nutritional Status (65) for assessment of nutritional status in older individuals, as it is the best validated instrument in this population (66). Further research developed and validated a shorter form of this scale (Mini-Nutritional Status - Short Form (MNA-SF)) (67) that is now widely used

in clinical research and practice in subjects age 65 and above. It is accurate to detect under-nutrition, able to detect significant changes, and has the ability to detect risk of malnutrition.

Again, detailed scoring guidelines in different languages are available for both versions. Although the SF version could be considered standard, some specific clinical trials requiring a more detailed nutritional assessment may considered using the full 30-items MNA instrument. A self-MNA that can be filled by the patient/research subject may simplify its use in most settings.

### *7.3. Recommendation: nutritional assessment*

It is recommended that assessment of nutritional 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 nutritional aspects of frailty of the older people included in these trials. The MNA-SF could be considered to be the preferred tool.

## 8. Frailty and multimorbidity

### *8.1. General considerations on multimorbidity*

The fast increase in life expectancy in recent years, together with reduced mortality from previously fatal diseases has turned many acute conditions into chronic diseases that last for the rest of the lifespan of an individual. The prevalence of most chronic diseases increases with age, so it is not surprising that many older individuals suffer from two or more chronic conditions, a situation named multimorbidity. Prevalence of multimorbidity in older persons ranges from 55 to 98%, and is higher with old age, female gender and low socioeconomic status (68).

Multimorbidity is characterised by complex interactions of co-existing diseases. Major consequences of multimorbidity are disability and functional decline, poor quality of life, and high health care costs. Usual medical diagnostic and therapeutic approaches focused on each single disease do not account for disease interactions and may impair health and functional outcomes. There is still little scientific evidence on how to care for such individuals, as multimorbidity is frequently used as an exclusion criterion for clinical trials in older people (1, 69).

Frailty and multimorbidity are closely related, although the interaction remains incompletely understood (70-72). Two main aspects need to be considered in the relationship between frailty and multimorbidity (also called comorbidity when referred to an index disease):

1) The frailty process is modulated by each disease and by the total burden of diseases; and

2) Frailty modifies the negative effects of diseases leading to adverse outcomes.

Multimorbidity may have an impact on the effect of drugs in older people in two ways:

a) a drug used to treat a given disease may have an impact on other concurrent disease(s) (i.e. beta blockers used for hypertension may impair control of diabetes or asthma);

b) the total burden of disease (multimorbidity) or other clinical situations may render a subject vulnerable to adverse effects of any drug, a situation further complicated by the interactions between multiple drugs used to treat multiple diseases, and by prescription cascades (using drugs to treat adverse events of other drugs).

Both a) and b) are often inadequately studied in clinical trials and problems derived of the use of new drugs in multimorbid individuals usually show up in the post-marketing setting, when the drug is extended to such patients in usual clinical practice. This section focuses on the second situation [b)].

Since Kaplan and Feinstein started measuring comorbidity in 1974, many instruments have been developed and used to measure multimorbidity. Some of them have been developed to be used in older people (Charlson Comorbidity Index, Chronic Disease Score, Cumulative Illness Rating Scale-Geriatrics, Geriatric Index of Comorbidity, Index of Coexistent Diseases, Kaplan). Of these, Geriatric Index of Comorbidity (GIC) and Cumulative Illness Rating Scale-Geriatrics (CIRS-G) seem to be the most accurate predictors of negative outcomes in older subjects (73). Most comorbidity scales are built on information obtained from medical records, administrative databases or from the patient.

### *8.2. Multimorbidity: Cumulative Illness Rating Scale - Geriatrics (CIRS-G)*

This scoring system measures the chronic medical illness ("morbidity") burden while taking into consideration the severity of chronic diseases in 14 items representing individual body systems.

The general rules for severity rating are: 0 (no impairment) to 4 (life-threatening/extremely severe impairment), based on clinical judgment. It has been validated in geriatric inpatients and outpatients, and in long term patients. Criterion validity has been confirmed using autopsy as gold standard, and the instrument has good inter-rater and test-retest reliability. It predicts mortality, hospital readmission, prolonged hospital stay and nursing home admission.

The availability of detailed guidelines for scoring (74), and its validation in different settings and populations of older subjects suggest that CIRS-G, a scale based on medical record can be employed in clinical practice as well as in clinical research (75). GIC may be a valid alternative.

### *8.3. Recommendation: multimorbidity assessment*

Measuring baseline multimorbidity of older subjects in a clinical trial may allow for a better characterisation of the population included, improving comparability with the real world clinical populations; and may also allow for a better understanding of the relationship between medicines and multimorbidity. The CIRS-G may be considered the instrument of choice.

## 9. Conclusion

This document provides a menu of instruments to characterise baseline frailty status, from which relevant instruments can be selected based on the PD profile of the investigational product and the objectives of the clinical trial development programme. . 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, as physical frailty has been more strongly correlated to susceptibility to adverse outcomes. This menu is not exhaustive and other validated instruments may be more suitable in specific circumstances. A broader aim is to encourage recruitment of patients into clinical trials that represent the target population for use of the product, as discussed in the ICH E7 Q & A and the Clinical Trials Regulation (EC) No 536/2014, and where appropriate to consider post-authorisation studies to include a frail population characterised at baseline using these instruments.

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