Regulatory considerations on frailty and sarcopenia

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What is the EMA?

~4000 Scientific experts from right across Europe

7 Scientific committees

over 1000 marketing authorisations recommended

1995 EMA established to evaluate medicines for use in the EU

28 Working parties

~840 Staff members
Content of this presentation

• The EMA Geriatric Medicines strategy

• Regulatory considerations on frailty as RCT stratification criterion

• Regulatory considerations on sarcopenia as potential indication
Cardiovascular drugs

- In Italy patients 65+ spend >65% of the pharmaceutical budget
- 63% of DDD
- 50% older subjects receive 5+ medications

* Extracted from "L'uso dei farmaci in Italia 2011" and Italian census 2011

Cerreta et al. NEJM 2012
EMA Geriatric medicines strategy (2011): TWO PRINCIPLES

Medicines used by geriatric patients must be of high quality, and appropriately researched and evaluated... 
for use in this population.

Improve the availability of information on the use of medicines for older people

Evidence based medicine

Informed prescription
Clinical Trials Regulation (EU) No 536/2014

Art 6

Member States will assess... “the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, explanation and justification is provided in accordance with...Annex I...”

∞∞∞∞

Annex I paragraph 17 point (y)

..justification for the gender and age allocation of trial subjects....if a specific gender or age group is excluded from or underrepresented in the trials, an explanation of the reasons and justification for these exclusion criteria...
CHMP 2016 pilot (in 10 products)

The EMA CHMP (committee for human medicinal products) in 2016 will do in depth analysis in approval documents of geriatric data (epidemiology, RCTs, Pharmacovigilance measures)

FDA drug trials snapshot

Sex, race and age in approved products (65+)
http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm
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Heterogeneity of the older population

The Comprehensive Geriatric Assessment (CGA) is the gold standard for the evaluation of health status of older subjects and hence also for frailty assessment and management. CGA evaluates several domains, e.g. general health, multimorbidity, polypharmacy, socio-economic factors, nutritional status, physical and cognitive function, disability.

... but it is impractical for routine characterisation of RCT populations
Regulatory guidance (ICH E7) categorises older patients on the basis of chronological age (65-74; 75-84; 85+)

**Chronological age** alone is a suboptimal predictor of susceptibility to adverse outcomes

Is the clinical trial population representative of the real world population?

Are there any validated and simple tools for clinical trial population frailty status characterisation?
Draft points to consider on frailty: Evaluation instruments for baseline characterisation of clinical trial populations

Document details

Download document: Draft points to consider on frailty: Evaluation instruments for baseline characterisation of clinical trial populations

Reference number: EMA/CHMP/970057/2011

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Email address for submissions: geriatrics@ema.europa.eu

Aim of frailty baseline characterisation

To characterise a clinical trial population at **baseline** – *not* to measure *change* in frailty status (not a clinical development outcome measure) on the basis of (pick one or more):

- Physical Frailty
- Cognitive Function
- Nutritional Status
- Multimorbidity

Frailty status (or lack thereof) may used to inform on regulatory decision (e.g, Pharmacovig.)
How have the instruments been selected?

- Ease of use
- Validation status and predictive value

Physical frailty preferred as general choice, but PD profile of drug may indicate cognitive/nutritional/multimorbidity should be chosen.
Frailty baseline characterisation

Physical Frailty

• Short Physical Performance Battery (SPPB)
• Walking speed (second choice)
Physical Frailty: SPPB

Advantages:

• Alternative to more complex measures
• It has been used extensively in clinical settings
• Reliably identifies increased vulnerability
• Predictive of adverse outcomes in older subjects
• Appears to integrate the effects of multiple facets of health and aging
• It 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

EMA/CHMP/778709/2015
Physical Frailty: SPPB

Limitations:
• not originally developed to identify frailty
• It can have a floor effect
• Requires some instrumentation (e.g. a chronometer, a 4-meter strip and adequate space to position it to measure gait speed) and training

Preliminary comments (consult. ends 31/5):
• What about the Fried criteria and the FRAIL scale, GetUP and Go, MiniCog...?
Frailty and Cognitive dysfunction

• Montreal Cognitive Assessment (MoCA) - preferred
• Mini Mental State Examination (MMSE) or the Modified Mini-Mental State Exam (3MS)
Frailty and Malnutrition

Mini-Nutritional Status- Short Form (MNA-SF)

(in those situations where the pharmacodynamic profile of a product indicates that this is appropriate)
Frailty and Multimorbidity

Cumulative Illness Rating Scale - Geriatrics (CIRS-G)

Post-authorisation use?
Conclusions on frailty as stratification in RCT

- Older people are often excluded from clinical trials
- Population enrolled in clinical trials should be representative of the target population
- Assessment of physical frailty and other related domains (cognitive dysfunction, malnutrition, multimorbidity) would allow a better characterization of the older population enrolled in clinical trials
- It would also allow the identification of subgroups of older subjects with a different risk to benefit ratio
- A better characterization of the older population might help the evaluation of efficacy and safety of drugs in the post-authorization phase
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Using an outcome measure to support a drug labeling claim

Claim

How you measure
(NB: content validity)

What you measure
(clinically relevant concept of interest)
How to develop a drug for sarcopenia?

• Is Sarcopenia a recognised condition?
• Models of disease/condition?
• How to define the population to be treated?
• Characteristics and severity that justify a clinical intervention
Sarcopenia: potential populations for clinical investigation

For example:

- Hip fracture
- COPD

Can a purely sarcopenic population be defined? Is “aging” an illness / condition?

Is there a common underlying mechanism?
How to develop a drug for sarcopenia?

• How do I measure a clinically meaningful effect?
• Does strength increase lead to functional improvement?
• minimum clinically important benefit?
Valid scales and biomarkers

Widely used does not mean validated

- The scale/biomarker content must be clinically meaningful
- Prognostic biomarkers (asymptomatic or early stage)
- Biomarker trajectory, disease activity and severity
- Biomarkers for prediction of response
- Confounding effects must be explored
How to develop a drug for sarcopenia?

What **endpoints** matter?

Which **tools** have face validity and are **validated** to correlate with a clinical outcome?

- Muscle mass (DXA, MRI, CT...)
- Muscle strength (Quantitative MS)
- Performance based measures (6MWT, SPPB...)
- PRO tools (PF-10, AM-PAC, IBM-FRS...)

How to develop a drug for sarcopenia?

Intervention as adjunct to exercise (diet?)

Reversal improves clinical outcome?

 Probably a co-primary endpoint:
 Performance based measure
 +
 Patient reported outcome
Conclusions

Please comment on frailty guidance


Deadline: 31/5/2016

Keep up with quality research work in sarcopenia

So we can build a strong chain!