EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Guidance on format of the risk management plan (RMP) in the EU part II: Module SIV - Populations not studied in clinical trials

Active substance	
Product(s) concerned (brand name(s)):	
MAH/Applicant name	

Data lock point for this module	<Enter a date>
Version number of RMP when this module was last updated	<Enter a version no>

This guidance should be used in conjunction with the information in Good Pharmacovigilance Practices: Risk Management Systems.

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This module should discuss the limitations of the clinical trial population in relation to predicting the safety of the medicinal product(s) in the market place. The titles in SIV.3 below are suggestions and the discussion should be tailored to the medicinal product and its intended use and so may include other categories where there has been limited or no research. Limitations may also arise due to use in a different setting.

SIV.1 Limitations of adr detection common to clinical trial development programmes

Clinical trial development programmes are unlikely to detect the following types of adverse reactions due to well-known inherent limitations. Based on the number of patients exposed, the duration of patient exposure, total dose of medicine, action of medicine etc., discuss what could have been detected.

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Which are rare (it may be appropriate to choose other ADR frequencies)	<E.g. 12,600 patients were exposed over the whole CT programme>	<E.g. ADRS with a frequency greater than 1 in 4,200 could be detected if there were no background incidence>
Due to prolonged exposure	<E.g. 3000 women were exposed to X for more than 4 years during which time there were no cases of endometrial carcinoma. 42 women in the treated experienced endometrial hyperplasia compared with 35 in the non-exposed group (2000)>	<E.g. There does not appear to be an effect on endometrial proliferation during the first 4 years of treatment. X is thought to .....etc.>
Due to cumulative effects	<e.g. specific organ toxicity>	
Which have a long latency		

SIV.2 Effect of exclusion criteria in the clinical trial development plan

Discuss the main exclusion criteria across the clinical trial development programme. (This should not be a list of exclusion criteria by trial but a discussion on the effect of exclusion criteria across the clinical trial programme and the implications for treatment of the target population).

Exclusion criteria which will remain as contraindications	
Criteria	Implications for target population
1	
2 etc.	

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
1		
2 etc.		

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

These categories are suggested headings as they are typically under-represented in the clinical trial programme. Their relevance will depend upon the medicinal product, the indication and the development programme. There may be other relevant categories which are applicable.

Children

Special consideration should be given to the experience in different paediatric age groups – e.g. ICH-E11 - since these relate to different physiological and anatomical development stages. If paediatric development has been limited to certain age categories then the implications for other paediatric age groups should also be discussed.

- Pre-term newborns
- Neonate (birth to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 years to e.g. 11 years)
- Adolescents (e.g. 12 years to 17 years)

Elderly

Implications on the use in patients of 65 and older should be discussed with appropriate consideration to the top ranges of the age spectrum. The effect of individual impairment should be discussed in the sections below but the effects of multiple (minor) co-existing impairments and also adverse reactions of particular concern in the elderly should be discussed.

- Use in different age ranges: e.g. 65-74, 75-84, >85
- Need for laboratory screening prior to use
- Effect of multiple co-existing impairments
- Adrs of special concern – e.g. dizziness, CNS effects
- Effect of multiple medications

Pregnant or breast feeding women

If the target population includes women of child-bearing age, the implications for pregnancy and/or breast feeding should be discussed. If contraception was a clinical trial requirement the following should also be discussed:

- Number of pregnancies and outcomes
- Analysis of why contraceptive measures failed – i.e. consideration of whether human error or an interaction between product and e.g. oral contraceptives
- Implications for use under less controlled conditions (i.e. if measures failed under the relatively strict conditions of a trial, what will happen in real life, and if necessary suggestions for improvement)

Patients with hepatic impairment

Patients with renal impairment

Patients with other relevant co-morbidity e.g.

- Cardiovascular
- Immuno-compromised including transplant patients

Patients with a disease severity different from the inclusion criteria in the clinical trial population

Sub-populations carrying known and relevant polymorphisms

The extent of pharmacogenetic effects and the implications of genetic biomarker use in the target population should be discussed where relevant. The implications for patients with/without a specific genetic marker/specific mutation or with unknown status should be stated - in particular where the indication requires genetic testing.

Patients of different racial and/or ethnic origin

*The implications for use in patients with different racial and/or ethnic origins should be discussed. In particular differences in the frequency or types of gene variants for drug metabolising enzymes may give rise to important differences in pharmacokinetics and/or frequency of adverse reactions. This variations in frequencies of particular alleles may have implications for drug use or for pre-treatment testing in patients of particular populations – e.g. HLA-B*1502 allele is associated with severe cutaneous adverse reactions to carbamazepine and is found in approximately 10% in some Asian populations but rarely in those of European descent.*

SIV.4 Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Missing information

Where the missing information from the clinical trial programme could constitute an important risk to the target population it should be considered to be a safety concern and should be stated here. If the missing information has been adequately investigated outside of the clinical programme this should be noted (with cross reference to the appropriate RMP section) in the comment section. Only safety concerns which are still outstanding should be carried through to RMP Part II Module SVIII.

Safety concerns due to limitations of the clinical trial programme		**Outstanding concern?**
Safety concern	Comment	Yes/No
1		Choose one of the following: • Yes • No
2 etc.		Choose one of the following: • Yes • No