EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Paediatric clinical trial assessments under the new CTR – from PIP to CTA
Description of the current situation

Enpr-EMA

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Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees.

Background – ACT EU PA8 methodology workshop (Nov 2023)

- Key challenges identified by stakeholders:
  - "The CTR requirement for pediatric clinical trials to have direct benefit for the individual taking part in the trial has not been implemented in a harmonized manner at national level." (*Report of the methodology guidance workshop 23 November 2023, p. 8*)
- Suggested ways forward to address the challenges:
  - "Clarify the CTR requirement for pediatric clinical trials to have direct benefit for the individual taking part in the trial, and the expectation for medical conditions that occur in minors and adults, but which manifest themselves in a different way at a young age. Harmonization is needed between EU members state views, including that of the ethics committees." (*Report of the methodology guidance workshop 23 November 2023, p. 9*)

Interpretation of CTR 536/2014 Art. 32

- CTR 536/2014 Art. 32:

Article 32

Clinical trials on minors

1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

(e) the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;

- → What exactly is the necessary ´data obtained´?

Background – Revised Declaration of Helsinki (Oct 2024)

- Vulnerable groups can also be harmed by <u>not</u> being included in medical research:

Individual, Group, and Community Vulnerability

19. Some individuals, groups, and communities are in a situation of more vulnerability as research participants due to factors that may be fixed or contextual and dynamic, and thus are at greater risk of being wronged or incurring harm. When such individuals, groups, and communities have distinctive health needs, their exclusion from medical research can potentially perpetuate or exacerbate their disparities. Therefore, the harms of exclusion must be considered and weighed against the harms of inclusion. In order to be fairly and responsibly included in research, they should receive specifically considered support and protections.

20. Medical research with individuals, groups, or communities in situations of particular vulnerability is only justified if it is responsive to their health needs and priorities and the individual, group, or community stands to benefit from the resulting knowledge, practices, or interventions. Researchers should only include those in situations of particular vulnerability when the research cannot be carried out in a less vulnerable group or community, or when excluding them would perpetuate or exacerbate their disparities.

WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN PARTICIPANTS
Adopted by the 18 WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 75 WMA General Assembly, Helsinki, Finland, October 2024

Problem statement

- **Lack of harmonization** (between NCAs/ECs) trigger a conservative approach on paediatric clinical trials assessments
- Perceived negative consequences for children:
  - Delay of patient access to innovative treatments
  - Limited incentives for pharmaceutical companies to initiate pediatric trials
  - Feasibility issues of pediatric trials
  - As a consequence: frequent off-label use
- This is however **a perception only** based on anecdotal evidence so far.

→ **Data evidence (as-is analysis)** is **highly warranted**.

→ Initiation of **project to analyze paediatric clinical trial assessments** in collaboration with CTCG and PDCO in a descriptive manner

Objective of project

Analysis of differences in the assessment of paediatric clinical trials under CTR 536/2014 by the CAs and ECs (if possible), to providing a baseline in support of potential solutions addressing the challenges as identified in ACT EU workshop and in light of the revised Declaration of Helsinki

Research questions

- **Question 1:** Are there differences in the assessment of paediatric clinical trial applications between EU member states?

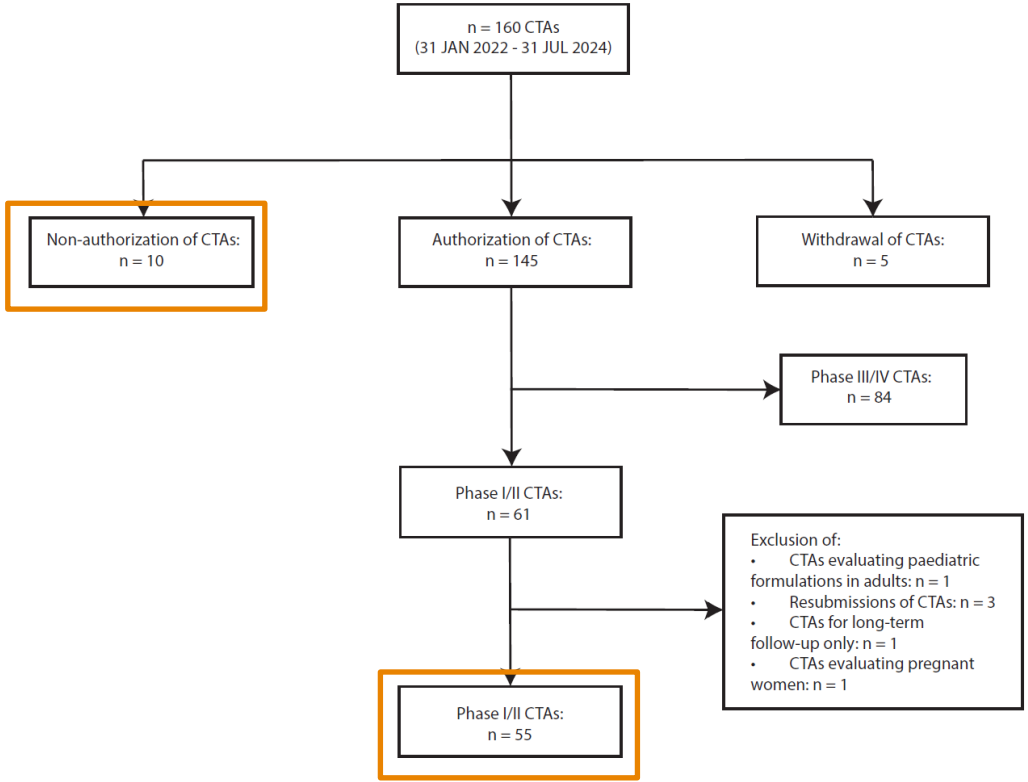
- **Question 2:** How is Art 32 interpreted by EU Member States?

- **Question 3:** Paediatric clinical trials have been discussed with EMA before submission (e.g. PIPs). How do national CAs and ECs take PIPs into consideration when assessing clinical trial applications?

Database

- Clinical Trial Information system (CTIS) was launched 31 JAN 2022
- 1 year transition period
- Mandatory since 31 JAN 2023
- Data cut off 31 JUL 2024:
  - **1 year** not mandatory (JAN 2022 – JAN 2023)
  - **1,5 years** mandatory (FEB 2023 – JUL 2024)

Paediatric trials in CTIS



Characteristics of authorized paediatric CTAs

	Phase I-IV (n = 145)	Phase I/II (n = 55)
Therapeutic Area, n (%)		
Neurology and Developmental disorders	42 (29)	20 (36)
Oncology	15 (10)	11 (20)
Respiratory Disease	9 (6)	2 (4)
Infectious Disease	10 (7)	4 (7)
Endocrinology	10 (7)	4 (7)
Haematology	4 (3)	1 (2)
Cardiology	11 (8)	4 (7)
Gastrointestinal disorders	13 (9)	4 (7)
Pain/ Anaesthesia	9 (6)	1 (2)
Allergy	2 (1)	1 (2)
Rheumatology	4 (3)	1 (2)
Dermatology	8 (6)	0 (0)
Psychiatry	1 (1)	0 (0)
Other	7 (5)	2 (4)
Sponsor-Type, n (%)		
Industry-sponsored	101 (70)	36 (65)
Academia-sponsored	44 (30)	19 (35)

Characteristics of non-authorized paediatric trials

	therapeutic area	sponsor	PIP	RMS	Phase	Assessment Part I	Assessment Part II
study 1	oncology	academia	No	MS1	I	Not acceptable	Acceptable
study 2	oncology	industry	yes	MS3	I/II	Not acceptable	Acceptable with conditions
study 3	oncology	academia	No	MS1	I/II	Not acceptable	Acceptable
study 4	oncology	industry	No	MS2	III	Not acceptable	Acceptable with conditions
study 5	infectious diseases	industry	No	MS5	I	Not acceptable	Acceptable
study 6	infectious diseases	industry	yes	MS1	II	Not acceptable	Acceptable
study 7	opthalmology	industry	No	MS4	III	Not acceptable	Acceptable
study 8	dermatology	industry	yes	MS2	III	Not acceptable	Not acceptable
study 9	neurology	academia	No	MS6	III	Not acceptable	Acceptable
study 10	neurology	industry	No	MS1	I/II	Not acceptable	Acceptable

MS = Member state, RMS = Reporting Member state

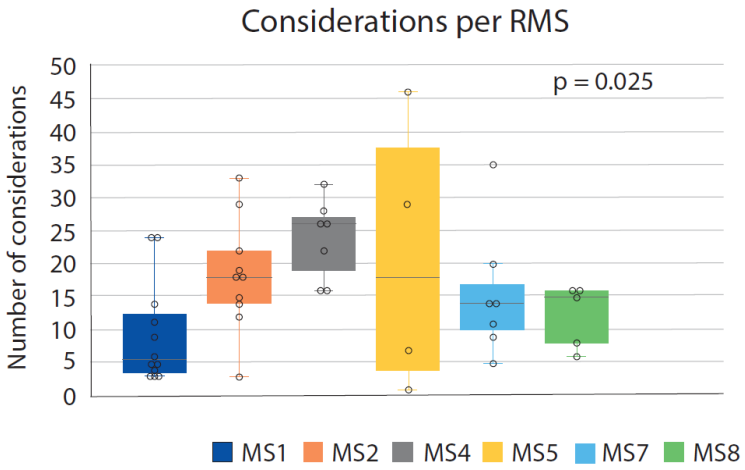
Main reasons for non-authorization

	therapeutic area	formalities	toxicity and safety	drug manufacturing and import	quality	inclusion exclusion criteria	study population and design	risk burden benefit analysis	study rationale	drug administration	dosing	proof of concept
study 1	oncology											lack of non-clinical d.
study 2	oncology							unfavorable			method	adult data, disease, PIP
study 3	oncology		high toxicity	distribution of IMP						formulation		
study 4	oncology	lapsed										
study 5	infectious d.						sample size, randomization			inconsistencies		lack of adult d.
study 6	infectious d.		unpredictable				design, cohorts	unfavorable			lack of adult/ adolescent data	
study 7	opthalmology						comparator drug					
study 8	dermatology							unfavorable				lack of adult data
study 9	neurology		uniformity of dose									
study 10	neurology		high toxicity							limited experience	method	lack of non clinical

→ Required evidence (requirement of non clinical/ adult/ adolescent data) seems to play an important role.

MS = Member state, RMS = Reference Member state

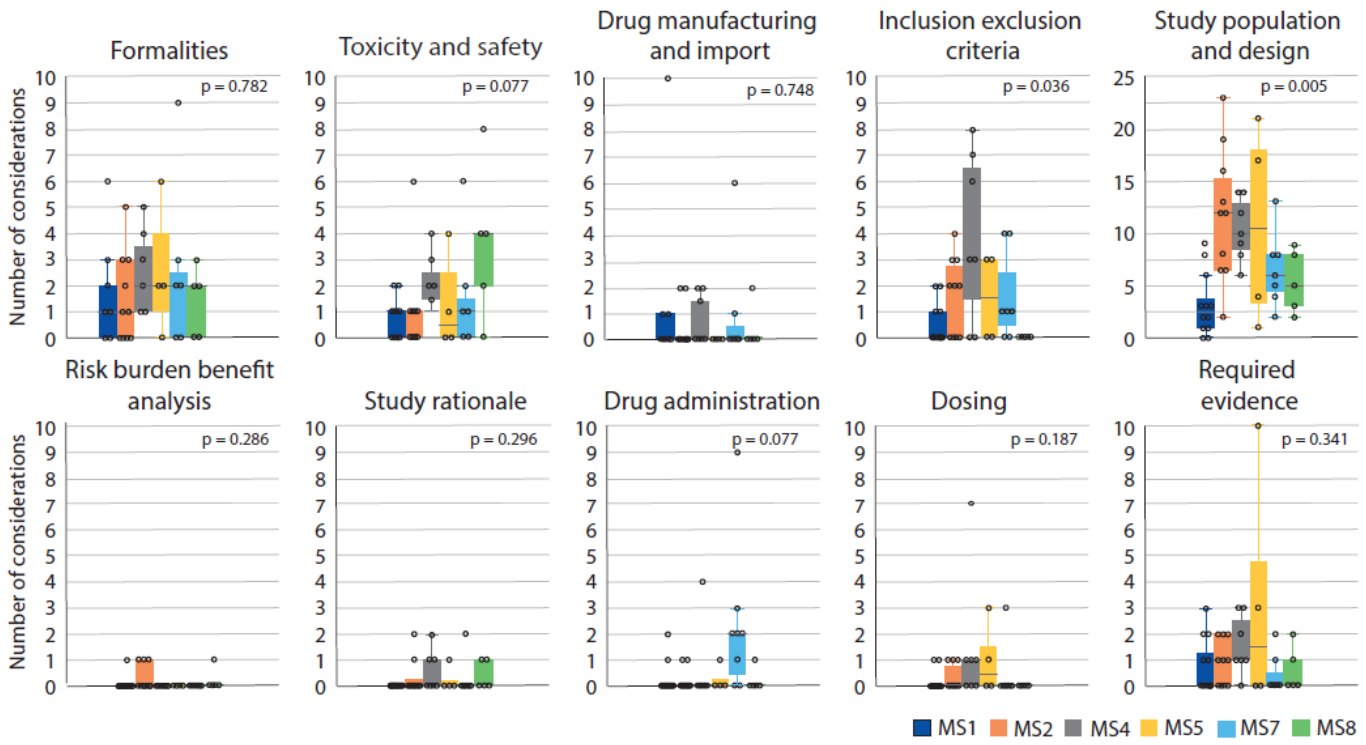
Clinical trial assessment (phase I/II CTAs): Considerations per MS when **RMS** (median) shows significant variability



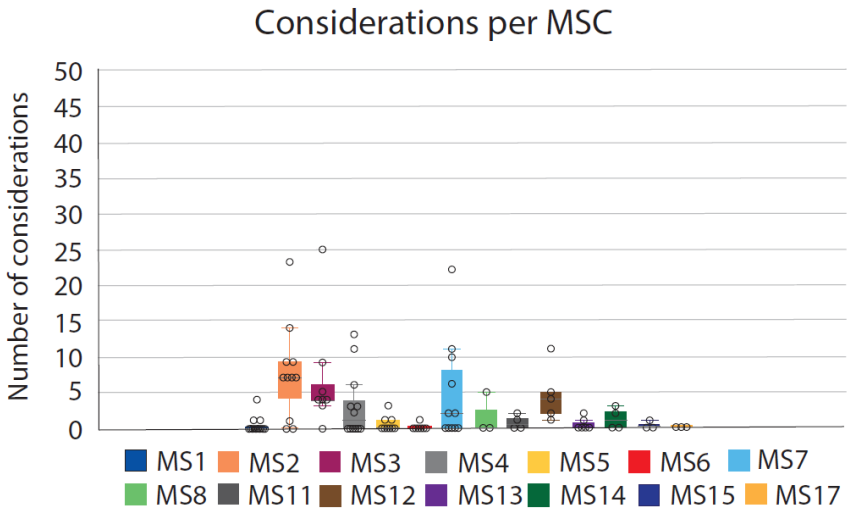
Only MS that are RMS for > 2 trials are shown.

MS = Member state, RMS = Reporting Member state

Clinical trial assessment: Considerations per MS per assessment issue when RMS (median)



Clinical trial assessment (phase I/II CTAs): considerations per MSC shows high variability

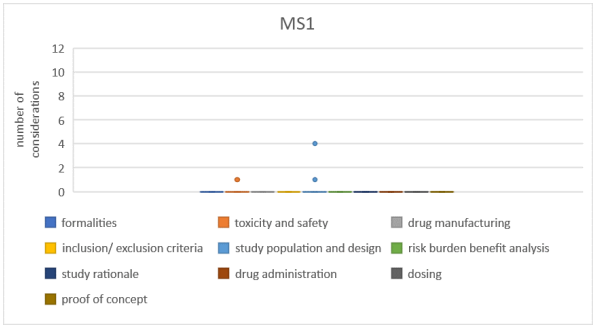


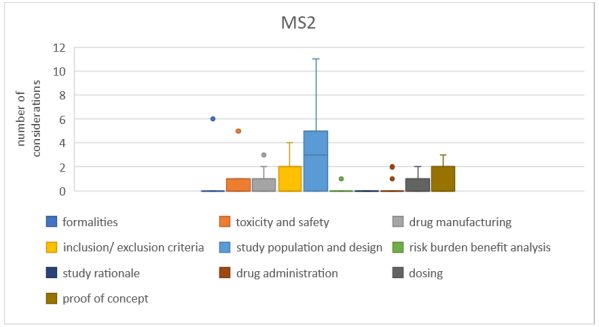
Only MSC that are MSC for > 2 trials are shown.

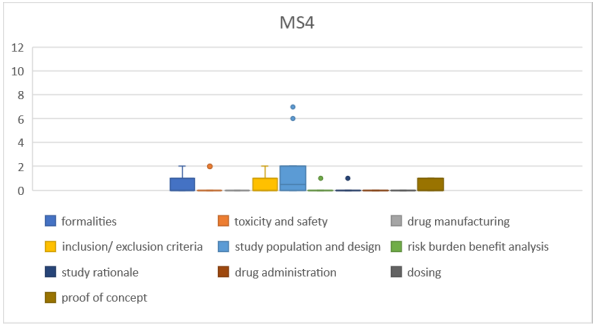
MSC = Member State Concerned

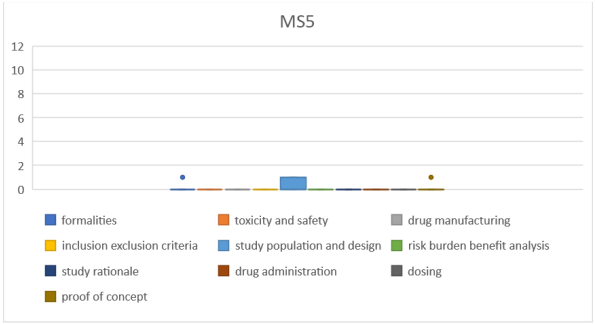
MS = Member State

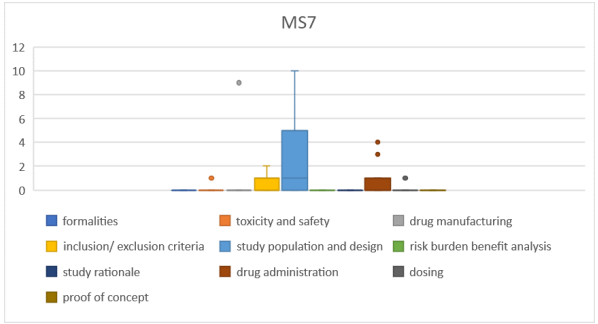
Number of considerations per Member State Concerned (MSC)

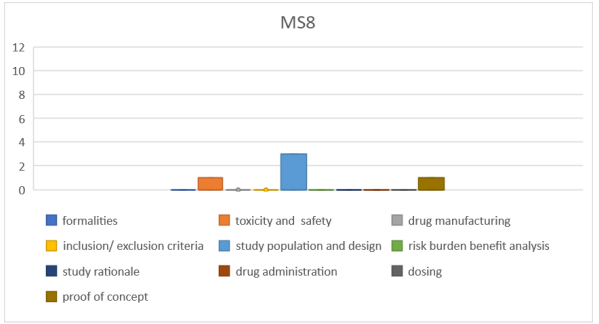






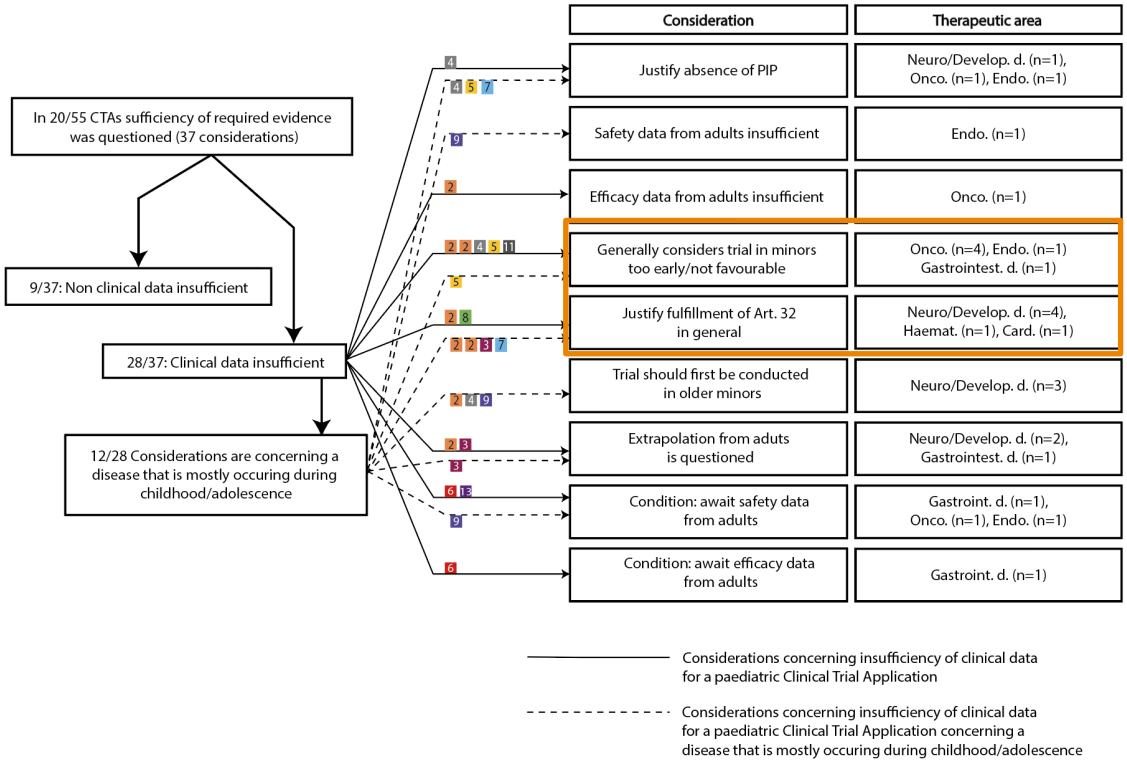






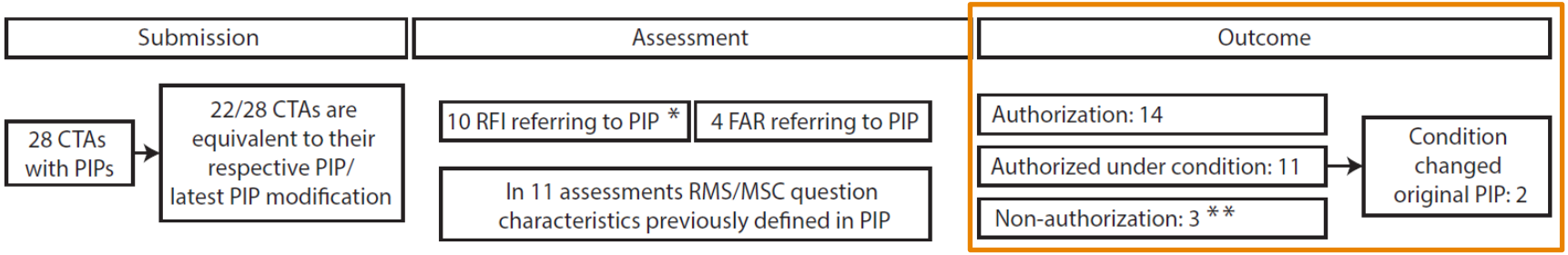
In the role of MSCs, MS demonstrate different levels of engagement in the assessment process.

Different interpretations of Art 32 in approved phase I/II CTAs



Most considerations regarding Art 32 either generally consider trial in minors too early/not favourable or requested that the fulfilment of Art 32 should be justified in general.

Role of PIPs differs in the Clinical Trial Assessment process



* 7/10 was to provide PIP (without contextual reference)

* * 2/3 non-authorized CTA with PIP were only partially equivalent to their PIP. Reasons for non-authorization were among others evidence prerequisite, risk-burden-benefit analysis.

CTA = Clinical Trial Application, PIP = Paediatric Investigation Plan, RFI = Request for Information, FAR = Final assessment report, RMS = Reporting Member State, MSC = Member State Concerned

Inclusion of Adolescents in Adult Trials is assessed differently and with Reluctance

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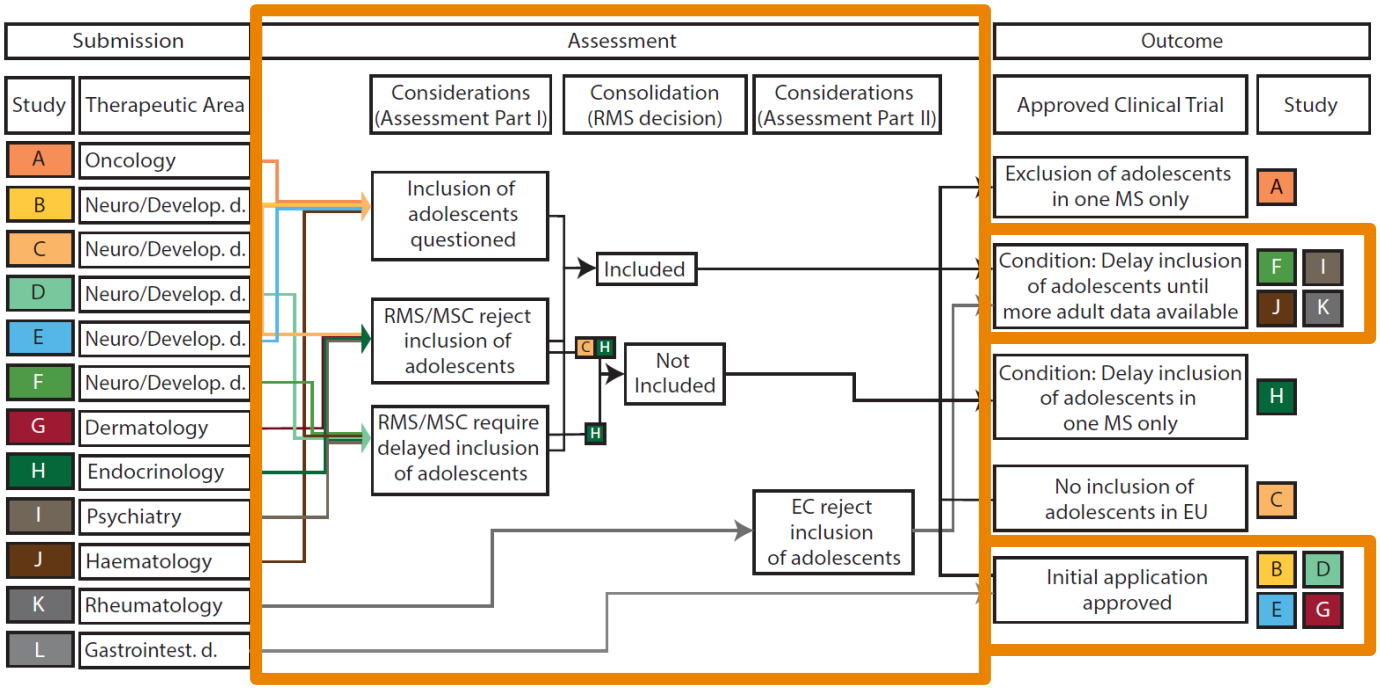

Conclusions

- Majority of paediatric CTAs were authorized (144 authorized CTAs, 10 non-authorized CTAs)
- Majority of PIP studies were approved, role of PIP in the assessment differs between MS
- Nevertheless, there is a **heterogeneity** in the assessment as well as the issues raised
- The **interpretation of Art. 32** (prerequisite of available data) seems to be a particular challenge in the assessment, the sufficiency of evidence is often questioned independent of therapeutic area
- Inclusion of adolescents in adult trials is in most cases accepted, but **dependent on MS** on how it is assessed and approved

→ Opportunity to engage exchange in overlapping interests between PDCO and CTCG

→ Provides basis to **develop technical alignments (eg guidance)** for the regulatory network (NCA and ECs) to support assessments of paediatric clinical trials, working towards **harmonization,** also in view **of revised DoH → ACT EU workshop on Paediatric Clinical Trials**

Thank you very much

This is a collaborative project between EMA, PDCO, CTCG, Accelerate and KiTZ Heidelberg

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Slides for further discussions

CTCG survey on paediatric CTAs

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1- Which EU/EE	2 - What is the officially recognized age range for			4 - Do you assess clinical trial applications differently when there is a PIP in place?				
Estonia	13-18	Yes	From an ethical point of	No		Early phase vs later phas		Please specify what kind
Ireland	13 - 17, but this may diffe	Yes	SExuakl maturation may	Yes	If a sponsor indicates tat	Early phase vs later phas		Pre-existing efficany and
Belgium	We have no legal definiti	Yes	FAMHP: both impact ass	Yes	FAMHP: We take into ac	Early phase vs later phas	One EC replied that the b	Joint FAMHP/EC respon
Spain	12-18	No		Yes	We take into consideratic	Early phase vs later phas		Enough clinical and non-
Italy	The officially recognised	No		Yes	For the sake of clarity,it i	Early phase vs later phas		Where no data in the pa
Croatia (Miz)	In Croatia, there is no un	No		No		Staggered approach pro		All the data/information r
Latvia	Not defined in legislation	No		Yes	We are taking PIP asses	Early phase vs later phas		Adolescents data would l
Denmark	MREC: Minors in Denma	No		No		Early phase vs later phas	DKMA CLINICAL ASSES	MREC: The fulfillment of
France	12	Yes	The differences betweer	Yes	PIP is a regulatory tool pr	Early phase vs later phas	rationale of the developm	Global safety data (not d
Slovak Republic	12-17 years	No		Yes	When a PIP is submitted,	Early phase vs later phas		PK and PD Data - essen
Finland	15 years =< - <18 years	No		Yes	We consider the recomm	Early phase vs later phas		Summary data of previou
Norway	No official lower limit (12	No		Yes	Key binding elements in F	Early phase vs later phas	Unmet need	At least interim data, dep
Germany (PEI)	12 to less than 18 years	Yes	Legal age and physiolog	Yes	Assessment of CTA shou	Early phase vs later phas	Factors such as product	It depends: For a conditi
Sweden	12 to 18 years	No		Yes	We always adhere to the	Staggered approach pro		Data in older children sh
Germany (BfArM	under 18	Yes	Information about the stu	Yes	More background informa	Early phase vs later phas	all aspects to be reflecte	Quality aspects: formulat
Hungary	12	Yes	16-18 years old childrea	No		Early phase vs later phas		Background of the disea
Netherlands	Some categories would b	Yes	Depends on how the dis	Yes	Why only explanatory not	Early phase vs later phas		Question 5 is difficult to a
Czechia	12 - 18 years	No		Yes	We carefully read PIP an	Early phase vs later phas	Drug class effect, PIP, ra	We expect robust justific

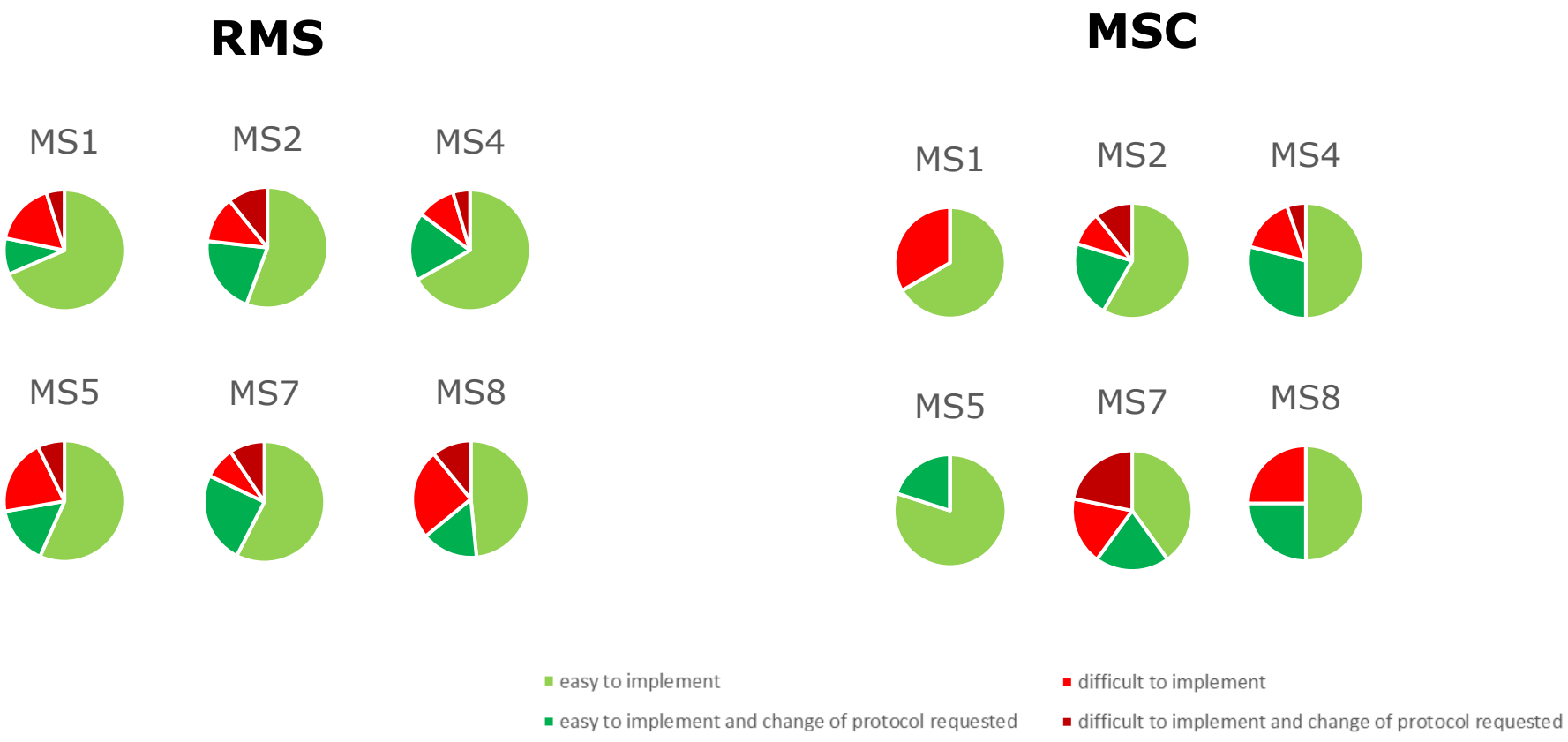
Comments of MS:

THere are differences in how different NCAs/ ethics interpret the various articles in their foundation documents. THis is something that can be explored

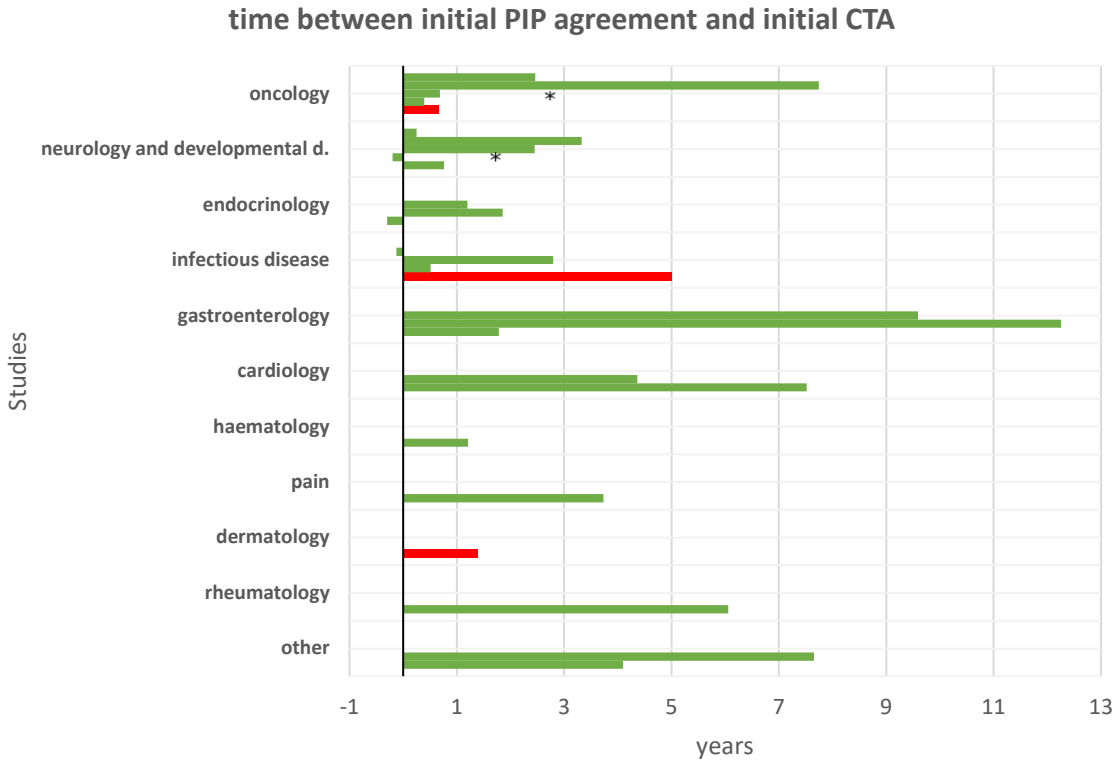
The assessment of paed. trials is challenging and the harmonised assessment required by CTR would call for interaction between PDCO and clinical trial assessors, maybe with CT assessors attending PDCO meetings and/or dedicated PDCO sessions for discrepancies PIPvsCTA conclusion.

We would welcome the development of more detailed guidelines to aid ethics committees and competent authorities in the interpretation of Article 32. Enhanced harmonization in this regard could significantly reduce variability in requirements, which is particularly crucial for studies conducted across different EU member states.

Significance and feasability



Time lapsed between initial PIP agreement and initial CTA



Green: authorized trials
Red: non-authorized trials

* Authorized under a condition that changed original PIP plan

While it was initially hypothesized that unauthorized CTAs with a PIP would show significant time gaps between PIP agreement and CTA submission, potentially leading to outdated scientific evidence, the analysis did not support this assumption.

Subject to final data cleaning