EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Perspectives on Regulatory Considerations in Treating Older Patients with Cancer

Frans Opdam
Internist-Clinical Pharmacologist, MD, PharmD, PhD – Netherlands Cancer Institute
Clinical Assessor Oncology – Dutch Medicines Evaluation Board

Also on behalf of

Francesca Cerreta
Senior Scientific Officer – European Medicines Agency

Representation of older patients in clinical trials

Enquiry from European Commission in 2006

European Medicines Agency

London, 14 December 2006
Doc. Ref. EMEA/498920/2006

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

ADEQUACY OF GUIDANCE ON THE ELDERLY REGARDING MEDICINAL PRODUCTS FOR HUMAN USE

Is the indication within the scope of the guideline?
Are at least 100 patients over 65 included?
Does the protocol include > 65 age range?
Does the protocol include > 75 age range?
Do the geriatrics constitute major proportion in the clinical database?
Are there exclusions based on age?
Are there exclusions based on co-morbidity?
Is there an evaluation for age related differences for efficacy?
Is there an evaluation for age related differences for dose response?
Is there an evaluation for age related differences for adverse events?
Is there a characterisation of special PK behaviour?
Is there a PK initial pilot trial young vs. elderly?
Is there a larger single dose PK study young vs. elderly?
Is there a multiple dose PK study young vs. elderly?
Is there an evaluation for demographic factors?
Is there an evaluation for physiological factors?
Is there an extensive renal excretion of active substance?
Is there an extensive hepatic excretion of active substance?
Is there a characterisation of abnormal renal function?
Is there a characterisation of abnormal hepatic function?
Does the drug have a narrow therapeutic range?
Is there a relevant Cyt P450 metabolism?
Are there drug-drug interaction studies?

ICH E7 Q&A (2010) 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. "*

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**

EMA Geriatric Medicines Strategy KEY POINTS

1. "…ensuring that the development and evaluation of new medicines takes into account **specific safety and efficacy aspects** related to aging, in accordance with current guidelines, particularly ICH E7"

2. "…**identifying gaps** in regulatory and scientific knowledge and taking appropriate measures to tackle them"

3. "…consideration for the need of specific **pharmacovigilance** activities"

4. "…fostering and utilising a **pool of clinical experts** to address specific issues as requested by the CHMP."

EMA views on top issues in geriatric oncology

1. A need to recognise that the population is shifting to a higher age demographic which will require attention to certain aspects such as increase participation to include a relevant proportion of older patients with respect to the epidemiology of the disease the treatment is being approved for
2. Need to consider what a positive benefit/risk balance in older oncology patients means. Do we need to look at alternative/additional clinical trial end points for older patients e.g. quality of life assessment as opposed to overall survival (may be more appropriate than for younger patients)?
3. Regulators should consider the acquisition of data pre- and post- authorisation and a suitable combination of registries/cohort trials to supplement RCTs to make sure a positive benefit/risk balance in older patients is supported by data.
4. A signal to companies that the requirements for ICH E7 Q&A are expected to be fulfilled to provide a minimal data set.

Representation of older patients in Phase I-III clinical trials (oncology)

Project overview

Key questions & focus:

1. How does the geriatric population in oncology clinical trials compare to epidemiology data?*
2. Inclusion/Exclusion criteria? Any biases?
3. Any trends observed with ADRs?

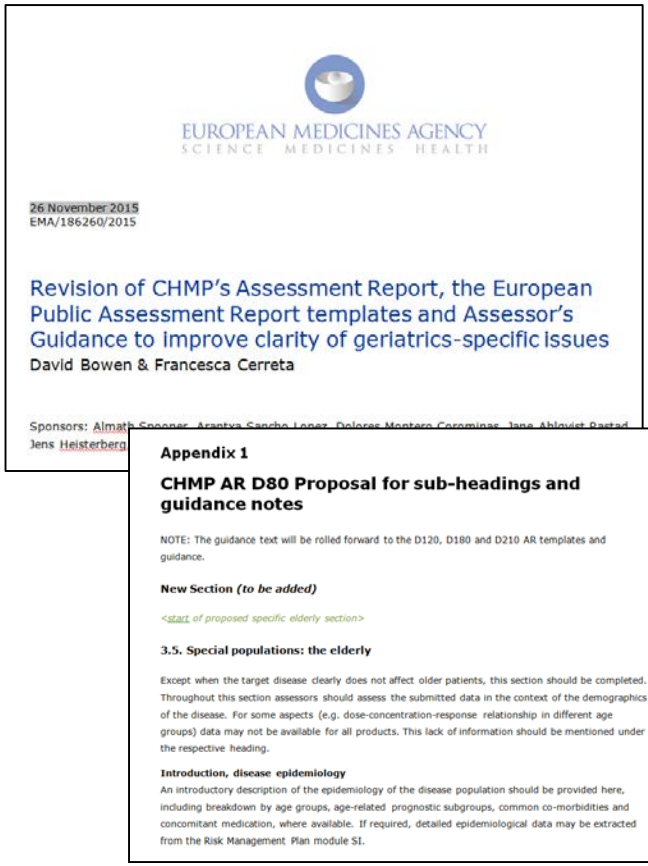
1. Obtain epidemiology data and identify highest incidence in males and females 0 to 85+ years in Europe (CI5X database)
2. Identify cancers with high incidence in geriatric population (i.e. 65-74 , 75 -84 and 85+ years)
3. Screen clinical trial for population data and inclusion/exclusion criteria in marketing authorisation of drugs used to treat these cancers *(EMA Oncology database, initial indication)
4. Evaluation of reported ADRs following the marketing authorisation of the medicinal product using EudraVigilance

EMA: Focus on the older patient

Revision of CHMP's Assessment Report, the European Public Assessment Report templates and Assessor's Guidance to improve clarity of geriatric-specific issues

- **New sub-section "Special populations: the elderly" within the Scientific Discussion**
  - **Epidemiology**, PK studies, dose-concentration-response relationship, elderly patients adequately represented in the studies, efficacy, safety, drug interaction, co-morbidities
  - Specific issues and concerns in elderly subjects that could impact the Risk Management Plan?
  - Are there gaps in the development programme relating to older subjects? Are available data meaningfully reflected in the product information? Should clarifications/data should be requested pre- or post-licensing?

- Benefit risk balance
  - Can the benefit-risk in the clinical trial population be considered valid for elderly subjects? Discuss any actions/cautions required.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 November 2015
EMA/186260/2015

Revision of CHMP's Assessment Report, the European Public Assessment Report templates and Assessor's Guidance to improve clarity of geriatrics-specific issues

David Bowen & Francesca Cerreta

Sponsors: Almath Spooner, Arantxa Sancho Lopez, Dolores Montero Corominas, Jane Ahlqvist Rastad, Jens Heisterberg

Appendix 1

CHMP AR D80 Proposal for sub-headings and guidance notes

NOTE: The guidance text will be rolled forward to the D120, D180 and D210 AR templates and guidance.

New Section *(to be added)*

<start of proposed specific elderly section>

3.5. Special populations: the elderly

Except when the target disease clearly does not affect older patients, this section should be completed. Throughout this section assessors should assess the submitted data in the context of the demographics of the disease. For some aspects (e.g. dose-concentration-response relationship in different age groups) data may not be available for all products. This lack of information should be mentioned under the respective heading.

Introduction, disease epidemiology

An introductory description of the epidemiology of the disease population should be provided here, including breakdown by age groups, age-related prognostic subgroups, common co-morbidities and concomitant medication, where available. If required, detailed epidemiological data may be extracted from the Risk Management Plan module SI.

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)

- Safety data by age groups, sex and race
  - 308 patients were <65 year old and 48 ≥ 65 year-old
  - > **CHMP requested a post-authorisation study as a multi-national post-approval database surveillance study including elderly patients**

- The PK/PD of the drug has not been adequately evaluated in patients > 65 years

  > **The MAH will complete an updated popPK analysis to definitively assess the effect of age on crizotinib PK**

EMA Points to consider on frailty: Evaluation instruments for baseline characterisation of clinical trial populations (DRAFT)

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

- As part of EMA Geriatric Medicines Strategy, the CHMP asked the Geriatric Expert Group (GEG) to perform an exploratory analysis of available scales for the characterisation of frailty status.

- Document outlines general principles that may be applied for baseline categorisation of older patients enrolled in a clinical trial or other clinical investigation based on their frailty status.
- Physical frailty

IMPORTANT INFORMATION REQUIRED

EUROPEAN MEDICINES AGENCY

Adequate data is available for age range?

Frail patients included?

Epidemiology

CT inclusion/exclusion criteria

Co-morbidities

Concomitant medication

Safety signals particularly relevant?
(e.g. dizziness, delirium, orthostatic effects, falls, sedation, bleeding, urinary retention, loss of appetite).

Appropriately grouped?

dizziness + falls + fractures + syncope reviewed together.

Anticholinergic effects?

eCTD Module	Age 65-74 number / total number (all ages)	Age 75-84 number / total number (all ages)	Age 85+ number / total number (all ages)
Efficacy and Safety Studies			
Human PK Studies			
Human PD Studies			
Biopharmaceutical Studies			

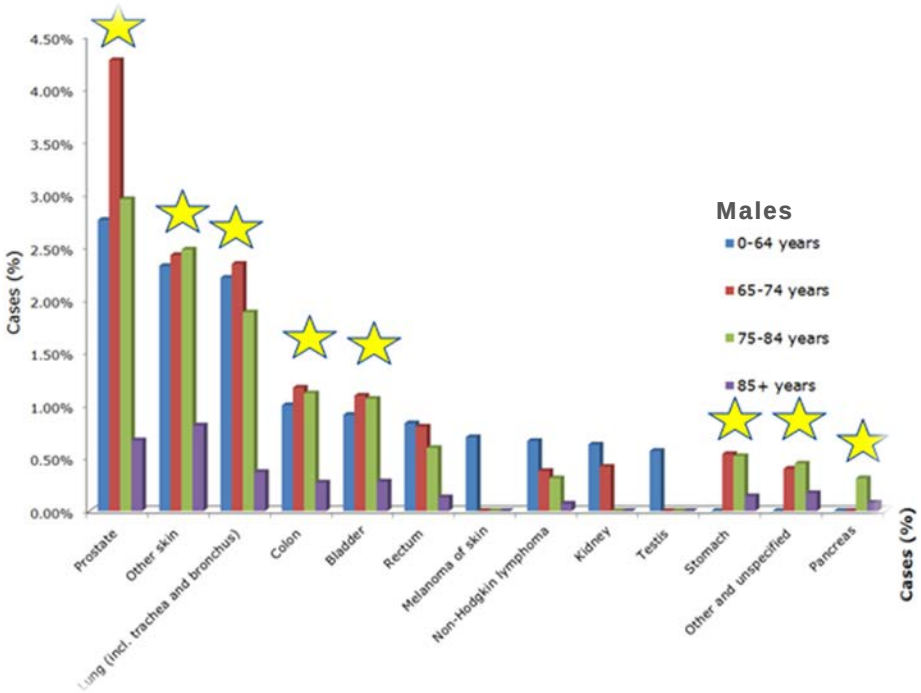
MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total ADRs				
Serious ADRs – Total				
- Fatal				
- Hospitalization/prolong existing hospitalization				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				

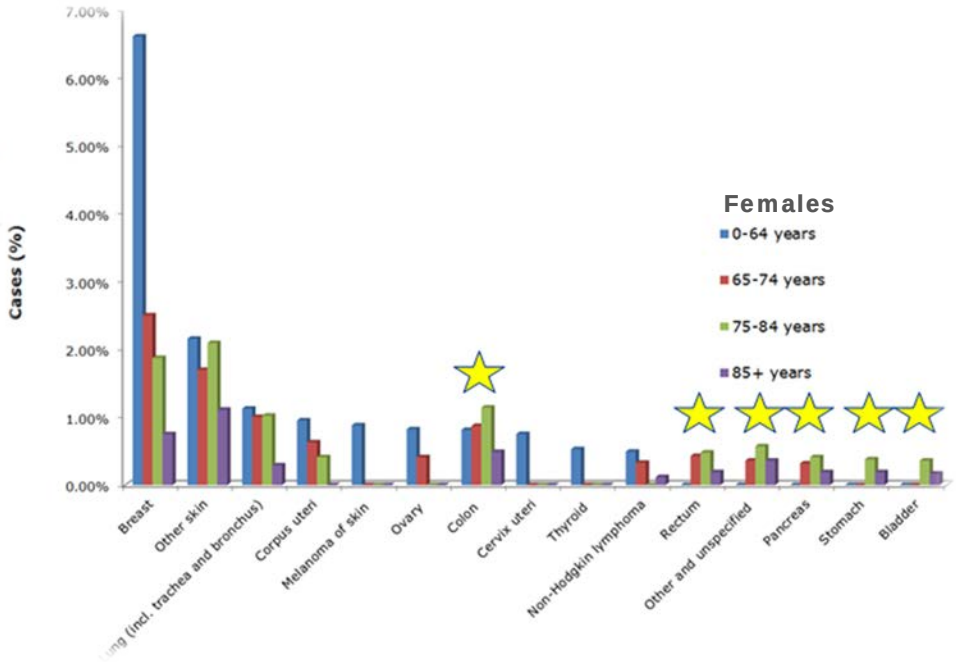
EMA views on how can Regulators help

1. By establishing a standard frailty assessment tool/screening instrument within physical, cognitive dysfunction, malnutrition and multimorbidity which can be used as a stratification tool for clinical trial inclusion.
2. By providing clear information in approval documents on benefit/risk in subgroups according to chronological age (e.g. 64-75, 75-84, 85+ years) and frailty status.
3. By exploring the possibility to reach an agreement on endpoints suitable for geriatric oncology patients with a focus on quality of life and preserving patient autonomy.

thanks for listening!

The Ten Most Commonly Diagnosed Cancers in Males & Females 0-85+ years 2003 – 2017 in Europe*





= Cancers with high incidence in geriatric population

*European countries include Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and United Kingdom

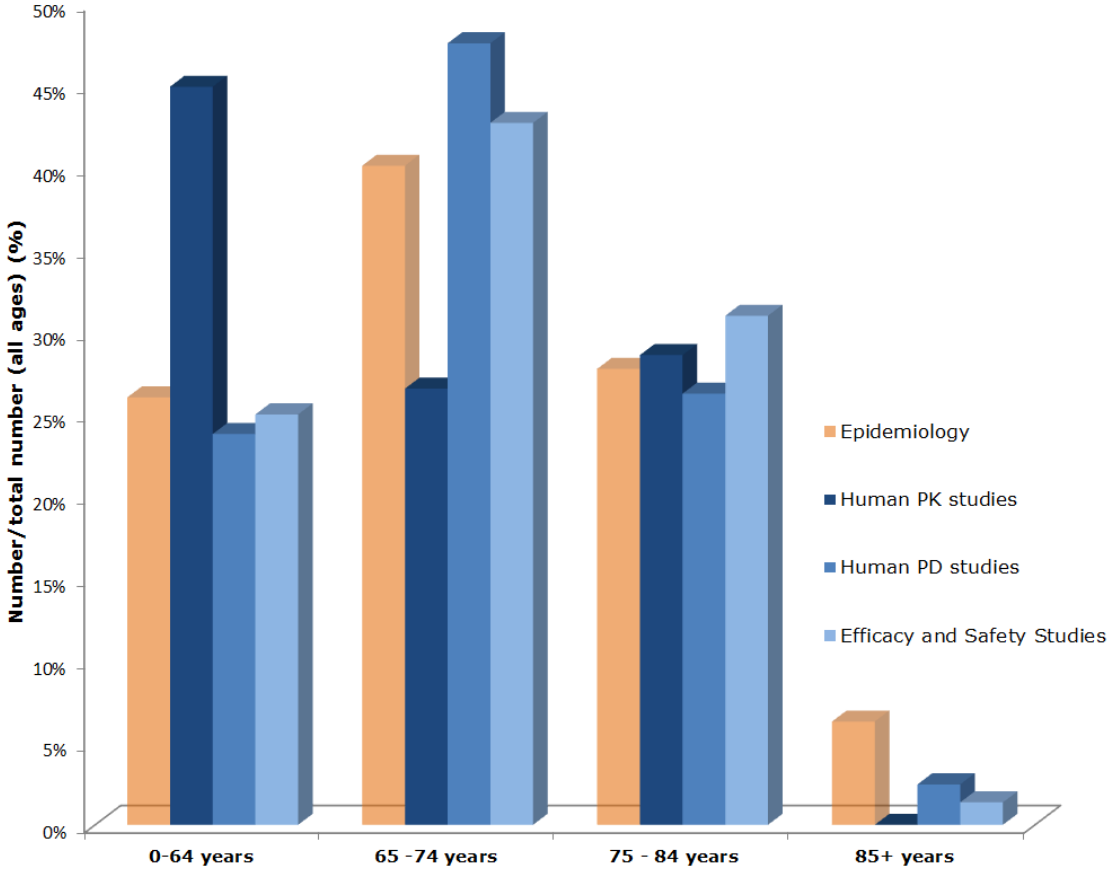
Take home messages

- Age bias in clinical research leads to uncertainty about risk and benefits in new treatments for older people.
- Greater effort should be made to include older people into clinical trials.
- Age alone is not sufficient criterion to reach conclusion on how product will perform in real life
- Reviewer should consider inclusion/exclusion criteria to decide whether results applicable to real life population. Frailty?
- Real World Data could provide a monitoring advantage useful for geriatrics:
  - Capture real clinical practice, adherence, compliance
  - Potential for safety and tolerability investigations.

Case Study: M1 stage prostate cancer drug A

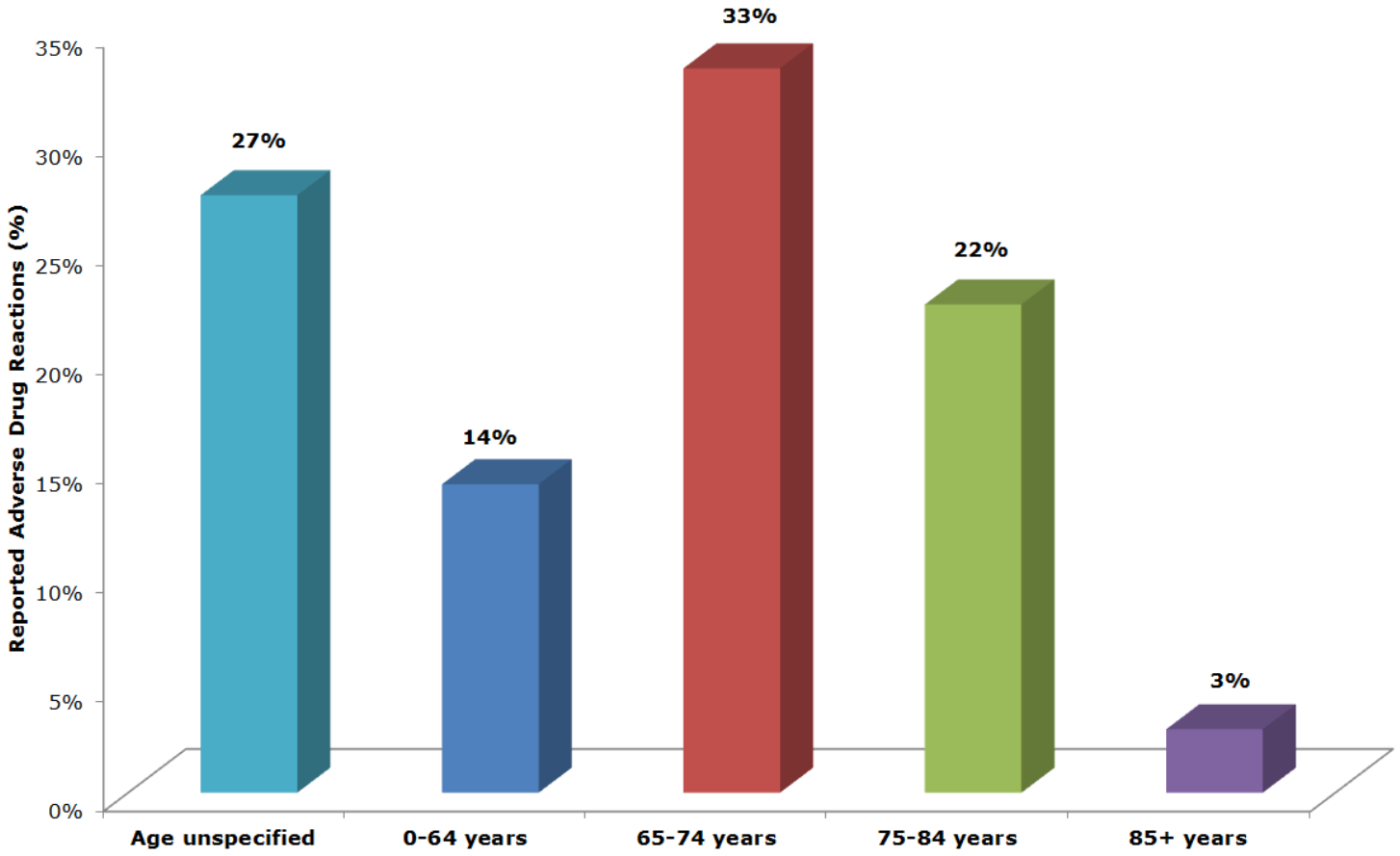
% of elderly patients (i.e. 65 to 85+ years) in human PK, human PD, efficacy and safety studies

ICH7 & EMA recommendations	
Are at least 100 patients over 65 included?	✓
Does the protocol include > 65 age range?	✓
Does the protocol include > 75 age range?	✓
Do the geriatrics constitute major portion in the clinical database?	✓ **(74%)**
Are there exclusions based on age?	→



Case Study: M1 stage prostate cancer drug A

Reported ADRs (since 2013)



Case Study: M1 stage prostate cancer drug A

inclusion/exclusion criteria

		INCLUSION			EXCLUSION			
Protocol	**Phase**	**ECOG ≤ 1**	**ECOG ≤ 2**	**Age**	**DM insulin dep.**	**Dementia**	**Severe uncontrolled disease**	**Cardiac & Other**
1	2		✓	> 40				Heart insufficiency, Grade 3 or 4 as specified in NCI-CTC criteria
2	2		✓	> 40				
3	3		✓					cardiac failure NYHA III or IV/unmanageable faecal incontinence
4	3		✓					

Case Study: Breast cancer drug A

inclusion/exclusion criteria

		INCLUSION			EXCLUSION			
Protocol	**Phase**	**ECOG ≤ 1**	**ECOG ≤ 2**	**Age**	**DM insulin dep.**	**Dementia**	**Severe uncontrolled disease**	**Cardiac & Other**
1	2	✓			✓		✓	
2	3	✓					✓	
3	2		✓				✓	
4	2	✓					✓	