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SCIENCE MEDICINES HEALTH

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

CHMP
PRAC
CVMP
COMP
HMPC
CAT
PDCO

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

The EMA Geriatric Medicines strategy

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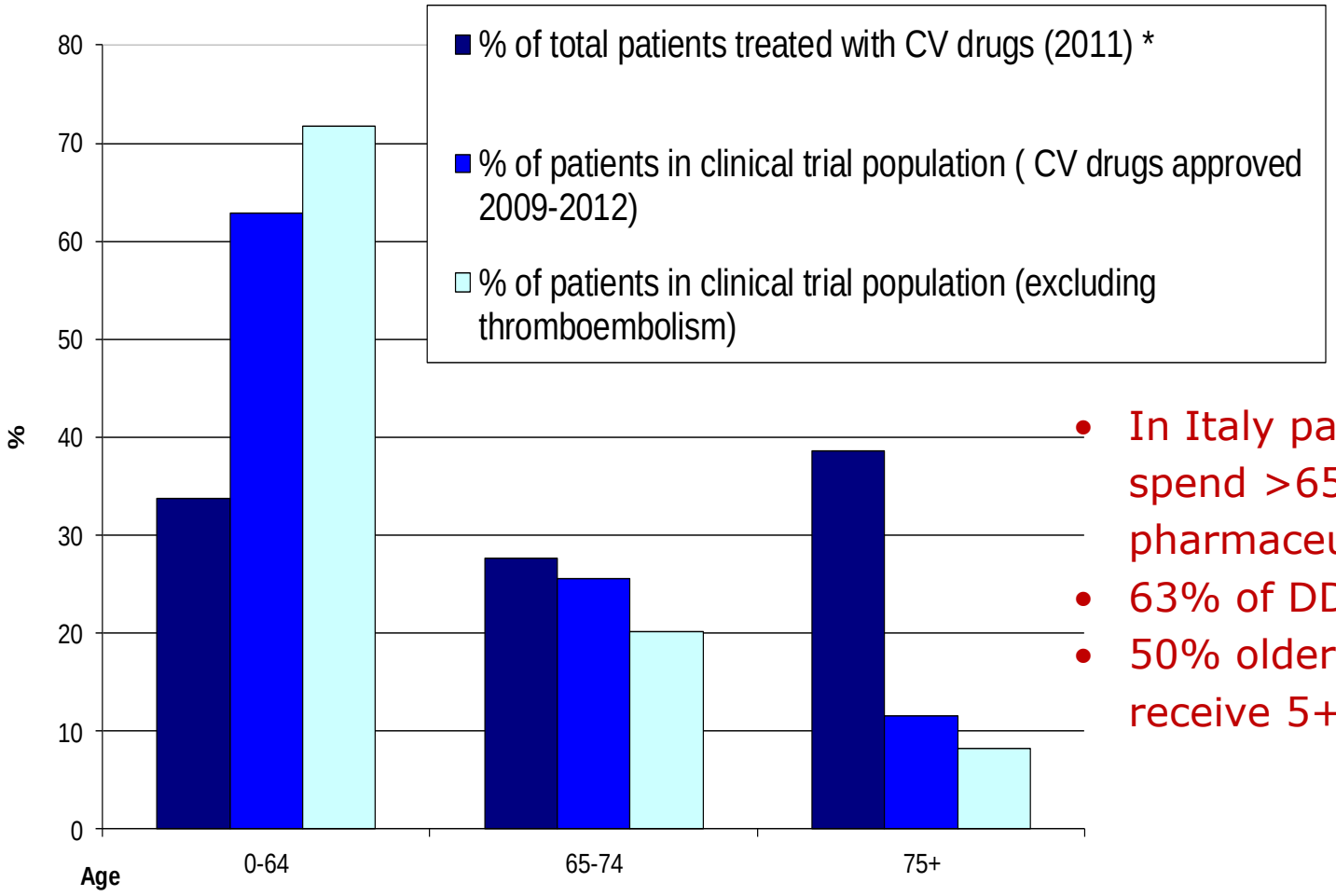
Cardiovascular drugs



- 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.

⇒ **Evidence based medicine**

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

⇒ **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

Frailty baseline characterisation

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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
Status	draft: consultation open
First published	21/12/2015
Last updated	21/12/2015
Consultation start date	21/12/2015
Consultation end date	31/05/2016
Email address for submissions	geriatrics@ema.europa.eu

Link: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/12/WC500199243.pdf

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.)

Points to consider on frailty: Evaluation instruments for baseline characterisation of clinical trial populations EMA/CHMP/778709/2015 **DRAFT**

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

Physical Frailty

- Short Physical Performance Battery (SPPB)
- Walking speed (second choice)

Physical Frailty: SPPB

Advantages:

EMA/CHMP/778709/2015

- 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

Physical Frailty: SPPB

EMA/CHMP/778709/2015

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)

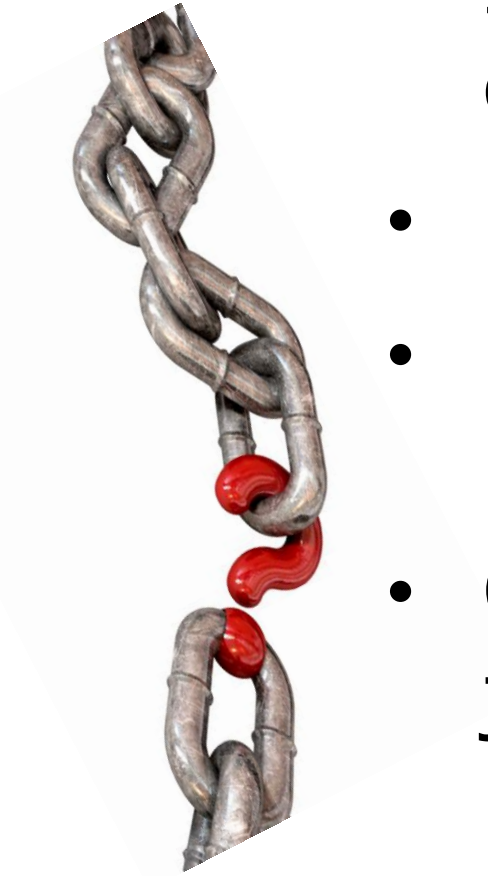
↑

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

Confounding factors are a big problem!

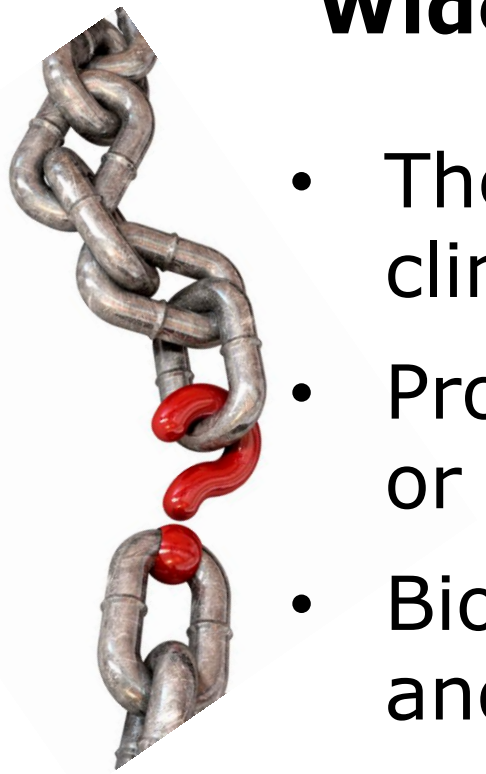
Can a purely sarcopenic population be defined? Is "aging" an illness / condition?

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?

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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

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/12/WC500199243.pdf

Deadline: 31/5/2016

Keep up with quality research work in sarcopenia

So we can build a strong chain!