Lessons from EMA (European Medicine Agency)

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EMA web page on medicines for older patients
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000249.jsp&mid=WC0b01ac058004cbb9

Courtesy to A. Gudmundsson for input

International recommendations

ICH E7 Recommendations (1994):

- A representative number of patients should be studied pre-authorisation (incl . older old)
- Categorisation based on chronological age
- Consideration to include comorbidities

EU Clinical Trials Legislation (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".*

Clinical Trials Regulation (EU) No 536/2014 Art 6

Key principles of the EMA geriatric strategy

- **Evidence based medicine**: Ensure that the medicines used by older people are of high quality and are studied appropriately in the older population, both before and after authorisation
- **Informed prescription**: Improve the availability of information for older people on the use of medicines

Drug Policy for an Aging Population — The European Medicines Agency's Geriatric Medicines Strategy

Francesca Cerreta, Pharm.D., Hans-Georg Eichler, M.D., and Guido Rasi, M.D.

NEJM 2012

A **Survey** of geriatric expertise in medicines evaluation at national regulatory agencies in Europe 2014

- 22 national regulatory agencies responded
- 2/21 agencies (10%) had a specific committee to assess medicines used by older people
- 12/21 agencies (75%) have access to ad-hoc geriatric advice
- Conclusion: Need for a greater involvement of geriatric expertise in medicines evaluation across Europe

A survey of geriatric expertise in medicines evaluation at national regulatory agencies in Europe: There is still room for improvement!

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EGM 2016:7;430–433

Examples of activities relating to EMA geriatric strategy

- EMA Geriatric Expert Group established in 2011
- EMA workshop on medicines for older people in 2012
- EMA scientific guidelines
- Geriatric reflections on product information
- Monitoring or 'pharmacovigilance’
- Reflection paper on physical frailty: Evaluation instruments for baseline characterisation of clinical trial older population (under consultation/drafting since 2015)

EMA (CHMP) Geriatric Expert Group established in 2011

- Input related to geriatrics on guidelines under consultation
- Advice on geriatric aspects of the development, assessment or safety monitoring of medicines
- Taking part in meetings where expertise on geriatrics is needed
- Contribute to the EMA geriatric implementation plan

Advice on product information for older people: example XALKORI

Lack of safety data reflected in SmPC and post authorisation measures

- ***Indication:***
  - Treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).
- ***CHMP Opinion:***
  - Of the 125 patients in study 1001, 18 (14%) were 65 years or older. Of the 261 patients in study 1005, 30 (12%) were 65 years or older. No patients in Studies 1001 or 1005 were 85 years or older. Clinical studies did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.
  - The MAH provided the requested analysis of safety data by age groups, sex and race. Overall, 308 patients were <65 year old and 48 ≥ 65 year-old. The rate of AEs is variable but the number of patients in two groups is rather low to reveal specific drug related safety issues in any of these age groups, especially elderly patients. Therefore, the CHMP requested a post-authorisation study as a multi-national post-approval database surveillance study including elderly patients is planned
  - The PK/PD of the drug has not been adequately evaluated in patients over 65 years of age and this information has been adequately reflected in sections 4.2, 4.4 and 5.1 of the SmPC. The MAH will complete an updated popPK analysis to definitively assess the effect of age on crizotinib PK using pooled data from clinical trials with the final report to be submitted on Q1 2013.

Baseline frailty evaluation in drug development

- Part of EMA geriatrics medicines strategy
- Encourage active inclusion of frail patients
- Ensure that trial population is representative of the target population
- Benefit-risk balance may be different for older patients with frailty
- Baseline physical frailty parameters set a priori
- Potentially useful for risk stratification
- Other important parameters not included: Cognition, nutrition and multimorbidity

BASELINE FRAILTY EVALUATION IN DRUG DEVELOPMENT

F. CERRETA[1], J. ANKRI[2], D. BOWEN[3], A. CHERUBINI[4], A.J. CRUZ JENTOFT[5], A. GUÐMUNDSSON[6], M. HABERKAMP[7], P. JANSEN[8], N. MARCHIONNI[9], S. MORGAN[10], E. RÖNNEMAA[11], M. PETROVIC[12], A. PILOTTO[13], M. ROSA[14], H. WILDIERS[15]

J Frailty Aging 2016

EMA Geriatric Expert Group and external experts identified **2 instruments** to assess baseline physical frailty with simple applicability and good predictive value for susceptibility to adverse outcomes

Parameters used for identifying a suitable frailty scale

- validation status
- predictive value
- ease of use
- time required
- ease of investigator's training
- feasibility of use across all therapeutic areas
- cost

Short Physical Performance Battery (**SPPB**)

Lower-extremity function by 3 measures:

- standing balance
- gait speed
- ability to rise from a chair

A summary score is created (0-12)

Takes 10-15 minutes

Among easily-applied instruments, SPPB has the best predictive value of adverse outcomes

Gait Speed

- Alternative (simpler) choice to the SPPB
- Less multifaceted and validated as the SPPB
- 4 meter walk is recommended

Gait speed cut offs defined with risk of negative outcomes:

- <0.4 m/s: very high risk
- 0.4 – 0.9 m/s: high risk
- ≥ 1 m/s: low risk

Take home messages

- **EMA Geriatric Expert Group** established in 2011
- **Geriatric input** on product information/label in early phase
- SPPB or alternatively Gait Speed are identifided as instruments assessing **baseline physical frailty** with simple applicability and good predictive value for susceptibility to adverse outcomes

Backup slides

Methodology

Short Physical Performance Battery (SPPB):

Five year survival by Age and Gait Speed Group
Pooled analysis of 9 major cohort studies

Table 2. Five- and 10-Year Survival in Men and Women by Age and Gait Speed Group

	5-Year Survival (95% CI), %[a]						
	Men			Women			
Gait Speed, m/s	Age 65-74	Age 75-84	Age ≥85	Age 65-74	Age 75-84	Age ≥85	Age 65-74
Speed <0.4	68 (47-82)	60 (38-76)	25 (15-36)	80 (71-86)	69 (58-78)	47 (40-54)	56 (23-80)
≥0.4 to <0.6	77 (72-81)	57 (49-64)	31 (24-39)	88 (85-90)	75 (68-80)	61 (50-70)	53 (41-64)
≥0.6 to <0.8	79 (74-83)	65 (57-71)	49 (35-61)	91 (89-93)	82 (78-86)	74 (69-78)	57 (52-62)
≥0.8 to <1.0	85 (82-88)	75 (69-79)	54 (43-64)	93 (91-95)	89 (86-91)	73 (59-83)	67 (62-71)
≥1.0 to <1.2	90 (85-93)	83 (76-87)	68 (57-77)	96 (94-98)	91 (87-94)	61 (35-79)	69 (63-74)
≥1.2 to <1.4	93 (86-96)	85 (79-89)	62 (46-74)	96 (94-97)	93 (87-96)	67 (5-95)	75 (40-91)
Speed ≥1.4	95 (89-97)	93 (86-96)	91 (51-99)	97 (94-99)	95 (72-99)	NE	93 (81-98)
All gait speeds	87 (82-91)	74 (65-81)	46 (39-53)	93 (91-94)	84 (80-87)	64 (58-70)	62 (58-66)

Studenski et al, JAMA 201

Abbreviations: CI, confidence interval; NE, not estimable due to small number of participants in categories.
[a] Survival estimates are derived from individual study Kaplan-Meier survival estimates that are pooled across studies