NDA Advisory Services

Vaccine Advice

Frailty evaluation instruments for baseline characterisation of clinical trial populations

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Disclaimer

- Although I have been a member of the CHMP, my presentation might not be the view of the CHMP, the European Medicines Agency (EMA), the Belgian Medicines Commission, neither of the Vaccine Working Party.
- My presentation is a personal viewpoint and binds in no way the organisations mentioned before.
- Thirdly, I am an (ex-)regulator and not a geriatrician… I am not a Frailty-evaluation expert

Declaration of interest

- I signed a non-exclusivity consultancy contract with
  - Novartis V
  - Crucell Holland BV
  - NDAreg
  - GSK
  - Inovigate
  - Gilead
  - Janssen
  - Takeda
  - ITS
  - Adimmune
  - …

Introduction

EMA has a PDCO… with very stringent legislation

And today EMA has a GEG… Geriatric Expert Group

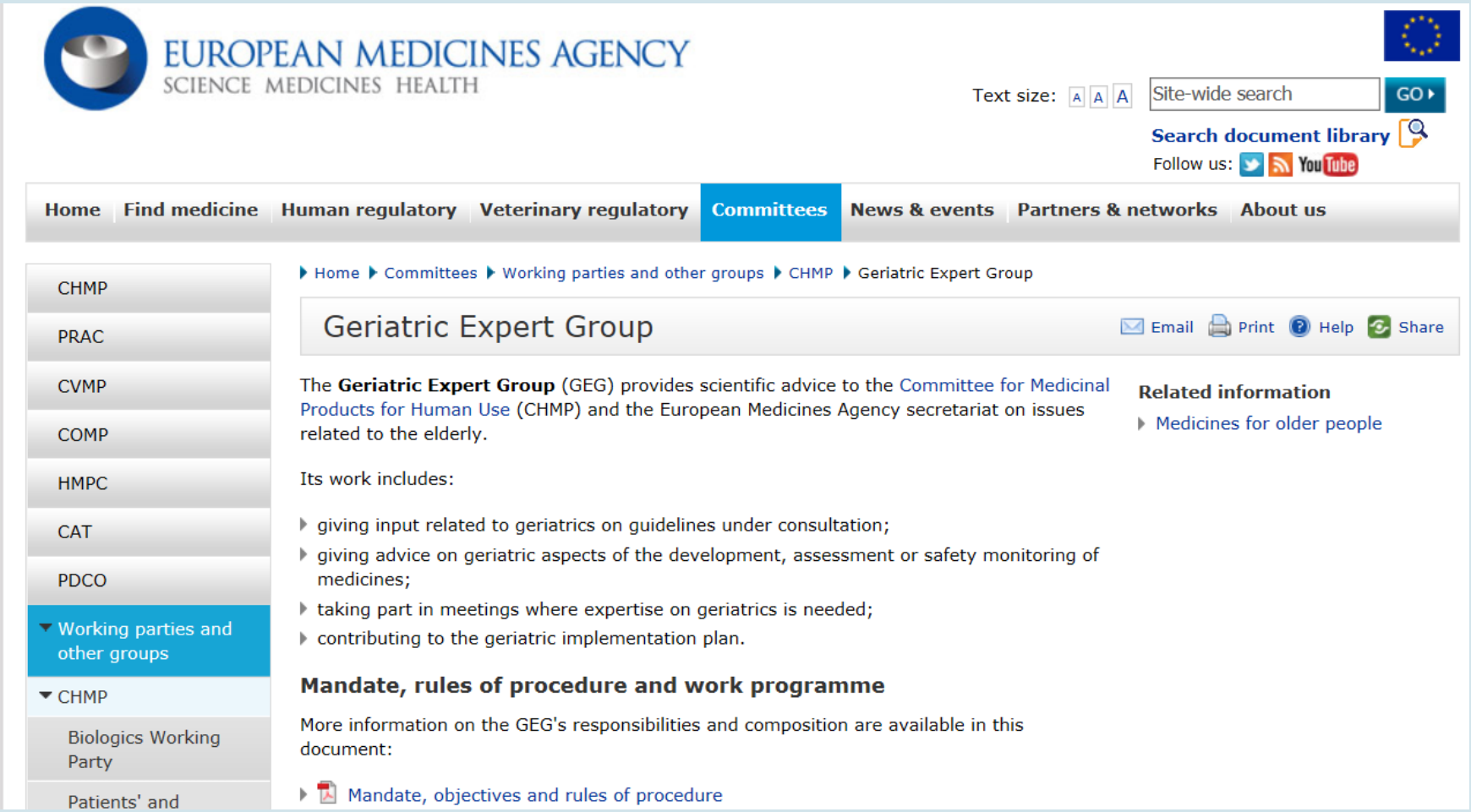
The differences between PDCO and GEG are huge:

- PDCO is a committee, GEG is a (virtual) working party
- PDCO has EU legislation, GEG had nothing, until very recent a draft guidance document
- PDCO PIPs are binding: compliance check:

  ⇒ Not compliant with the PIP: no start of a registration procedure

Introduction

GEG



http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000100.jsp&mid=WC0b01ac0580473f01

Introduction

GEG

Members

Below (in alphabetical order of surname) are the current **members** of the GEG. The members' declarations of interests are available in the European expert list.

- Joel Ankri
- Antonio Cherubini
- Adalsteinn Gudmundsson
- Paul Jansen
- Niccolo' Marchionni (Chair)
- Susan Morgan
- Mirko Petrovic
- Hans Wildiers

Introduction

GEG

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 December 2015
EMA/CHMP/778709/2015
Committee for Medicinal Products for Human Use (CHMP)

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

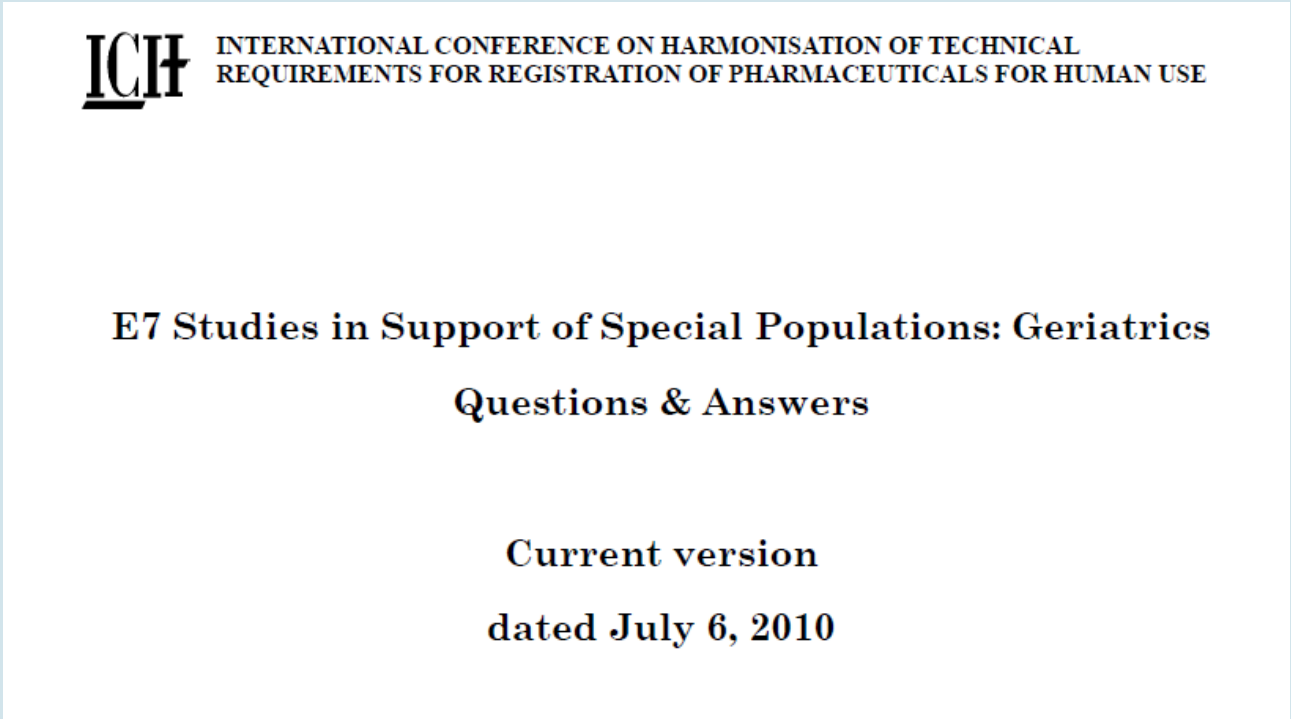
Draft

Draft agreed by Frailty PtC drafting Group	March 2015
Draft agreed by Working parties	May 2015
Draft agreed by Guidelines Consistency Group	November 2015
Adopted by CHMP for release for consultation	16 December 2015
Start of public consultation	21 December 2015
End of consultation (deadline for comments)	31 May 2016

Introduction

Other important references:

- **ICH E7 Q&A:**
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Q_As/E7_Q_As_step4.pdf



ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

E7 Studies in Support of Special Populations: Geriatrics

Questions & Answers

Current version

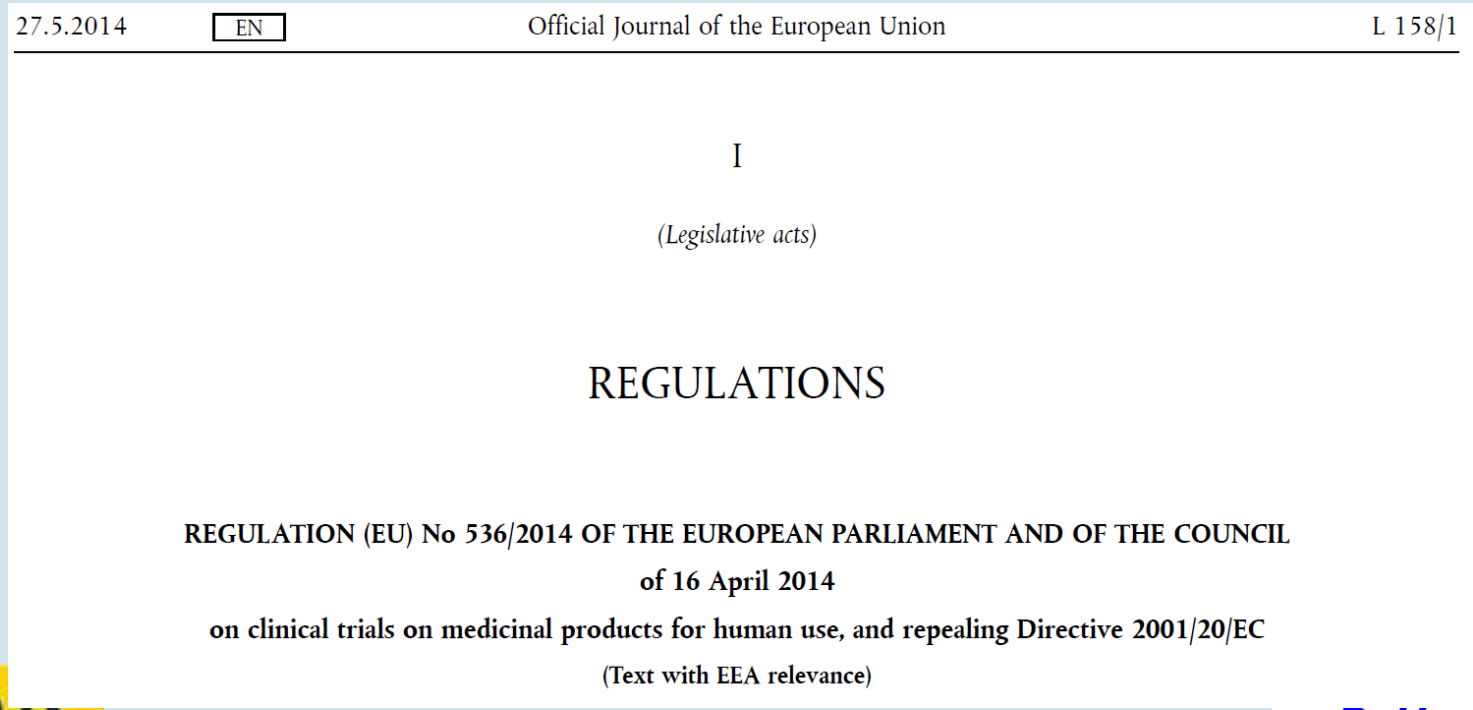
dated July 6, 2010

Introduction

Other important references:

- **ICH E7 Q&A:**
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Q_As/E7_Q_As_step4.pdf

- **Clinical Trials Regulation, (EU) No 536/2014**



27.5.2014 EN Official Journal of the European Union L 158/1

I

(Legislative acts)

REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 16 April 2014

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

(Text with EEA relevance)

Introduction

Other important references:

- ICH E7 Q&A:
- Clinical Trials Regulation, (EU) No 536/2014
- 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);

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Other important references cont.:

- 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

Introduction

Points to consider document… not a strong status ☺

- ❑ Regulations (EC)
- ❑ Directives (EC)
- ❑ Guidance documents
  - WHO/ICH/PhEU monographs
  - CHMP/PRAC/PDCO/… EMA
    - ⇒ Guideline, concept paper, draft guidance
    - ⇒ Question & answer document
    - ⇒ Reflection paper
    - ⇒ Points to consider
- ✓ Guidance documents are what they are, if you follow them: you are at the safe side, if not you have to discuss why you didn't follow

Points to consider on Frailty

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. .

Points to consider on Frailty

Coming back to the regulation:

- **Clinical Trials Regulation, (EU) No 536/2014**
  Article 6:

— 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, the explanation and justification provided in accordance with point (y) of paragraph 17 of Annex I to this Regulation; the current state of scientific knowledge; whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; and, where applicable, any opinion formulated by the Paediatric Committee on a paediatric investigation plan in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council ([1]);

This is translated by the PtC document as:

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.*

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.

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*.

Points to consider on Frailty

The following aspects of frailty are considered:

- physical frailty,
- cognitive dysfunction,
- malnutrition and multi-morbidity,

Recommended **scales** categorising patients in these domains on the basis of their **frailty status** have been defined.
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 Pharmaco-dynamic (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 PtC provides an overview of validated and therefore recommended instruments for characterisation of patient profiles for frailty and related states including cognitive impairment, malnutrition and multi-morbidity.

Points to consider on Frailty

This is a very general document concerning…

Several specific instruments to measure

- physical frailty,
- cognitive function,
- nutritional status and
- multimorbidity

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.

Points to consider on Frailty

This is a general document further analysing:

1. **Physical Frailty**
2. **Frailty and cognitive dysfunction**
3. **Frailty and malnutrition**
4. **Frailty and multi-morbidity**

Points to consider on Frailty

This is a general document further analysing:

1. Physical Frailty

The scales identified that 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 are:

- SPPB,
- Gait Speed (though not as well validated, nor as multifaceted as SPPB)

Points to consider on Frailty

This is a general document further analysing:

2. Frailty and cognitive dysfunction

The following scales are suggested to be used in clinical trials for cognitive function:
1) 50). The 3 MS is an expanded version of the MMSE to yield better psychometric properties (51). *Mini Mental State Examination (MMSE)* - or the abridged version Modified Mini-Mental State Examination (3 MS) score (
2) Montreal Cognitive Assessment (MoCA)

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.

Points to consider on Frailty

This is a general document further analysing:

3. Frailty and malnutrition

The use of the 30 points Mini-Nutritional Status for assessment of nutritional status in older individuals, as it is the best validated instrument in this population

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.

Points to consider on Frailty

This is a general document further analysing:

4. Frailty and multi-morbidity

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

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.

Discussion (1)

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

- This is a draft document, thus work in progress
- Although its status is rather weak: PtC, two points are clearly made:
  - ⇒ For the elderly age stratification is needed, but
  - ⇒ Frailty analysis is recommended
- The document is very general:
  - ⇒ the word immunogenicity does not occur in the text
  - ⇒ No specific recommendations are given for neither for cardio-, endocrino, neuro-… etc

Discussion (2)

- The document is out for consultation and thus improvements can be made provided we give positive criticism
- What criteria/scale should be used for vaccine trials?
  - ⇒ Rockwood's Frialty Index???
  - ⇒ Others???

Conclusions

- ⇒ Good step forward: there is a document.
- ⇒ However, still work in progress
- ⇒ Discussion on how to evaluate best frailty for immunogenicity trials should take place
- ⇒ The Vaccine scientific community should help to improve the document to avoid problems/discussions later in the development of new products for elderly

Thank you for your attention!
Questions?