Workshop for assessors from NCAs and MRECs on paediatric clinical trials

Meeting report

14 and 15 July 2025

An agency of the European Union

Contents

Introduction

On 14 and 15 July 2025, the Clinical Trial Coordination Group (CTCG), Paediatric Committee (PDCO) and Methodology Working Party (MWP) organized a workshop for assessors from NCAs and ethics committees to discuss real cases of paediatric clinical trial applications which show different assessment approaches across EU/EEA. This workshop is a direct follow up to the ACT EU multi-stakeholder methodology workshop, which identified harmonization in the interpretation of CTR Article 32 (inclusion of minors in clinical trials) in the assessment of paediatric clinical trials as a priority.

The objective of the workshop was to strengthen collaboration between national competent authorities, CTCG, ethics committees and the PDCO by bringing together all regulatory decision makers in the ecosystem of paediatric drug development.

Through discussion and exchange on real use cases, the workshop provided an opportunity to address the challenges of assessing paediatric clinical trials under the Clinical Trials Regulation (CTR) as well as to develop together with the participants potential solutions for addressing inconsistencies in the interpretation of Article 32 of the CTR, in context of the revised Declaration of Helsinki, while ensuring ethical and scientific rigor.

Setting the scene

Moderators: Marianne Lunzer (CTCG chair, Austrian Agency for Health and Food Safety (AGES), Austria) and Monique Al (Central Committee on Research Involving Human Subjects (CCMO), Netherlands)/Vice-chair CTCG/Co-chair MedEdthicsEU).

Presenters: Laura Fankhauser (Hopp Children's Cancer Center Heidelberg (KiTZ) Germany), Dominik Karres (Paediatric Medicines Office EMA) and Sabine Scherer (PDCO member, Federal Institute for Drugs and Medical Devices (BFARM) in Germany), Martine de Vries (Head of the Department of Medical Ethics and Health Law Paediatrician Leiden University Medical Center, Department of Medical Ethics & Health Law, The Netherlands).

Key messages

- Despite regulatory progress, children remain underrepresented in clinical development, delaying access to innovative treatments and increases off-label use.
- There are differences in interpretation of Article 32 and variability in how Member States assess paediatric clinical trials.
- The revised Declaration of Helsinki emphasises that excluding vulnerable groups (like children) from research can potentially perpetuate or exacerbate their disparities.
- Patients and caregivers are often willing to accept higher risks and burden, especially in life-threatening conditions.
- Greater involvement of patient representatives in trial planning, regulatory and ethical discussions is essential.

Results from a descriptive analysis of paediatric clinical trial assessments revealed that there is significant variability in how Member States assess trials. Particularly, differences were noted in the interpretation of Article 32(1)(e), (f), (g) of the CTR (especially around "direct benefit" and the required evidence, e.g.

proof of concept; need for adult evidence). With regards to the inclusion of adolescents in adult trials, Member States differ in their acceptance, often requiring additional adult data to be generated first.

It also showed that there is inconsistent use of paediatric investigation plans (PIPs) in assessments, with some Member States being more conservative, leading to none, delayed authorisation or authorisation only with certain conditions of trials despite the clinical trial application (CTA) being in line with an agreed PIP; appreciating that of course evidence may have evolved after the initial PIP agreement over time

This first description of this as-is analyses provided the foundation for the subsequent discussions. It underpinned the need for more harmonised interpretation of Article 32, but also value submission of the full PIP into a CTA, to allow scientific considerations reflected upon during the clinical trial assessment process.

It was emphasised that there are common challenges within the ecosystem of drug development in general. Those hold true across diseases and populations. But it remains key to acknowledge paediatric specificities, as represented by the EU Paediatric Regulation.

Paediatric specific clinical development challenges, mainly related to small patient numbers due to disease prevalence, reflected upon in context of current methodological guidelines, such as ICH E11A on the use of extrapolation were discussed. It was emphasised that the key principle behind the use of extrapolation is to avoid unnecessary clinical trials in children whenever possible. And to using existing evidence from across populations and/or same in class products, as appropriate, in support of a paediatric clinical trial design, which addresses clear scientific questions in order to move forward in addressing identified unmet medical needs. This was complemented by the experience from the PDCO and how these considerations are reflected in the PIP assessment.

From the regulation, the discussion moved to the principle of equitable access to health care through research and how to view paediatric clinical trials in context of the revised Declaration of Helsinki and CRT Article 32. It was highlighted that the revised Declaration of Helsinki emphasises that excluding vulnerable populations (like children) from research can potentially perpetuate or exacerbate their disparities. Therefore, the harms of exclusion must be considered and weighed against the harm of inclusion. This paradigm shifts from a "no unless" to a "yes, if justified" mindset should be taken into account when designing and reviewing paediatric clinical trials; as in line with relevant guidelines, such as E11A. It was concluded that justice and equitable access to research must be central to a scientific and ethical review.

Panel discussion

Moderator: Anette Solli Karlsen (PDCO member, Norwegian Medical Products Agency (NOMA), Norway)

- Industry perspective
- Academic perspective
- Patient perspective

Panellists: *Scott Diede from Industry (MSD), Michel Zwaan from Academia [Prinses Maxima Centre Utrecht, Netherlands] and Tomasz Grybek from Patient perspective [Eurordis Rare Diseases Europe] Laura Fankhauser (Hopp Children's Cancer Center Heidelberg (KiTZ) Germany), Dominik Karres (Pediatrics Medicines Office EMA) and Sabine Scherer (PDCO member, BFARM Germany), Martine de Vries (Head of the Department of Medical Ethics and Health Law Paediatrician Leiden University Medical Center, Department of Medical Ethics & Health Law, The Netherlands)*

The panellists provided additional perspectives, with the industry representative highlighting challenges with inconsistent assessments and subsequent delays in trial approvals. The academic perspective stressed the need for early engagement with regulators and patients/ caregivers at stage of trial design and pointing to the need for paediatric clinical trials which are acceptable to all regions globally. The patient/ parent representative stressed that patients and caregivers are often willing to accept higher risks, especially in life-threatening conditions and raised the concern that their voices remain underrepresented in trial design discussions and in clinical trial assessments.

The panel discussed the value of potential alignment in the interpretation of Article 32 across NCAs and ethics committees. Reflecting on ways to improving exchange and learnings across regulatory decision makers (such as PDCO, CTCG/ NCAs and ethics committees). It was discussed how established platforms, like the CTCG assessor's roundtable can be used more targeted and efficient to enable discussions and alignment. The challenges in applying the revised Declaration of Helsinki and CIOMS guidelines consistently were touched upon, pointing to the need for ways to further enhancing ethical review practices.

Breakout sessions

Moderators: Marianne Lunzer (CTCG chair, AGES Austria) and Monique Al (CCMO Netherlands /Vice-chair CTCG/Co-chair MedEdthicsEU)

Breakout group topics

The breakout session groups were introduced. This were closed meetings for NCA and Ethic Committees (EC members only). Real use cases of clinical trial applications were discussed.

The use cases were chosen to represent of the following key issues:

Dosing; clinical trials without prospect of direct benefit; what is sufficient proof of concept and how much adult data is needed; methodological challenges in relation to extrapolation; inclusion of adolescents in adult trials; situation of prospect of direct benefit/benefit to the group; minimum burden and risk; challenges seen from a patient perspective; how to support a global development.

Five groups discussed in individual breakout sessions these use cases with a focus on potential solutions.

Feedback from the breakout groups and Conclusions

Moderators: Marianne Lunzer (CTCG chair, AGES Austria) and Monique Al (CCMO Netherlands /Vice-chair CTCG/Co-chair MedEdthicsEU)

A recurring theme coming out of all five groups was the need for better alignment:

- Between (NCAs) and Ethics in context of clinical trial approvals.
- Inconsistent interpretations of Article 32 of the CTR and the revised Declaration of Helsinki remains a barrier in the assessment of paediatric clinical trials.
- Between regulatory decision makers such as PDCO and NCAs and Ethics in context of a PIP agreement leading to a clinical trial application

The groups discussed the cases in light of the interpretation of Article 32 (CTR), with a particular focus on:

- Article 32.1(e) on the amount of adult data needed before including minors
- Article 32.1(f): relation to the medical condition of the minor
- Article 32(g): direct benefit vs group benefit with minimal risk/burden.

Here the value to develop a common EU-wide interpretation were emphasized, especially regarding:

- What constitutes "minimal additional risk."
- When group benefit justifies inclusion without direct benefit.

The value of inclusion of adolescents in adult trials was raised, with a strong support for including adolescents when scientifically justified. Here it was proposed for sponsors to justify exclusion, not just inclusion. It was however flagged that some Member States may have national laws or practices that hinder such inclusion, pointing to the need for a better understanding of national legal frameworks.

All groups agreed that there remains a need to further develop and/or update practical tools and guidance, such as:

- Calling for a decision-making framework supporting the assessment of paediatric trials.
- Consider updating the recommendation paper on ethical considerations in clinical trials with minors.
- Considering developing a sponsor guidance on what to include in a paediatric CTA, including full PIP Decision, including its Annexes if available).
- Need for further regulatory clarification on how to apply e.g. use of extrapolation.

Next steps

Moderators: Marianne Lunzer (CTCG chair, AGES Austria) and Monique Al (CCMO Netherlands /Vice-chair CTCG/Co-chair MedEdthicsEU)

Analyses to better understand hurdles in MSs:

Survey on national laws

Current 'guidance landscape' fit for purpose?

Analyse the document Ethical considerations for clinical trials with minors to see if an update is needed in the light of the workshop discussions and conclusions

Need to develop an assessor's best practice document on considerations specific for paediatric trials

Guidance for sponsors directing towards good justification of inclusion of minors and provision of full PIP as part of the submission dossier, early engagement of investigators and patients, guidance should aim to explain paradigm shift (DoH, CTR)

Enable information sharing, discussions and learnings across decision makers (from PIP to CTA):

Organise meeting on interpretation of CTR art 32 e, f, g (PDCO, NCA, Ethics)

Implement process for sharing and discussing critical cases between CTCG and PDCO

Involvement of stakeholders, but also regulatory decision makers, such as ethics committees in guidance/Q&A updates (such as Q&A on paediatric dosing) created by PDCO, CTCG and MWP as co-author or in commenting phase

Closing remarks from CTCG, PDCO and MWP

Moderators: Marianne Lunzer (CTCG chair, AGES Austria) and Monique Al (CCMO Netherlands /Vice-chair CTCG/Co-chair MedEdthicsEU), Brian Aylward (PDCO chair), Kit Roes (MWP chair)

Key messages

- Timely workshop to address relevant issues related to assessment of paediatric clinical trials in EU/EEA
- Clear message to continue this dialogue between regulatory decision makers, Ethics, investigators, sponsors and patient representatives
- Concrete follow up actions, including formal implementation of a collaboration between PDCO and CTCG
- Acknowledgement about the importance to extend methodology implementation activities, such as related to ICH E11A Guideline to include also, e.g. clinical trial assessors and ethics committees
- Acknowledgement to everyone who has contributed to this workshop.

More information

The Accelerating Clinical Trials in the EU (ACT EU) initiative aims to develop the European Union further as a competitive centre for innovative clinical research. ACT EU seeks to deliver on the clinical trial innovation recommendations of the European medicines agencies network strategy and the European Commission's Pharmaceutical strategy for Europe.

ACT EU builds on the Clinical Trials Regulation (CTR) and Clinical Trials Information System (CTIS) launched on 31 January 2022. The European Commission, EMA and Heads of Medicines Agencies launched ACT EU in January 2022 and run the initiative together, establishing a steering group in March 2022. The programme's strategy paper features ten priority action (PA) areas that are the basis for the ACT EU workplan.

The third version of the ACT EU workplan was published on December 2024 and sets out deliverables and timelines for the programme for 2025-2026.

Glossary

ACT EU	Accelerating Clinical Trials in the European Union
CTA	Clinical Trial Application
CTCG	Clinical Trials Coordination Group
CTR	Clinical Trial Regulation (Regulation (EU) No 536/2014 of the European Parliament and of the Council)
EC	Ethic Committee
EU/EEA	European Union/ European Economic Area
ICH E11	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population
MS	Member States
MWP	Methodology Working Party
NCA	National Competent Authority
NCA	National Competent Authority
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan

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Workshop for assessors of paediatric clinical trials

ACT EU Paediatrics Trials in EU/EEA

Day 1, 14 July 2025

Welcome and opening speeches

Peter Arlett (*Head of Data Analytics and Methods Task Force at the EMA*)

Marianne Lunzer *(CTCG Chair/AGES-MEA)*

Monique Al *(CTCG Vice-chair, MedEthicsEU Co-chair/CCMO)*

14 July 2025

Session 1: Setting the scene

Moderators: Marianne Lunzer and Monique Al

14 July 2025

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

Presented by Laura Frankhauser *(Collaborating Expert in the Paediatric Medicines Office and Clinical Trialist at the Hopp Children´s Cancer Center Heidelberg)*

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.

Content

- Background and Problem statement
- Objective and research questions
- Results
- Conclusions

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

Analyses 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

A survey was developed with CTCG chairs to reflect approaches of MS during the assessments of paediatric clinical trial applications:

1. What is the considered age of adolescents in your country?
2. Do you consider legal and physiological (biological) age differently in a clinical trial application? If yes, how?
3. Do you assess paediatric clinical trial applications differently when there is a PIP in place? If yes, how?

4.a. Would any of the following factors) influence the type and/or amount of data expected as a pre-requisite to fulfil article 32 1e? Please chose:

- Early phase vs later phase
- Staggered approach proposed in the CT
- Adolescents to be included vs small children
- Approved product (adults in another indication vs not approved, approved for pediatric use (other indication)
- Other: (free text field)

4.b. Which type of data would be expected taking into account the factors above?

Research questions

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

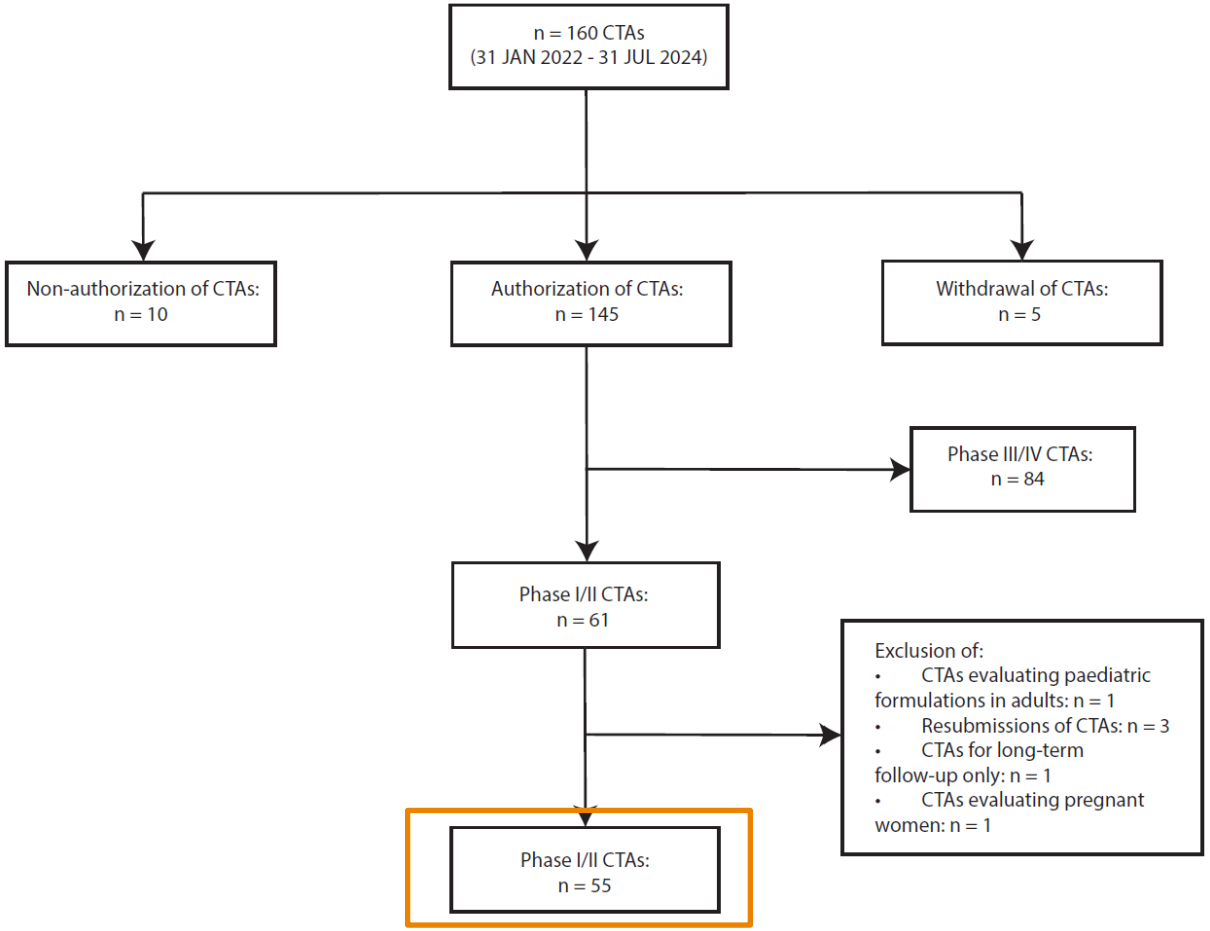
- **Question 2:** How is Art 32 interpreted by EU Member States?

- **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 = Reference Member state

Main reasons for non-authorization

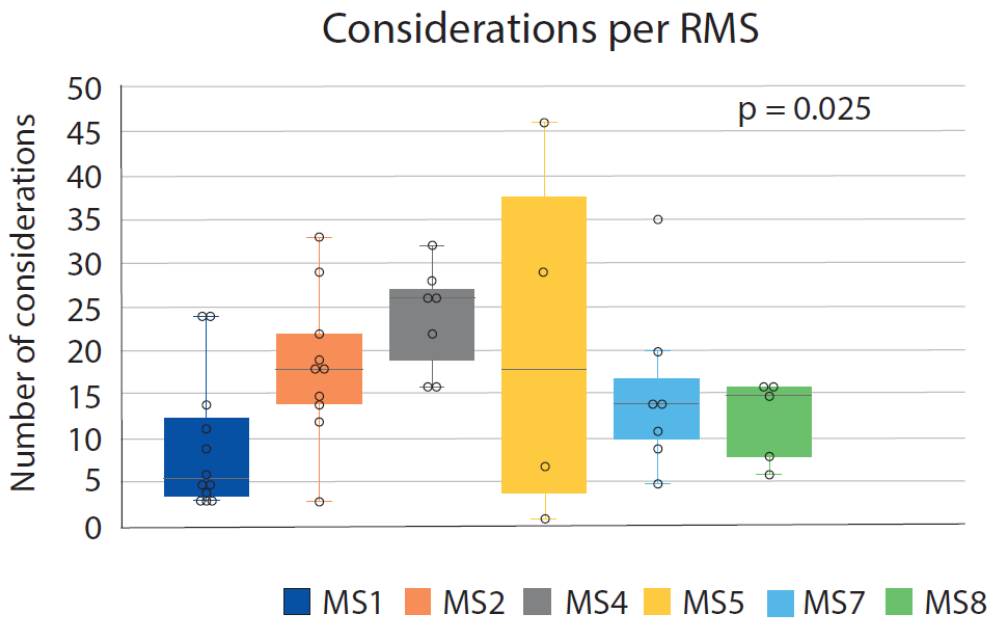
	therapeutic area	formalities	toxicity and safety	drug manufacturing and import	quality	inclusion exclusion criteria	study population and design	risk burden benefit analysis	study rationale	drug administration	dosing	proof of concept
study 1	oncology											lack of non-clinical d.
study 2	oncology							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

Subject to final data cleaning

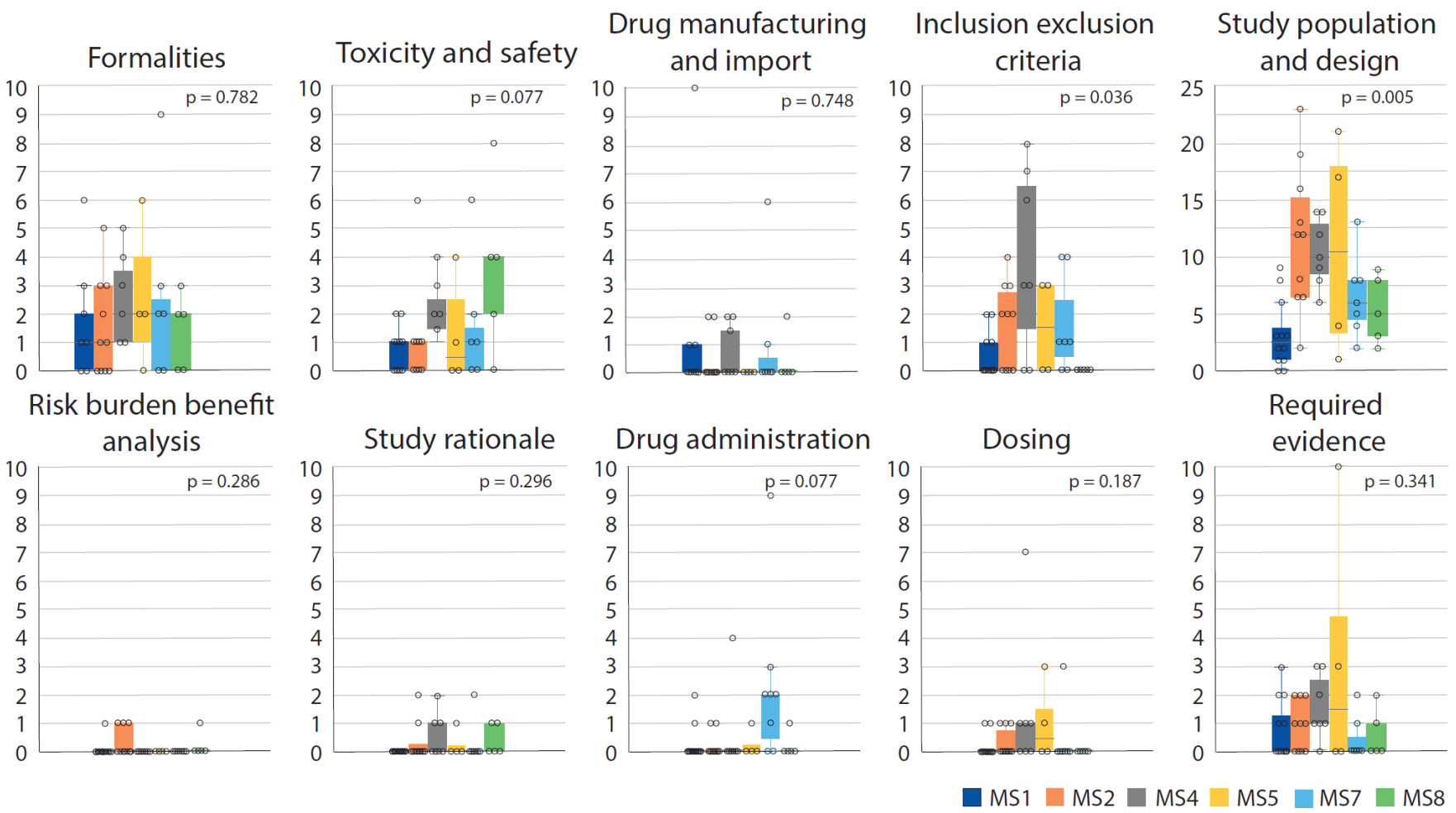
Clinical trial assessment (phase I/II CTAs): Considerations per MS when **RMS** (median)

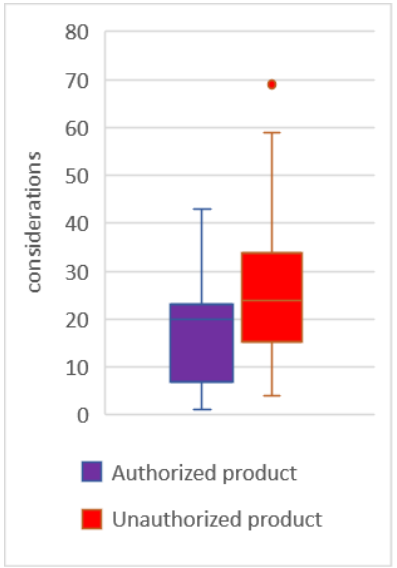


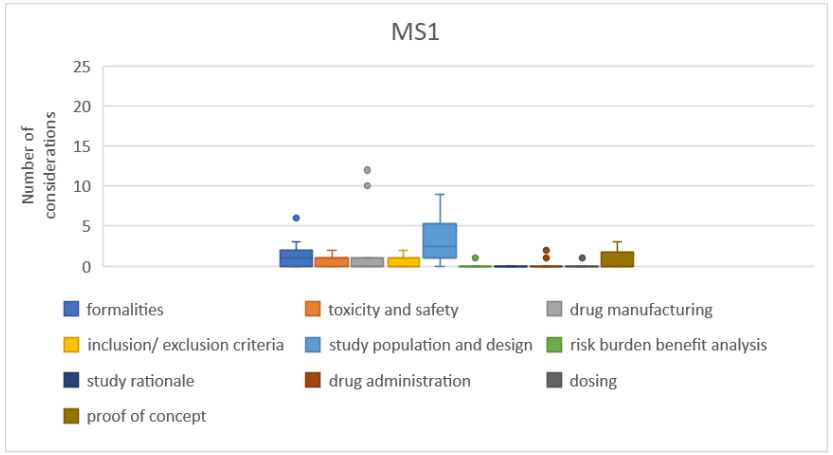
Only MS that are RMS for > 2 trials are shown.

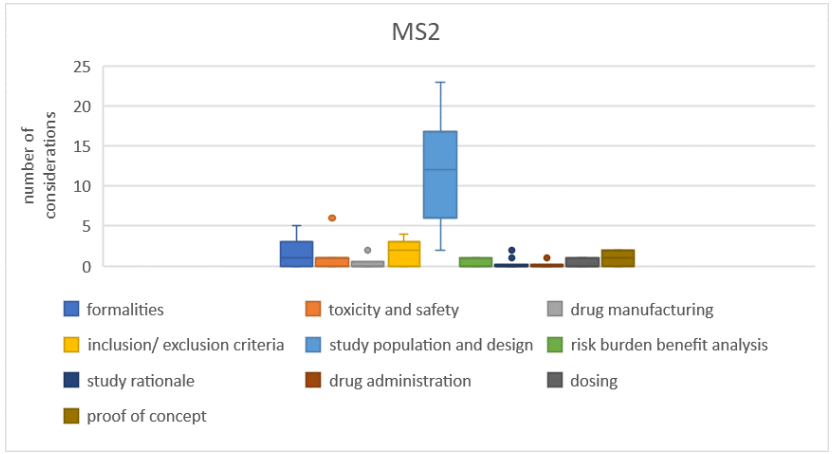
MS = Member state, RMS = Reference Member state

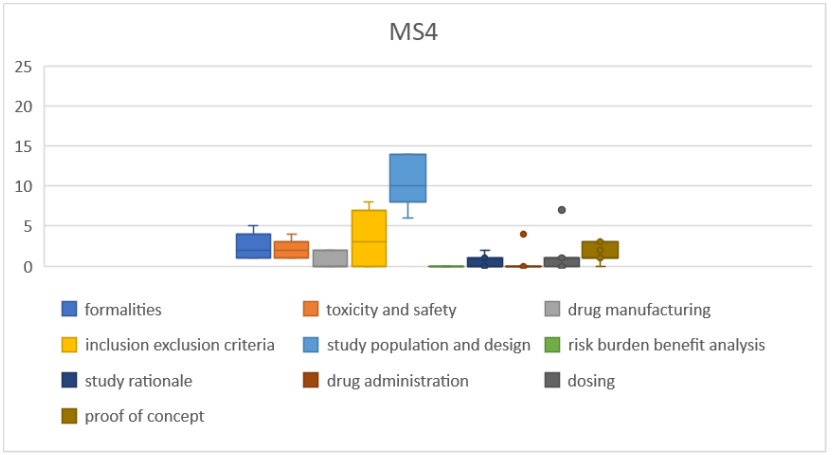
Clinical trial assessment: Considerations per MS per assessment issue when RMS (median)

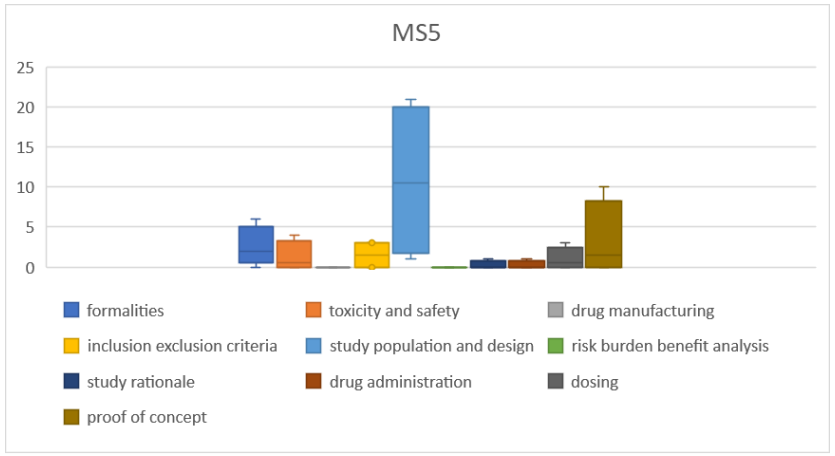


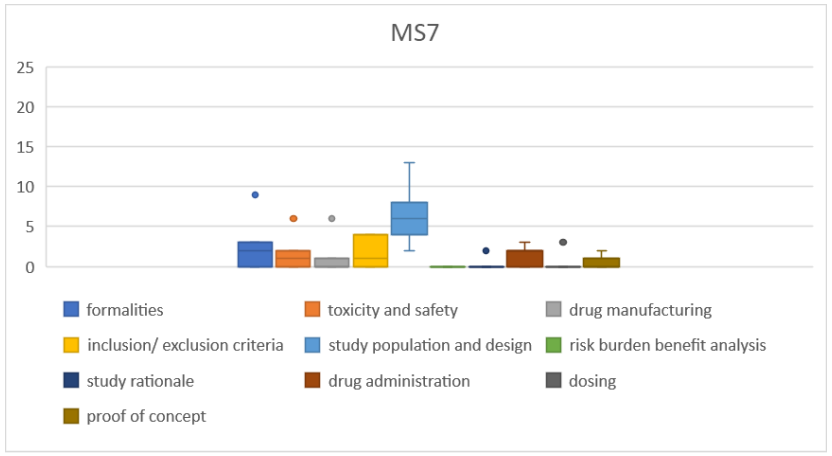


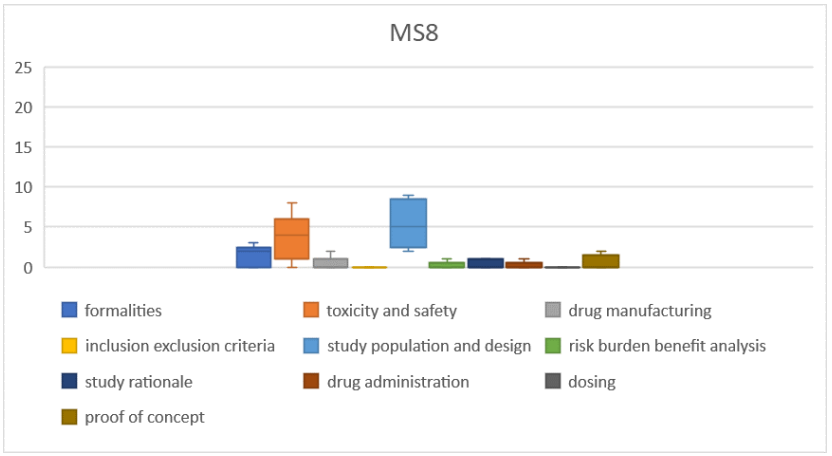






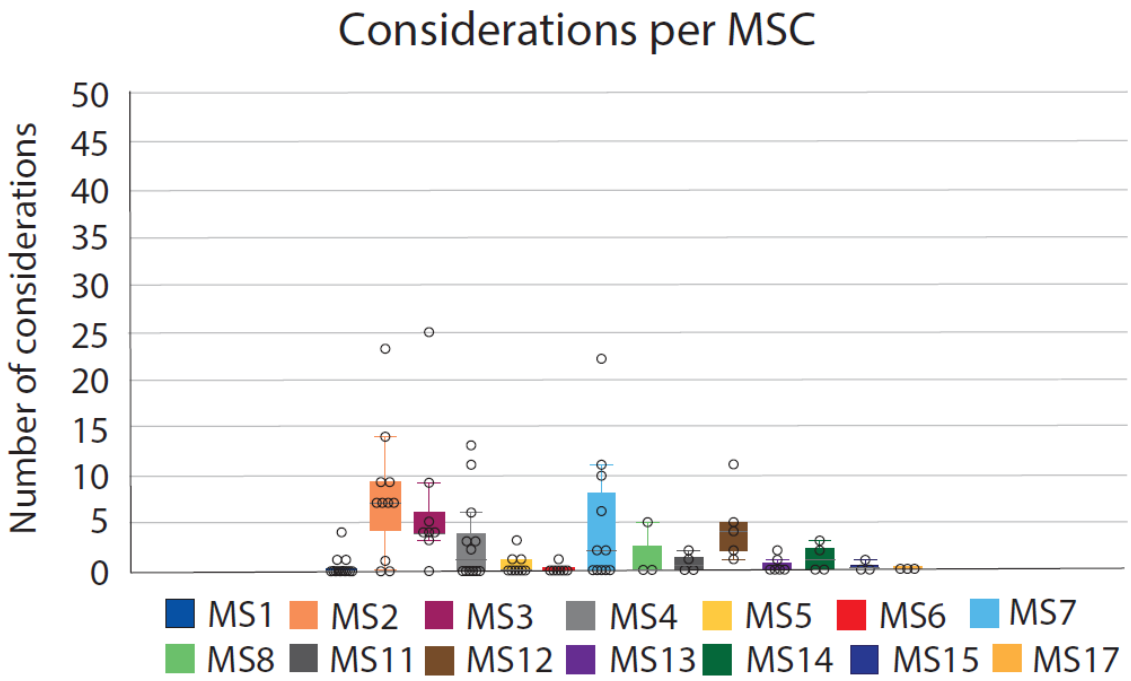




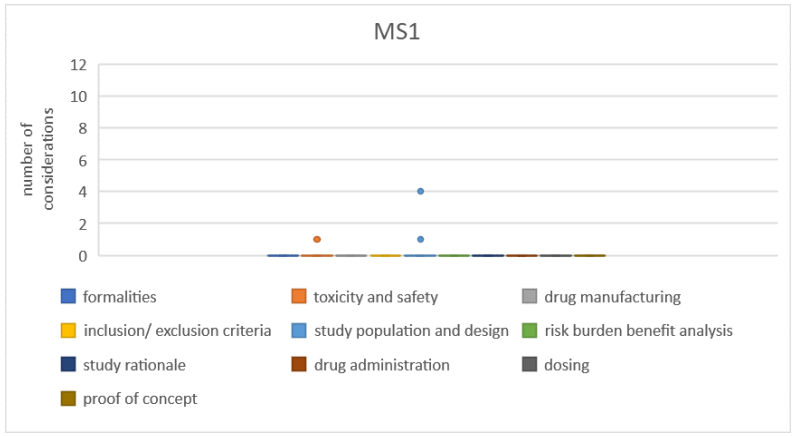


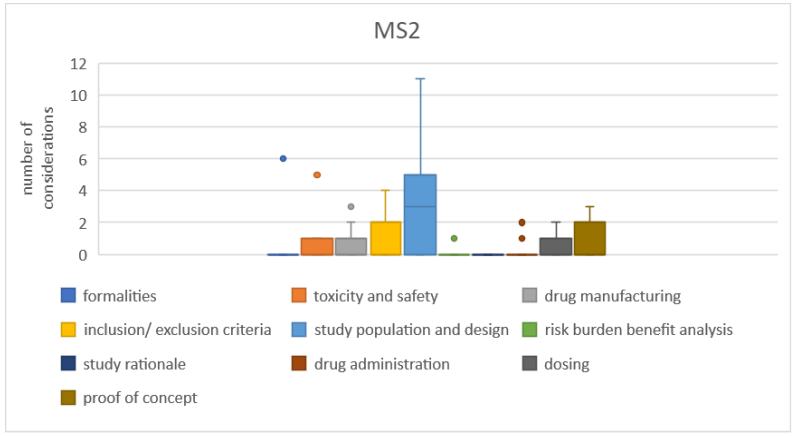
Member States focus on similar issues but apply varying degrees of ‘details’ in their approaches. This offers the opportunity to further discussions.

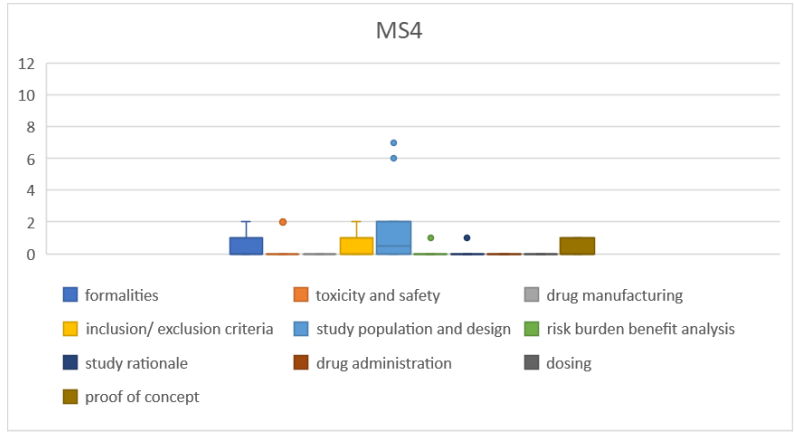
Clinical trial assessment (phase I/II CTAs): Considerations per MS when **MSC** (median)

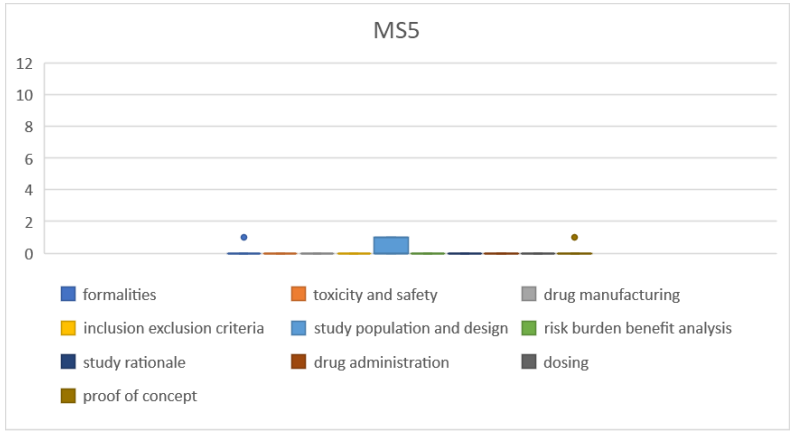


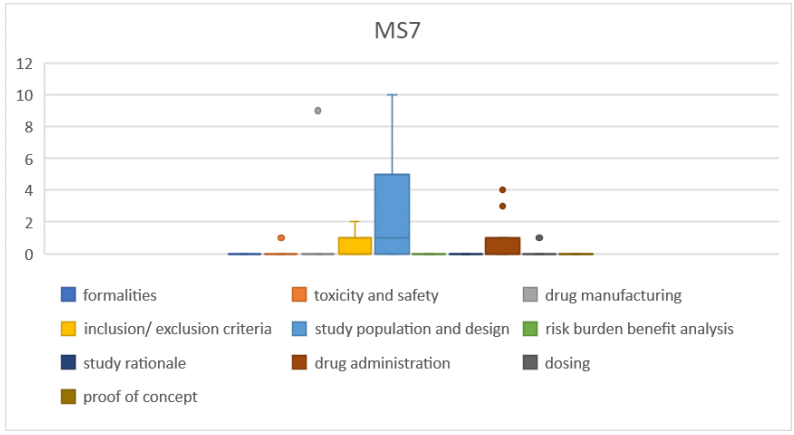
Only MSC that are MSC for > 2 trials are shown.

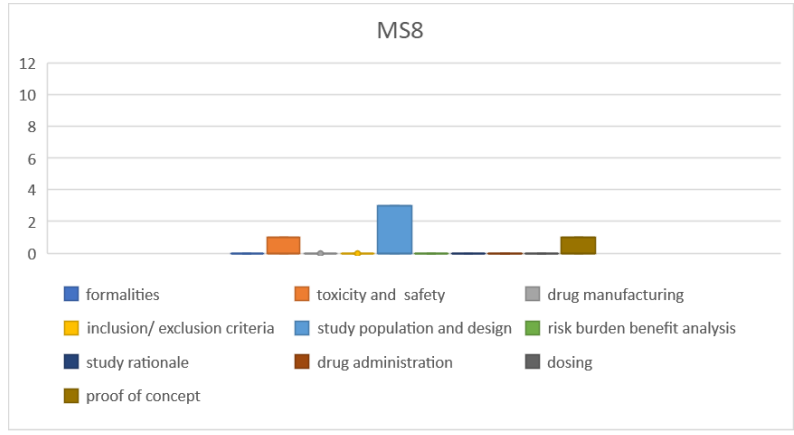






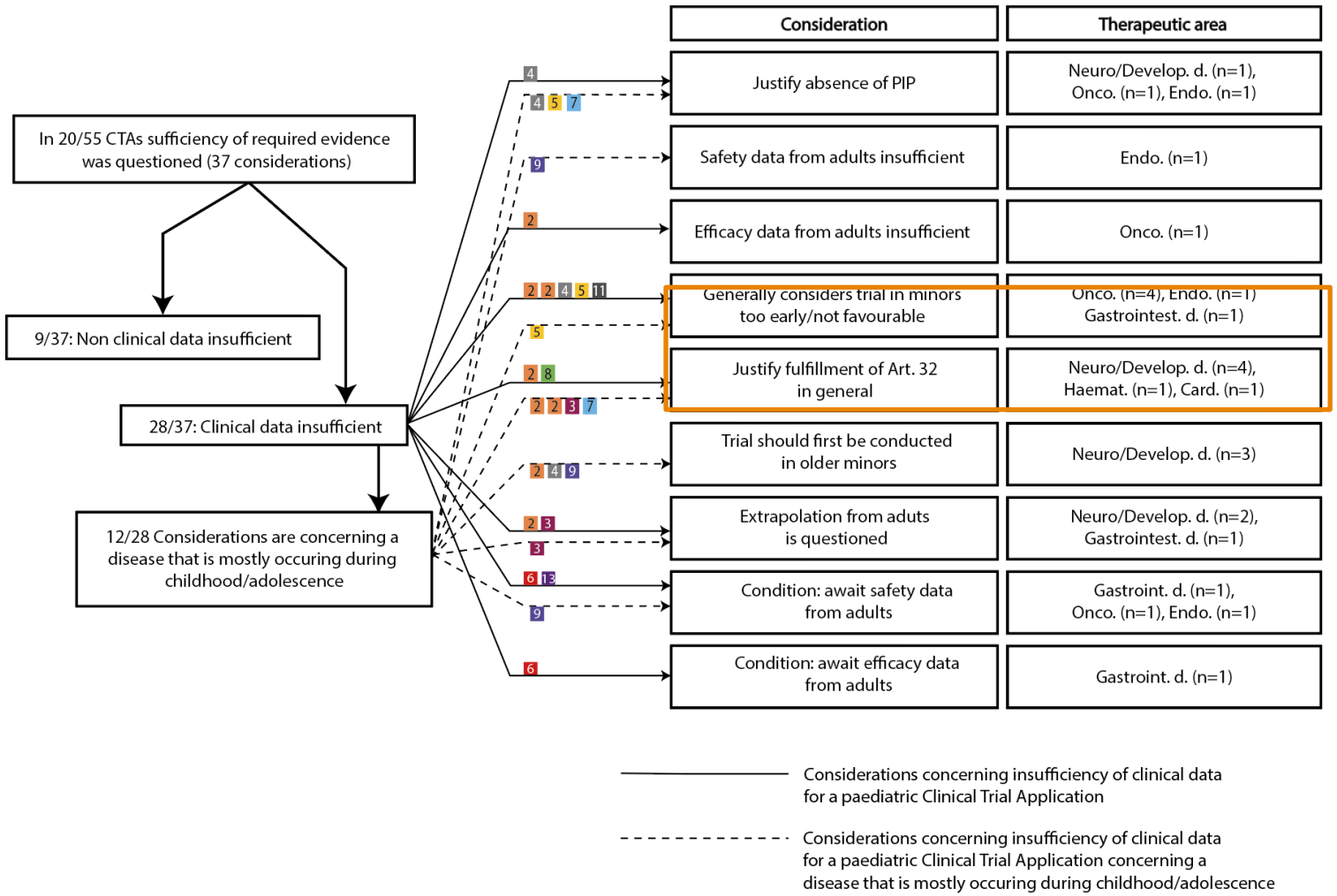






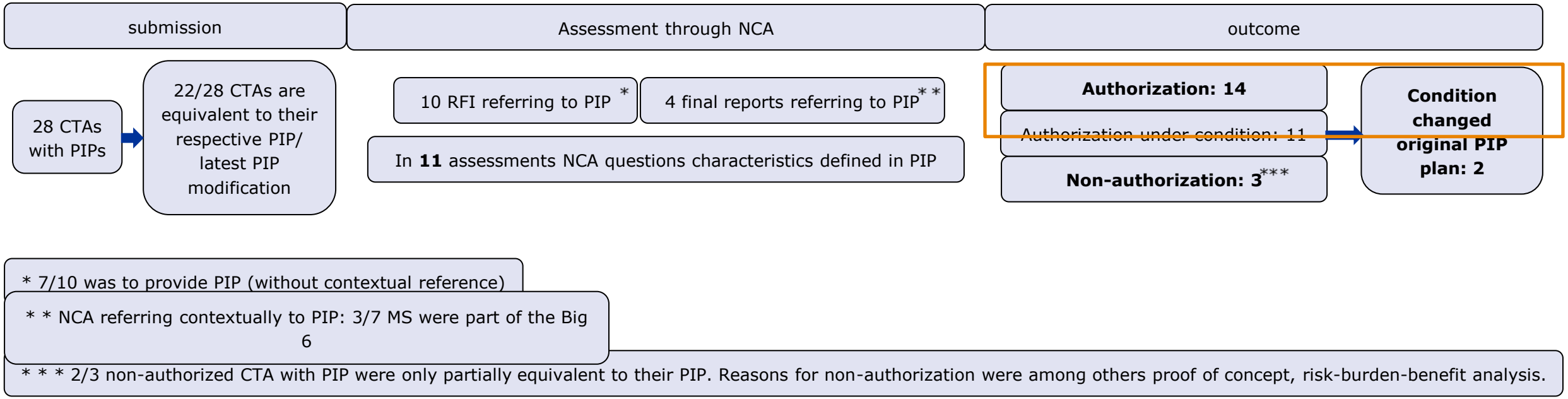
In the role of MSCs, MS demonstrate different levels of engagement in the assessment process.

Interpretation 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.

Phase I/II paediatric trials with PIPs

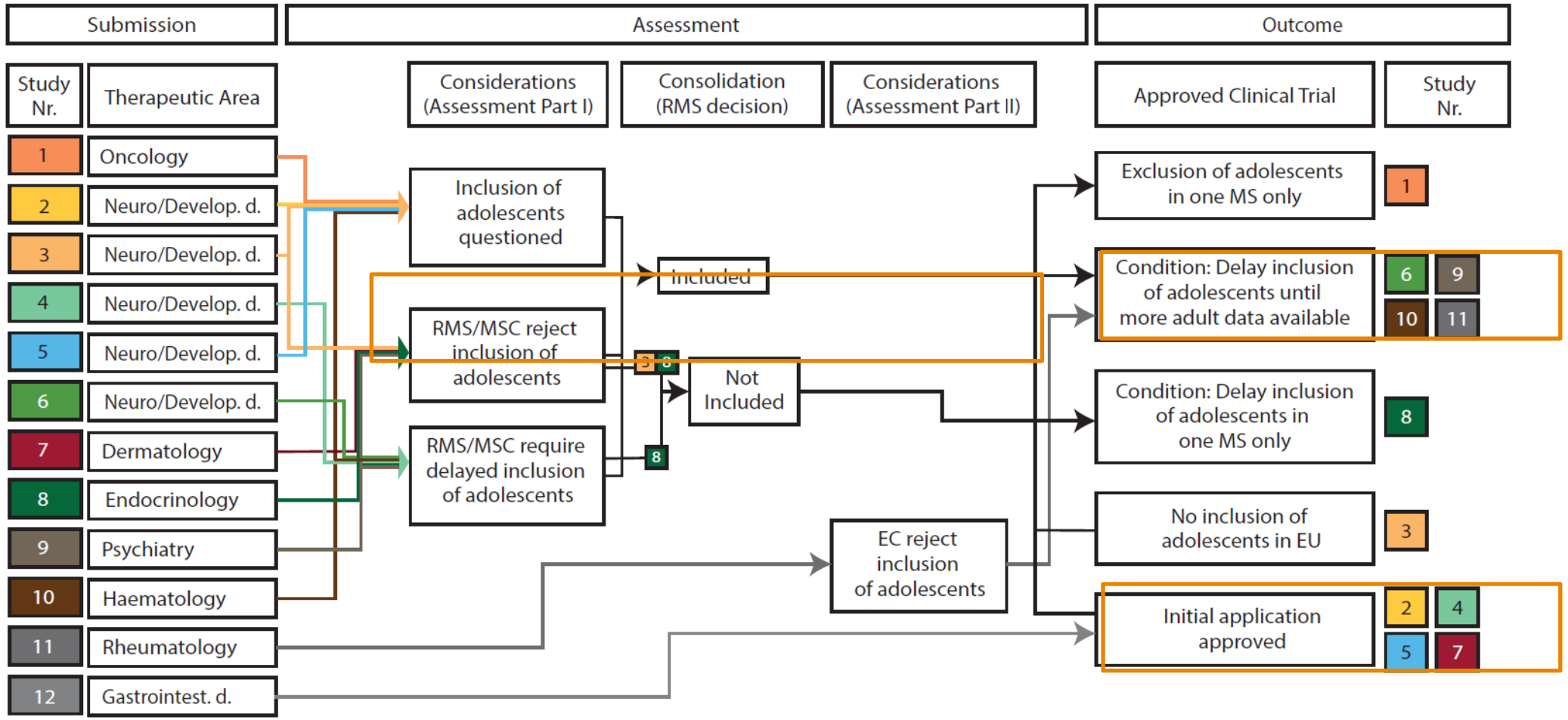


- In 11 assessments, NCA questioned characteristics of the CTA, that were already decided by PDCO in the PIP.
- In the end, two clinical trials were approved under a condition, that substantially changed the trial from its respective PIP.
- PIP´s importance in assessments ranges widely: From being disregarded by MS and changing principal trial characteristics to being treated as decisive, overriding MS considerations

Non-authorized trials with PIPs

	therapeutic area	CTA equivalent to PIP	differences CTA - PIP	RFI referring to PIP	final report referring to PIP	reason for non-authorization
study 1	oncology	partial	indication, study design	No	yes	proof of concept, risk-burden benefit analysis, dosing
study 2	infectious d.	yes		yes	no	proof of concept, risk-burden benefit analysis, toxicity and safety, study population and design
study 3	dermatology	partial	study design	No	yes	proof of concept, risk-burden benefit analysis

Adult/Adolescent phase I/II trials



Findings:

- In 1/12 CTAs the inclusion of adolescents was not questioned, rejected or required to be delayed and the initial CTA was approved.
- In 11/12 CTAs the inclusion of adolescents was either questioned, rejected or required to be delayed.
- In 2/12 CTAs, considerations regarding the inclusion of adolescents was deleted by the RMS.
- In 4/12 CTAs, the initial CTA was approved.
- In 8/12 CTAs, the assessment led to a delayed inclusion of minors, minors were excluded in EU sites or minors were excluded in certain MSC of the CTA.

CTCG survey on paediatric CTAs

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 v	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 pae
Croatia (Miz)	In Croatia, there is no un	No		No		Staggered approach prop		All the data/information re
Latvia	Not defined in legislation	No		Yes	We are taking PIP asses	Early phase vs later phas		Adolescents data would b
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 physiologi	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 prop		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 childrear	No		Early phase vs later phas		Background of the disea
Netherlands	Some categories would b	Yes	Depends on how the dise	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.

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

→ Opportunity 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**

Thank you very much

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

Acknowledgments:

EMA: Dominik Karres, Franca Ligas, Giovanni Lesa

PDCO: Anette Solli Karlsen, Sabine Scherer, Sylvie Benchetrit

CTCG: Marianne Lunzer, Monique Al

KiTZ Heidelberg: Cornelis van Tilburg, Olaf Witt, Ruth Witt

Accelerate: Adra Ivziku, Teresa de Rojas

ALADDIN

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

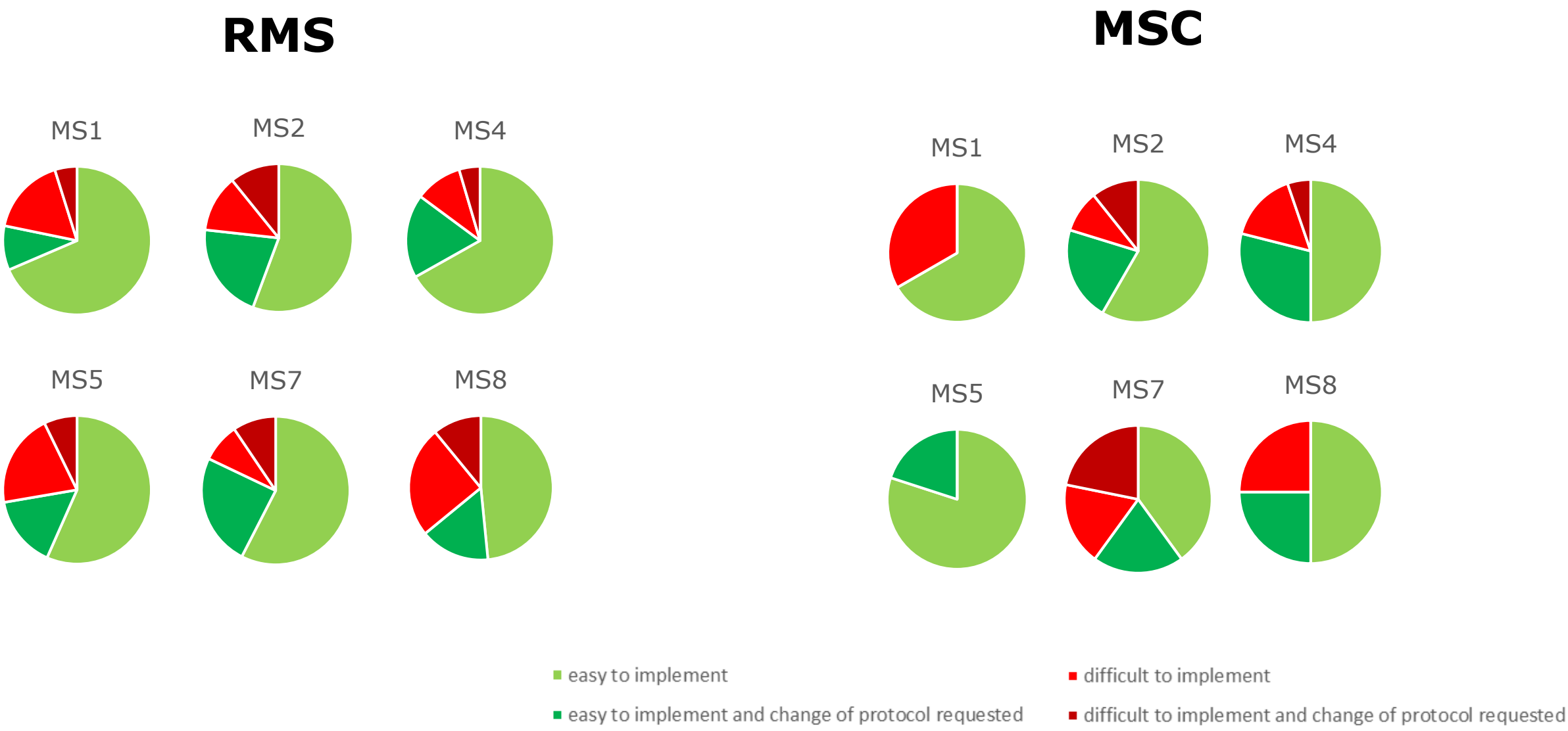
KiTZ
Hopp Children's Cancer Center
Heidelberg

German Cancer Research Center (DKFZ)
Heidelberg University Hospital
Heidelberg University

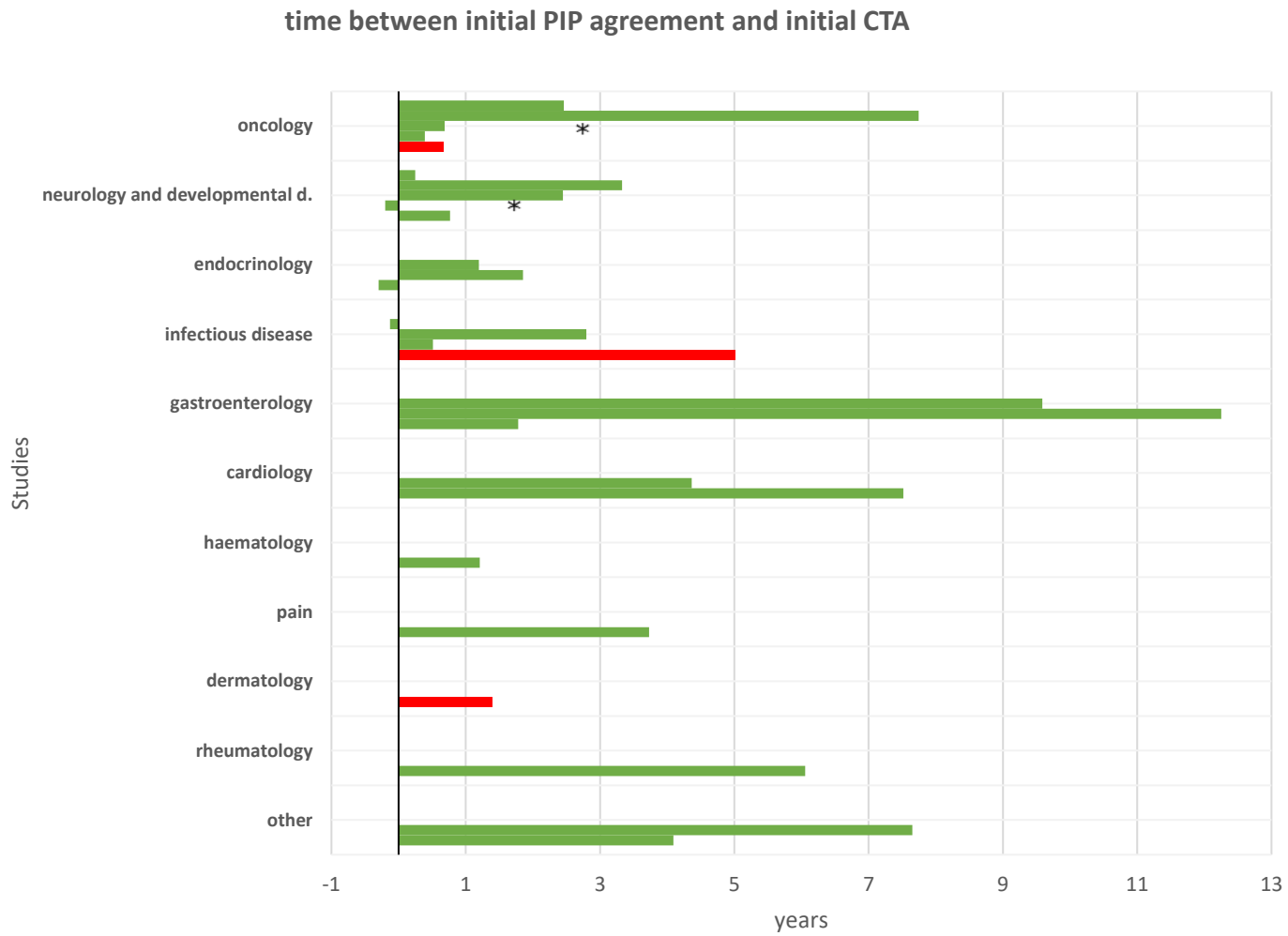
Any questions: l.fankhauser@kitz-heidelberg.de

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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

Questions?

EMA
EUROPEAN MEDICINES AGENCY

Paediatric specific clinical development challenges – methodological considerations and their use in practice.

Dominik Karres (*Paediatrics Medicines Office, EMA*)

Sabine Scherer (*PDCO, BfArM Germany*)

14 July 2025

Drug development takes place in an ecosystem

- Drug development and access to (novel/ essential) involves different stakeholders and decision makers (with different objectives) at different time points

- Key to identifying barriers within this ecosystem (eg ranging from content, process to capacity)
  - developing solutions (guidance etc) together, educating on the latter to
  - ensuring consistency in implementation, including feedback loop to learn and adapt (in case of eg ‘guidance white spots’)

- Paediatric specificities to be acknowledged

Paediatric specificities and regulatory challenges

- **Paediatric drug development** primarily occurs in **vulnerable** population, **rare disease space**, and is **highly regulated** (eg Paediatric Regulation, CTR)

- Growing **pipelines of innovative products**:
  - How can we **identify and support timely initiation and completion of development** efforts in children for products that address existing **unmet medical needs?**
  - There is a **need to foster an innovative R&D environment** that **allows** for the **evolution of scientific knowledge** and considers changing evidence and unmet needs

- **Regulatory decision making** on mandated paediatric developments **cannot occur in isolation** and requires acknowledgement of broader implications – whilst **respecting** the **different remits and scopes**

Actions to support the development of medicines for children

- Increased alignment of data requirements between decision-makers

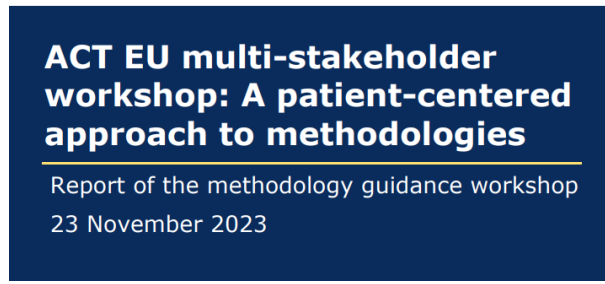
- ‘Clarify the CTR requirement for paediatric clinical trials to have direct benefit for the individual taking part in the trial….’
  ‘Harmonisation is needed between EU members state views, including that of the ethics committees.’


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 February 2023
EMA/635567/2022
Paediatric Medicines Office

Boosting the development of medicines for children
Closing report of the European Medicines Agency and European Commission (DG Health and Food Safety) action plan on paediatrics

European Commission
EMA EUROPEAN MEDICINES AGENCY
HMA Heads of Medicines Agencies


ACT EU multi-stakeholder workshop: A patient-centered approach to methodologies

Report of the methodology guidance workshop
23 November 2023

→ Continues need for (developments of) adequate (methodology) guidance

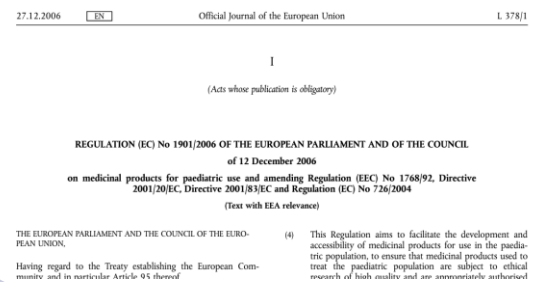
https://accelerating-clinical-trials.europa.eu/system/files/2024-03/ACT%20EU%20multi-stakeholder%20workshop%20on%20methodology%20guidance%20%E2%80%93%20report.pdf

https://www.ema.europa.eu/en/documents/report/boosting-development-medicines-children-closing-report-european-medicines-agency-european-commission_en.pdf

EMA

Paediatric drug development

EUROPEAN MEDICINES AGENCY



27.12.2006 EN Official Journal of the European Union L 378/1

I

(Acts whose publication is obligatory)

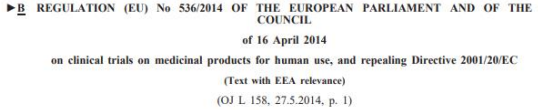
REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 12 December 2006
on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community and in particular Article 95 thereof

(4) This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised

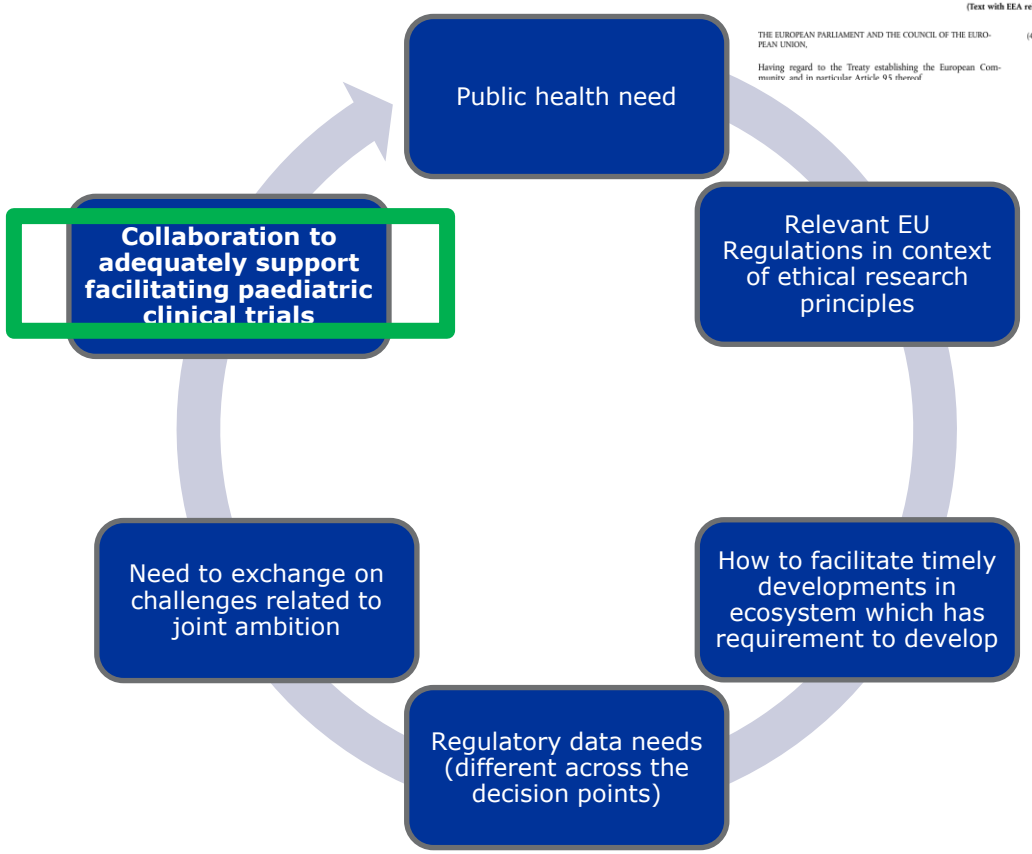
*



►B 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)
(OJ L 158, 27.5.2014, p. 1)

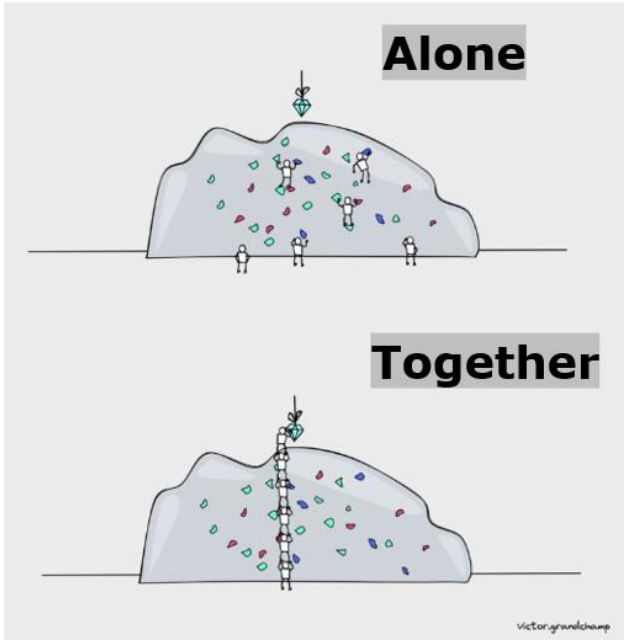
WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN PARTICIPANTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013
and by the 75th WMA General Assembly, Helsinki, Finland, October 2024



Research and Development (R&D)

to authorisation, access and practice change



- https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32006R1902&qid=1621344480633
- https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02014R0536-20221205
- https://www.wma.net/policies-post/wma-declaration-of-helsinki/

Clinical development – use of extrapolation

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 August 2024
EMA/CHMP/ICH/205218/2022
Committee for Medicinal Products for Human Use

ICH E11A Guideline on pediatric extrapolation

Step 5

Transmission to CHMP	8 March 2022
Adoption by CHMP	24 March 2022
Release for public consultation	06 April 2022
Deadline for comments	06 August 2022
Final adoption by CHMP	25 July 2024
Date for coming into effect	25 January 2025

EMA

Extrapolation – ICH E11A Guideline

'an approach to providing evidence in support of effective and safe use of drugs in the pediatric ***population when it can be assumed that the course of the disease and the expected response to a medicinal product*** *would be* ***sufficiently similar*** *in the pediatric [target] and reference (adult or other pediatric) population'*

- Its use should be **agreed prospectively** and based on **scientific considerations,** approached as **a continuum**

- It starts with the **clinical question** and is about **identifying** (**extrapolation concept**) and **addressing uncertainties** (**extrapolation plan**)

→ quantitative tools, like M&S, statistical approaches (eg Bayesian stats), RWD may be leveraged to **fill gaps in knowledge** and/ or **reduce uncertainties**

https://www.ema.europa.eu/en/ich-guideline-e11a-pediatric-extrapolation-scientific-guideline

Extrapolation, an iterative process for understanding….

- the existing information available: PK, PD, end-points
- the gaps in information needed to inform development
- ways to generate additional information when needed

How does Paediatric Extrapolation work?

- **Analysis of existing data** from adult populations informs trials and development for pediatric populations, reducing the need for additional clinical trials in children

- One or more **reference** populations (e.g. adults and/or children) being relevant to the **target** population (e.g. other paediatric population), is quantified and used as a basis for further development

What is it **not**

- It is **not following a decision tree** with binary decisions '…whether the *disease and expected response to treatment can be considered sufficiently similar* between a target and reference population is *not simply* a "**yes** or **no**" question'

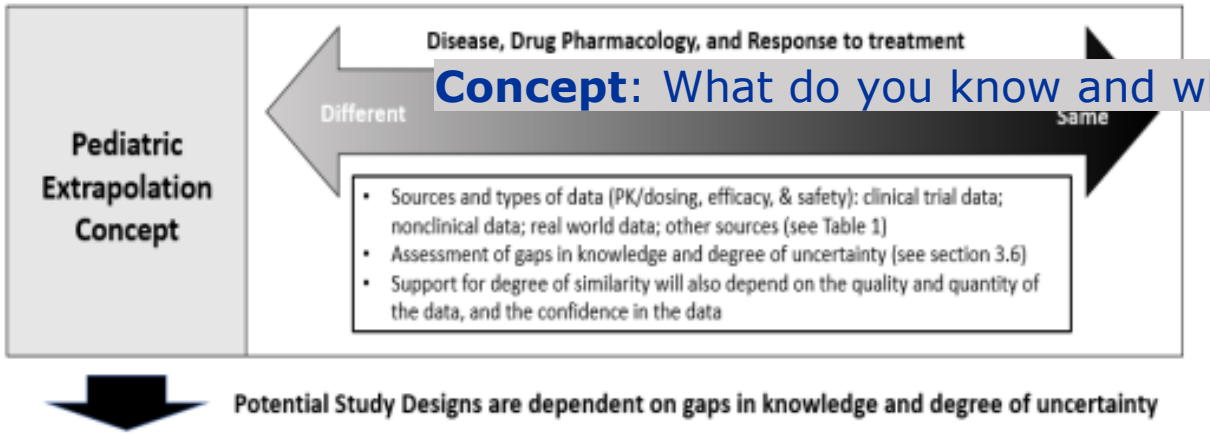
→ Important as regards '**disease similarity**' related to inclusion of adolescents in adult studies

- **Not a 'tool'** used to **retrofit available data** to support a benefit/risk assessment

- **Not a 'tool'** used because **one knows a development is 'unfeasible or challenging to complete'** over time

Extrapolation as a continuum: Concept and plan

Figure 1: Pediatric extrapolation as a continuum



Concept: What do you know and what do you not know

Understanding of the factors that can influence

- drug pharmacology
- response to treatment
- safety

in both the reference and target population

Plan: Design study(ies) which address the uncertainties you have identified – becoming the **proposed (PIP) study(ies) (eg CT protocols)**

The design of the study(ies) and/or analyses should reflect the similarities and differences, as well as the **necessary information** that **needs to be collected** to **address the gaps in knowledge** identified in the extrapolation concept.

https://www.ema.europa.eu/en/ich-guideline-e11a-pediatric-extrapolation-scientific-guideline

https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.17396

Paediatric Extrapolation Plan – Study Design Approaches

- Exposure matching approach
- PK/PD (biomarker) approach
- Efficacy studies including:
  - Single-arm studies
  - Externally controlled studies
  - Concurrent controlled studies

More than one study design may be appropriate to meet the objectives of the extrapolation plan

Use of modelling and simulation:

An essential tool in paediatric drug development to address ethical constraints, data gaps, and logistical challenges, optimize dosing, and accelerate the development of safe and effective treatments for children.

- To assess similarity of disease and response to treatment
- To examine and inform study design,
- To derive dosing recommendations,
- To test and confirm assumptions,
- To predict the effects of the drug in the target population.

Extrapolation of safety? - It is not about providing a basis to justify less safety data collection

- Known on- or **off-target effects** relevant to pediatric safety?
- Data needed to account for age-specific short- **and longer-term adverse effects** in the target pediatric population?
- How does the expected **treatment duration** compare with the target pediatric population?
- How do the expected **drug exposures** in the reference and target pediatric populations compare?
- Does the exposure needed to target a specific PD effect or clinical response **predict a specific toxicity** in the target pediatric population?
- What information is already known **from non-clinical data** that can be leveraged to the target population?
- Are there **other differences**? A background therapy used in a target population that may potentiate a safety signal but is not used in the reference population, excipients in the formulation for the reference population?

Inclusion of adolescents in adult studies

Age inclusive research

4.1.1. Inclusion of adolescents in adult trials

The enrollment of adolescents into adult clinical trials may hasten adolescent access to safe and effective treatments as well as accelerate the gathering of needed pediatric data. Historically, pediatric trials have not been initiated until after adult development has been completed and/or after the drug has been approved for adults. As a result, enrollment into pediatric trials may be slow due to the off-label pediatric use of the drug, further delaying broader pediatric and adolescent access to effective treatments. Inclusion of adolescents in some disease- and/or target-appropriate adult trials may address this problem. If the adolescent results are used to bridge the extrapolation of adult efficacy and/or safety to other pediatric populations, the similarity of disease, drug pharmacology, and response to treatment between these other pediatric populations and adolescents, and any gaps in knowledge, should be addressed.

The decision to include an adolescent cohort in an adult clinical trial assumes the disease, drug pharmacology, and response to treatment are sufficiently similar between the adolescent and adult patients. As such, the objective(s) of including adolescents and adults in a single trial should be framed within the context of the extrapolation concept. Additional data to inform adolescent dosing may not be necessary as adolescent and adult PK are generally similar. In such situations, specific consideration pertaining to the impact of lower body weight on dosing in adolescents should be carefully considered. In cases when there is a wide safety margin, higher exposures may be acceptable in the adolescents with lower body weight compared to adults when administered the same recommended adult fixed dose.

FDA U.S. FOOD & DRUG ADMINISTRATION

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

26 March 2021

Common Commentary - EMA/FDA
Common issues requested for discussion by the respective agency (EMA/PDCO and FDA) concerning paediatric oncology development plans (Paediatric Investigation Plans [PIPs] and initial Pediatric Study Plans [iPSPs])

Paediatric clinical development:

EMA position for PIP applications

Discuss opportunities for inclusion of adolescents in adult studies to accelerate development in this age group, especially in situations where the clinical indication spans the adult and adolescent age group such as in Hodgkin lymphoma, some sarcomas, melanoma, including a discussion on disease similarity allowing to use extrapolation as supporting methodology.

The gold standard remains evidence generation as part of a randomised controlled trial (RCT). However, should there be reasons, e.g. lack of equipoise or feasibility making the conduct of an RCT not possible, justifications

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

27 August 2024
EMA/CHMP/ICH/205218/2022
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Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials
Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/180203/2019
European Medicines Agency
Human Medicines Research and Development Support Division
Paediatric Medicines Office

Prof Gilles Vassal
Chair of Accelerate and President of Innovative Therapies for Children with Cancer in Europe (ITCC)
(Gilles.Vassal@gustaveroussy.fr)

Dr Nathalie Gaspar and Chris Copland (Nathalie.GASPAR@gustaveroussy.fr and chriscoplandatyork@gmail.com)
Co-Chairs of the Accelerate Working Group – Fostering Age Inclusive Research (FAIR)

Dear Dr Gaspar, Professor Vassal and Mr Copland

RE: Foster Age-Inclusive Research

The EMA and its Paediatric Committee (PDCO) follow closely and with great interest the Accelerate's FAIR (Foster Age-Inclusive Research) initiative, aiming to facilitate timely access of novel therapies for children with cancer. In this respect the EMA and PDCO took also note of the FDA's Draft Guidance for Industry on 'Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials' (published in June 2018).

The PDCO reviews Paediatric Investigation Plans (PIPs) for medicines for treatment of children with cancer, as mandated by the EU Paediatric Regulation. With the goal of fostering timely studies in the paediatric population, we generally request early initiation of studies in adolescents, either by inclusion of adolescents in adult trials or by conduct of an adolescent trial in parallel to the adult program, whenever this is scientifically justified. Of course, PIPs are evaluated on a case-by-case basis and thus this strategy is not universally applicable.

https://www.ema.europa.eu/en/documents/other/common-commentary-ema/fda-common-issues-requested-discussion-respective-agency-ema/pdco-fda-concerning-paediatric-oncology-development-plan paediatric-investigation-plans-pips_en.pdf
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e11a-pediatric-extrapolation-step-5_en.pdf
https://irp.cdn-website.com/c584cf91/files/uploaded/PDCO-letter-to-FAIR-Group-supporting-age-inclusive-research-1.pdf
https://www.fda.gov/media/113499/download

Use in practice

- PDCO’s approach

Some general remarks

- One of the main tasks of the PDCO is the adoption of **Paediatric Investigation Plans** (PIP) that define the development program which generates the data required for a paediatric indication -> **PIP opinion** (legally binding)

- In accordance with the Paediatric Regulation the **PIP should be agreed early** during the development program (after completion of adult PK study)

- As the paed. program is not supposed to delay the adult marketing authorization at least **parts of the paed. program are usually deferred**

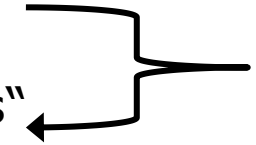
- If the agreed program is no longer feasible or changes are required during the CTA a **modification of the PIP opinion** can be requested

Main challenges to the timely completion of a PIP

- **Recruitment of paed. studies often faces problems -> repeated modifications to reduce the requirements -> less data -> license ???**

Reasons:

- Low number of available pts.
- Competition between products in „crowded areas"



Especially, when condition is mainly based on adult needs (e.g. diabetes II)

- Reluctance to enroll in clinical trial
- Demanding protocols (effect on pt. and care-giver)
- For substances, which are already on the market, off-label use is preferred over participation in a clinical trial

-> **delays in starting the paed. program lead to further delays in conducting paed. studies and ultimately in achieving the paed. MA, in the meantime off-label use is common**

Ways to address these challenges

- Careful use of **deferrals**
- *Usually, PDCO does **not defer the initiation** of the first study of the paed. program -> issues with timing of adult MA submission?*

- **Involve clinicians and pts./care-givers** in designing the program
- *The **SR-template** has been revised to better reflect the stakeholder involvement*
- *PDCO regularly requests **input from pts./care-givers and clinical expert groups**, e.g. within EnprEMA*
- ***Feasibility assessments** before the study is started are essential*

Ways to address these challenges

- **Global/multi-national multi-center trials**
- ***Choosing the trial sites*** *is in the remit of the applicant*
- ***PDCO interacts with FDA*** *to facilitate global programs*
- *Low* ***number of centers*** *(low interest, protocol not approved) renders trial more difficult to conduct*
- ***Decentralized elements*** *can reduce the burden on the pts./caregivers and therefore can be helpful*

Ways to address these challenges

- **Use of new methodologies to reduce the sample size**
- ***M/S techniques*** *are used to define the paed. dose based on the adult exposure*
- *If justified,* ***extrapolation*** *of data from older source to younger target populations can reduce the necessary sample size and complexity of the trial, but* ***in most cases additional paed. data is necessary***
- *Data can be borrowed to reduce the sampe size in a* ***Bayesian approach,*** *if justified*

-> It is important that the extrapolation plan is also considered early in the process when the adult program is designed

Ways to address these challenges

- **Include paed. pts. in adult studies**

- *Unless there are specific risks or concerns identified based on the MoA, the available non-clinical, safety or efficacy data,* ***PDCO generally encourages the inclusion of adolescent pts. in adult trials*** *under the assumption that at the time when the study starts additional supportive data will be available*
- ***But approving clinical trials is not in the remit of the PDCO*** *and PDCO sees the program early ->* ***efficacy or safety profile might change*** *when more data becomes available*
- *On the other hand,* ***not including paed. pts. might also be harmful*** *as it delays the development and promotes off-label use*

-> ***Clear criteria when paed. pts. can be included in the adult program are currently missing -> additional guidance would be helpful***

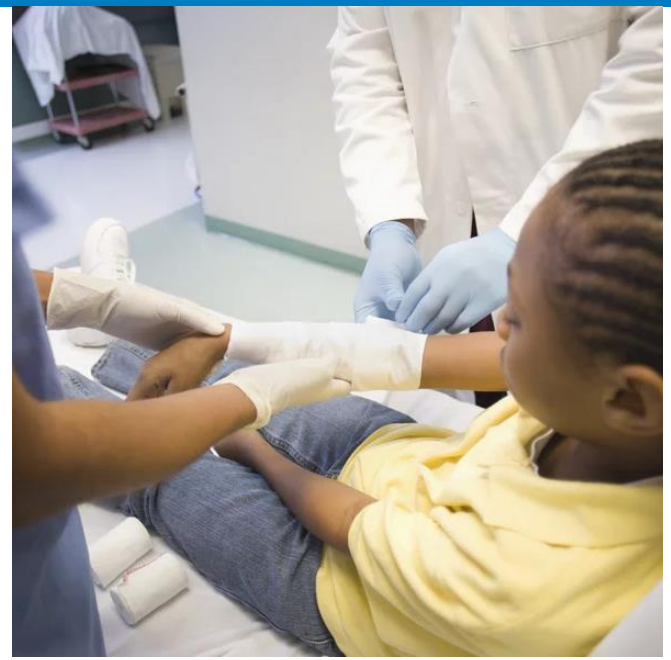
Questions?

Leiden University
Medical Center

Equitable access to healthcare through research

Paediatric clinical trials in the context of the revised Declaration of Helsinki and CTR article 32

Prof. Martine C. de Vries
Department of Medical Ethics & Health Law



Medical Research Ethics review

Scientific validity

Informed consent

Risk benefit ratio

Vulnerable populations

Vulnerable subjects in the CTR

Vulnerable subjects in the CTR

Specific rules for the following groups of vulnerable subjects:

- Incapacitated subjects
- Minors
  - see article 32 CTR, questions 9.1 and 9.4 Q&A CTR, and Ethical considerations for clinical trials with minors;
- Pregnant and breastfeeding women
- Clinical trials in emergency situations

CTR art. 32: clinical trials on minors

- 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;
- Trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;

(explain why the trial can only be performed in this particular patient group)

(often: step-by-step inclusion)

CTR art. 32

Scientific grounds for expecting that participation in the clinical trial will produce:

(i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or

(ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.

(Risk proportionate)

Ethics review under the CTR

- Step-by-step inclusion:
  - How much adult data is needed?
- When group specificity: risk proportionate
  - What exactly is prospect of direct benefit? (only after adult data? Or theoretical mechanism of action?)
- Not: justice proportionate

The no-unless dilemma

- Fundamental principle: protecting vulnerable subjects

- Fundamental principle: improving care, especially for vulnerable populations

Medical Research Ethics review

Scientific validity

Informed consent

Risk benefit ratio

(social) justice?

Vulnerability in DoH 2024 (and CIOMS)

Declaration of Helsinki 2024

- No mention of “child” or “minor” (or other categories)
- “Vulnerability” and “incapacitated” guidance
- Vulnerable versus particularly vulnerable
- The 2024 revision explicitly highlights the need for fair and responsible inclusion of vulnerable populations to ensure research results are broadly useful and socially just
- Paradigm change: Justifying exclusion rather than inclusion

DoH art 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.

DoH art 28

Persons incapable of giving free and informed consent are in situations of particular vulnerability and are entitled to the corresponding safeguards. In addition to receiving the protections for the particularly vulnerable, those incapable of giving consent must only be included if the research is likely to either personally benefit them or if it entails only minimal risk and minimal burden.

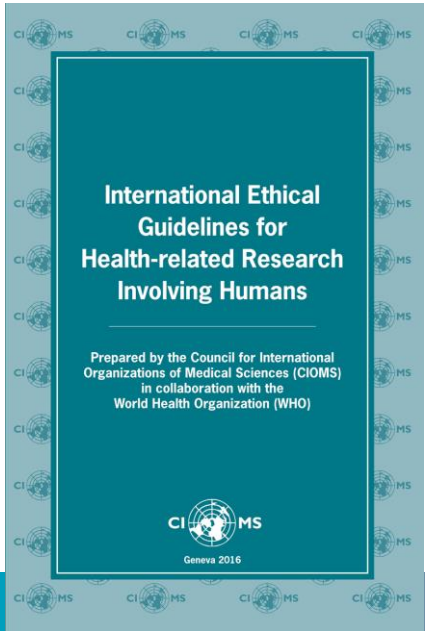
DoH art 19

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.

CIOMS 2016 – guideline 3

Because categorical exclusion from research can result in or exacerbate health disparities, the exclusion of groups in need of special protection must be justified.

Groups that are under-represented in medical research should be provided appropriate access to participate.



DoH 2024

A global ethical manifesto with strong emphasis on justice, fairness, equity, and explicit statements on benefiting vulnerable groups.

Strong normative language: mandates inclusion when justified, safeguards, assent + consent, and benefit sharing.

Requires researchers to consider distributive justice, ensuring that results and interventions reach participants and communities equitably.

EU Clinical Trial Regulation

A binding legal framework for EU trials, with detailed technical requirements and supporting ethical guidance, especially for children.

Children can be included when scientifically warranted, with strict safeguards, minimal risk, and age-appropriate design.

Focuses on transparency and procedural compliance. Detailed implementation guidance.

Ethical considerations

Group label warranted?

- Traditional approach has been to identify entire groups as vulnerable
- Has led to overprotection AND underprotection
- Rather: look at the characteristics that may make a person (or in some cases a group) vulnerable:
  - individual characteristics: relatively or absolutely incapable of protecting own interests
  - contextual characteristics: some feature of the circumstances (temporary or permanent) in which they live makes it less likely that others will be vigilant about, or sensitive to, their interests.

Step-by-step approach warranted?

- Why first in adults / people who are able to give consent?

- Distinctive physiologies and health needs > justify exclusion and inclusion!

  - Responsiveness (targeted at their health needs)
  - Group specificity: disease only in certain group, or group is needed
  - Risks should be minimized and minimal
  - Subsidiarity principle: first in a non-vulnerable group

Prospect of direct benefit?

CTR: There are scientific grounds for expecting that participation in the clinical trial will produce […] a direct benefit

DoH: Potential benefit; Likelihood of benefit; Foreseeable benefit; Anticipated benefit

What exactly is prospect of direct benefit? (only after adult data? Or theoretical mechanism of action?)

Conclusion

- Take DoH (and CIOMS) into account in ethical review
- After all we are an ethics committee (and not only a compliance committee)
- Both are complementary: DoH articulates *why and what* justice requires, while the EU CTR defines *how* child inclusion and equitable access are implemented in practice
- Prevent groups from over- and under protection by inadequate use of vulnerability label
- Vulnerability toolbox/specific protections may vary per group (CIOMS)
- Vulnerability implies need for specific protections (CIOMS)
- But does not mean: exclusion

Leiden University
Medical Center

Thank you!

m.c.de_vries@lumc.nl

Session 2: panelists presentation and discussion

Moderated by Anette Solli Karlsen (*PDCO member, NOMA*)

14 July 2025

An Industry Perspective

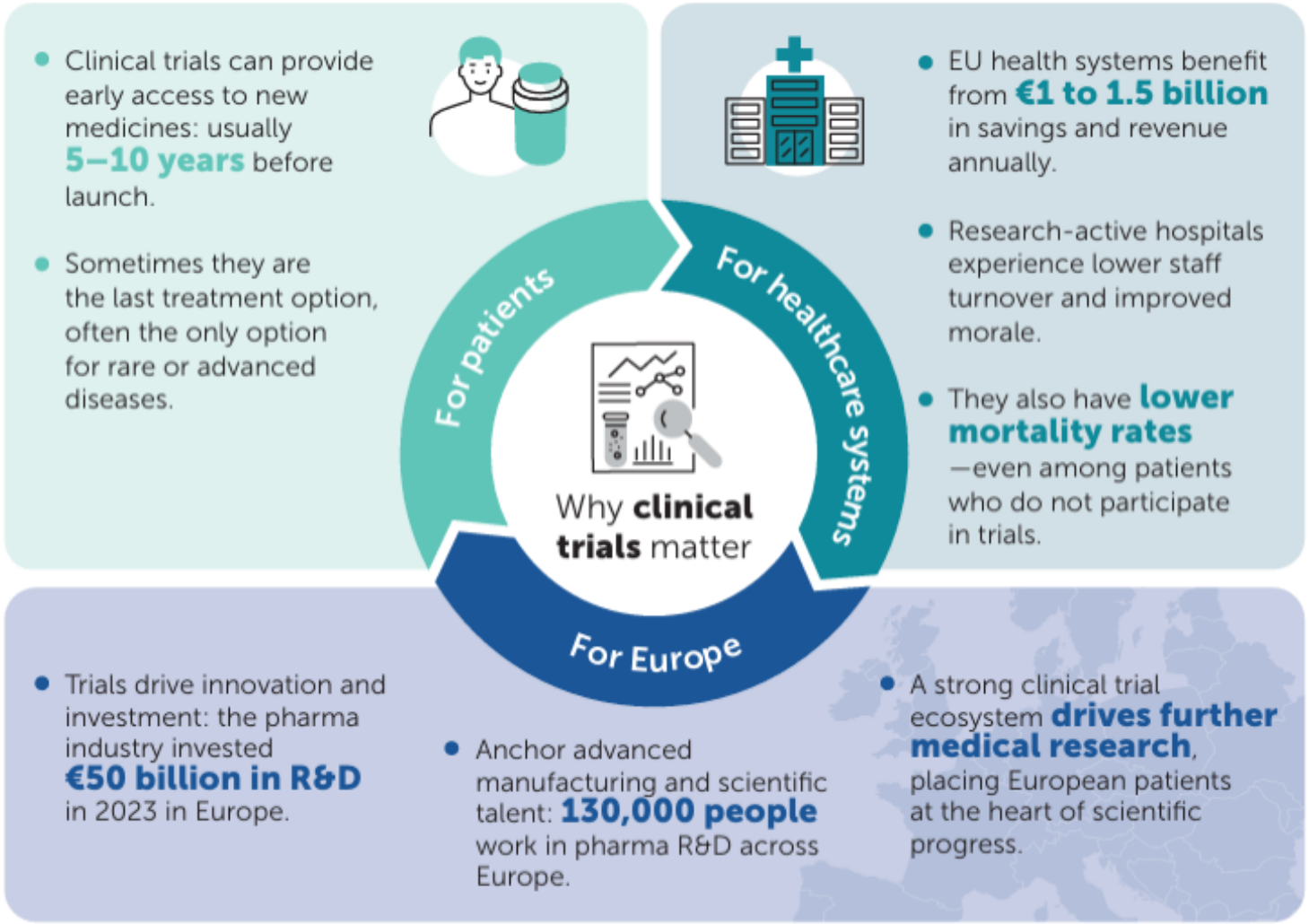
ACT EU Paediatrics Trials in EU/EEA
Workshop on the Assessment of Clinical Trials Applications involving Paediatric Patients

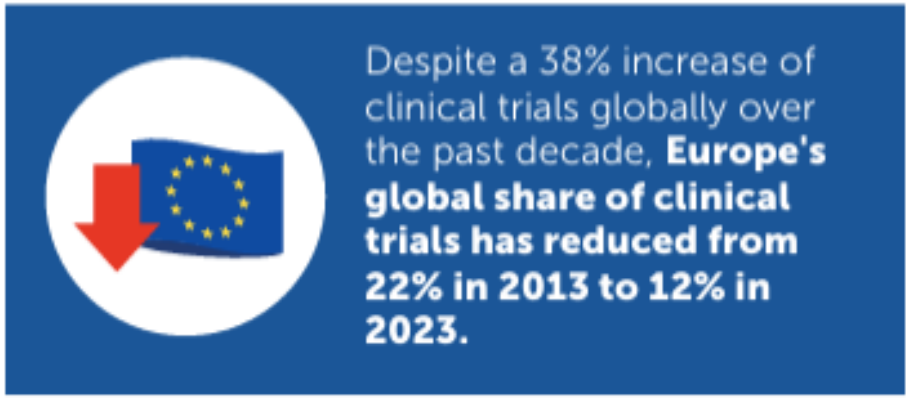
July 14, 2025

Scott J. Diede, MD, PhD

Executive Director, Clinical Research, MSD

Why clinical trials matter and what is the problem?

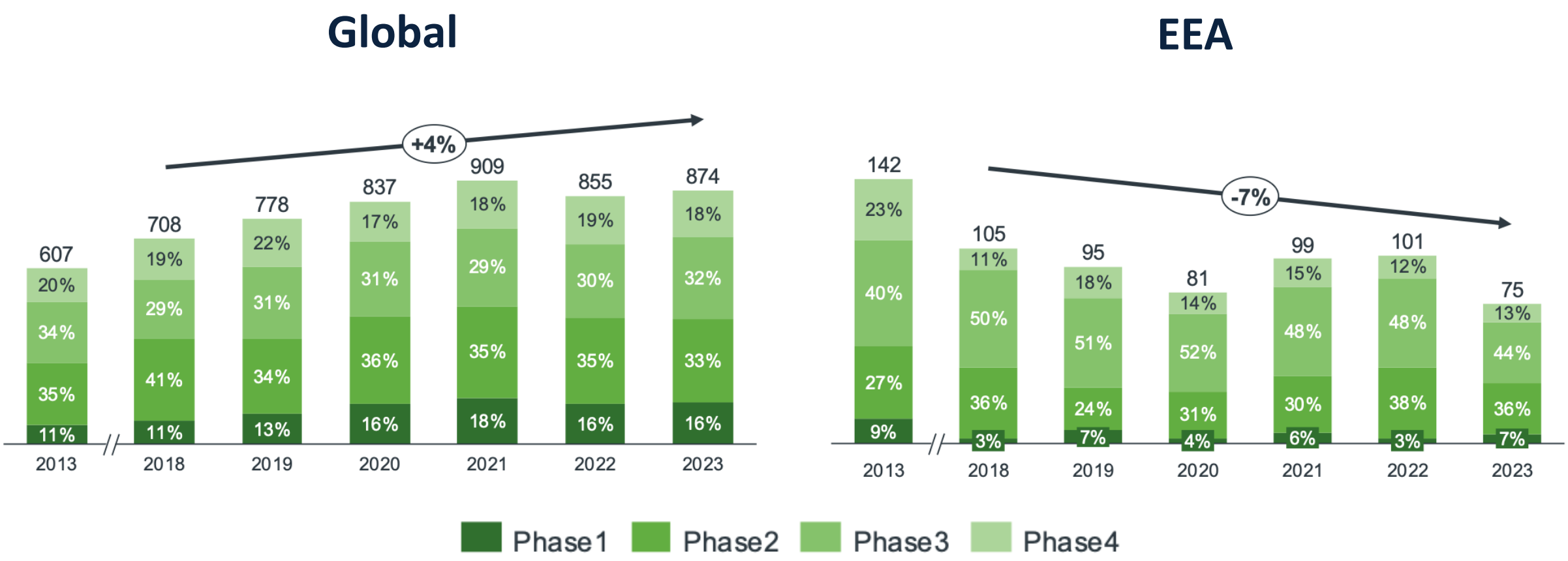




efpia-clinical-trials.pdf

assessing-the-clinical-trial-ecosystem-in-europe.pdf

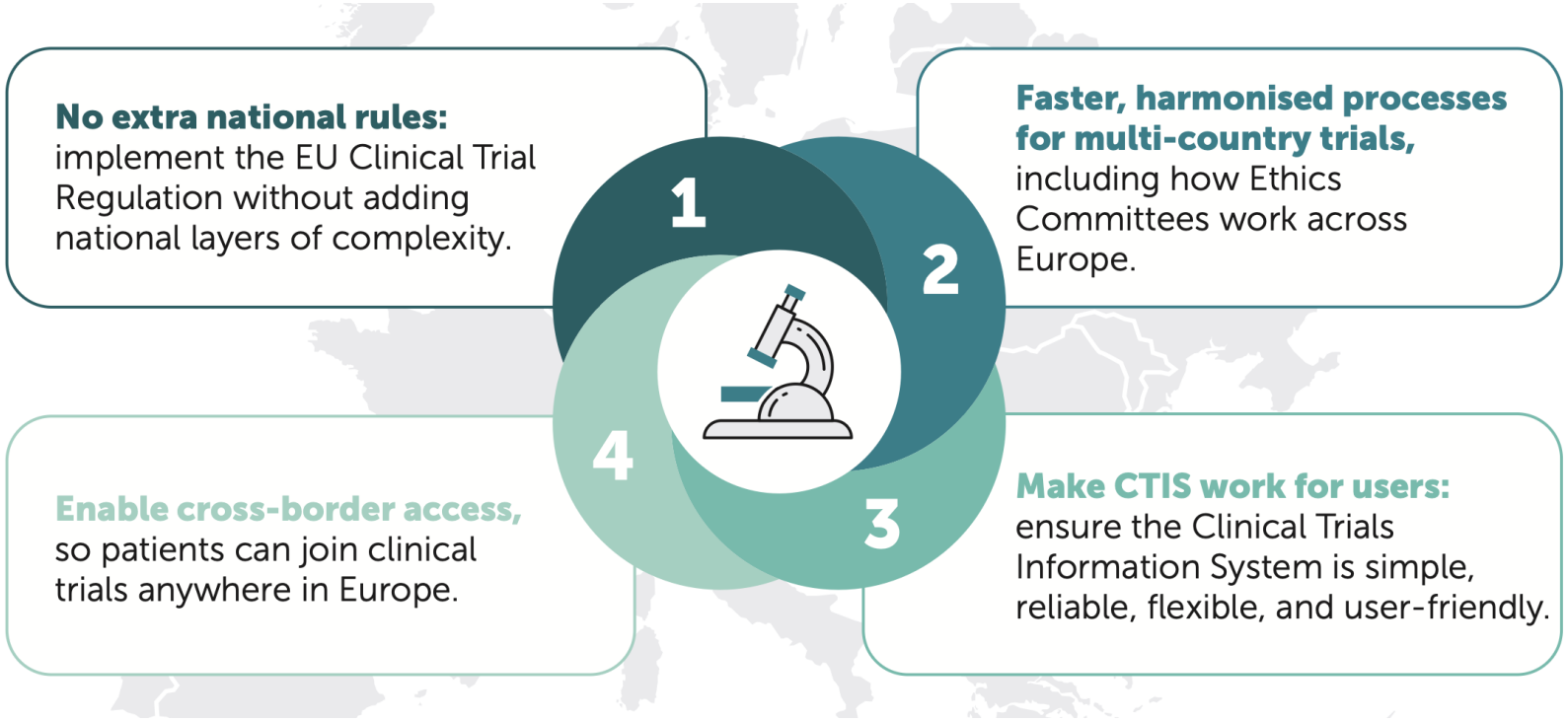
The number of paediatric trials are declining in the EEA



Number of paediatric clinical trial starts by phase (2013, 2018-2023, Phase 1-4)

assessing-the-clinical-trial-ecosystem-in-europe.pdf

Europe needs to function as a unified region – what is needed?



efpia

Improving EU Clinical Trials: Proposals to Overcome Current Challenges and Strengthen the Ecosystem

efpias-list-of-proposals-clinical-trials-15-apr-2025.pdf

Why is this particularly important for paediatric trials?

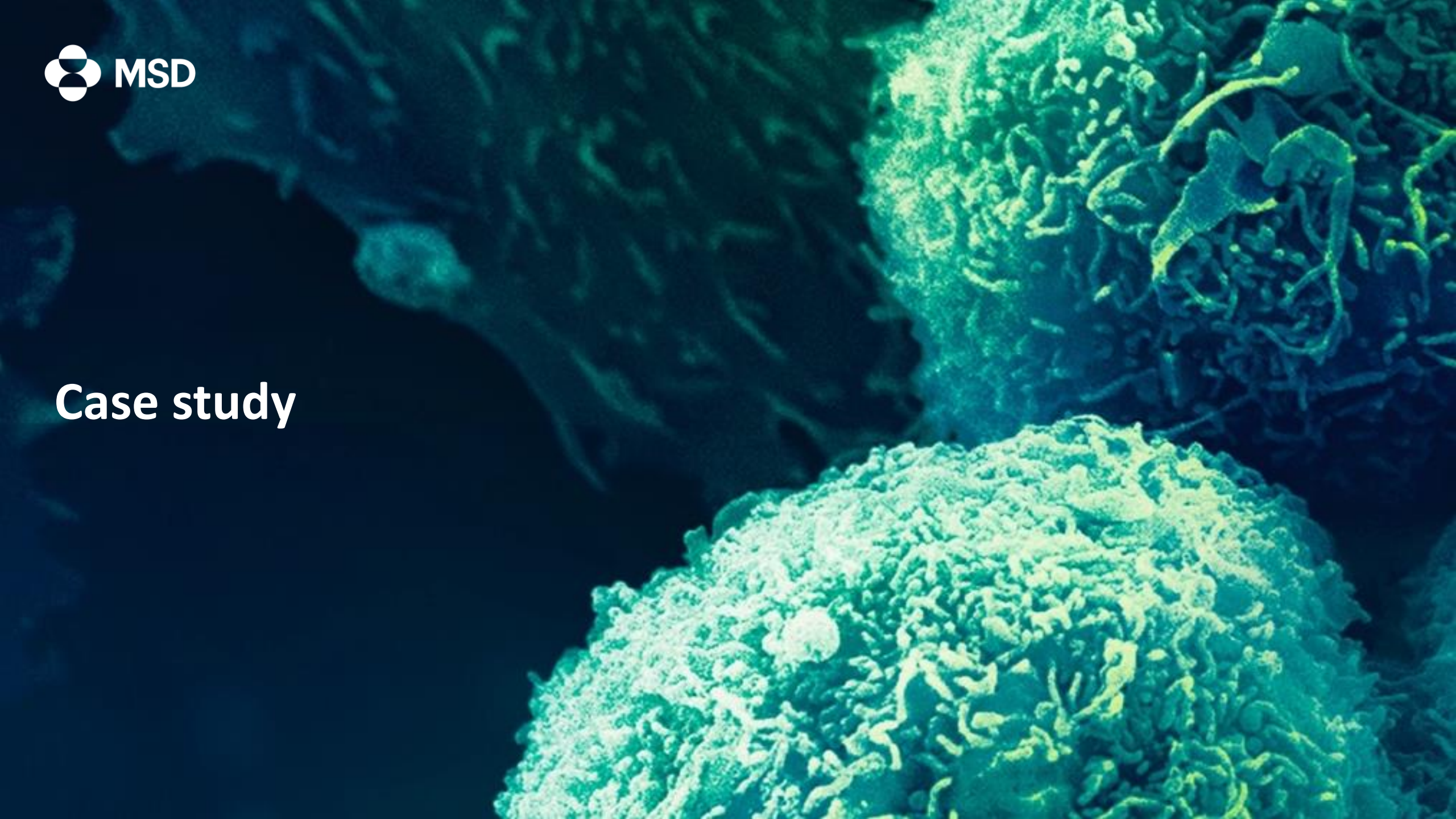
- **Global clinical trial protocols**
- **Small dispersed populations**
- Execution needs to be **fast**, **predictable** and **flawless** to speed up drug development → bring new treatments for patients
- **Risk of EU being left out** (global competitive recruitment)

Europe needs to function as a unified region

A simplified, fit for purpose and predictable regulatory system is needed

MSD

Case study



What has happened?

Development of a first-in-class novel compound for oncology adult indications

PIP submitted in parallel to iPSP for blood and solid tumor indications

Agreement with PDCO and FDA on paediatric study in 4 different tumor types in both indications

During CTA review only 1 of 4 tumor types was approved to be studied in children

Interactions with the rMS and CTA re-submission with further scientific justification

No change and 3 remaining tumor types can’t be studied in EU.

EU-specific Annex to the global study protocol had to be written

What was the problem during the CTA?

Submitted in 11 EU MS a paediatric study design fully aligned with PIP and iPSP

Received 90 questions to respond within only 12 days (32 Clinical, 7 Non-clinical, 51 CMC). In addition a fully published amended protocol needed to be generated and submitted during this timeframe.

Part I conclusion: **Acceptable with Conditions**

- ➔ **Study protocol authorized for only 1 of 4 tumor types agreed with PDCO**
- ➔ **Tumor type 1 is different from the tumor types studied in adults and for which most data are available**

Key concerns raised:

- The information regarding biomarker expression in different tumor types in children is scattered and incomplete
- The information on efficacy in adults is not sufficient for inclusion of children in a clinical trial
- Agreed on the large medical need for these children, however the data generated on tumor expression and efficacy in adults does not provide a sufficiently solid rationale to include children in a clinical trial at this moment

What was done?

- Informal interactions with EMA
  - Highlighted misalignment between PIP and CTA outcomes
  - Explored possibility for a joint meeting with PDCO and the CTA rMS
- Interaction with rMS to:
  - Better understand rationale for rejection and whether same concerns were raised by several MS
  - Explore possibility for joint meeting with PDCO and the CTA rMS
  - Align on possible next steps: rMS agreed to submission of CTA substantial modification (SM) to further justify the targeted tumor types
- Submission of a SM
  - Submitted Cover Memo with further scientific justification on the biomarker expression information for all 4 tumor types and all available efficacy & safety data from the adult indication development
  - No protocol modification submitted at this stage

What was done?

- Outcome of SM
  - 4 questions with the major concerns remaining
  - Company developed EU-specific Annex to global protocol to only include patients with tumor type 1

- Impact:

➔ Delay in opening the paediatric study (due to SM) with limited scope in EU (only 1 of 4 tumor types)

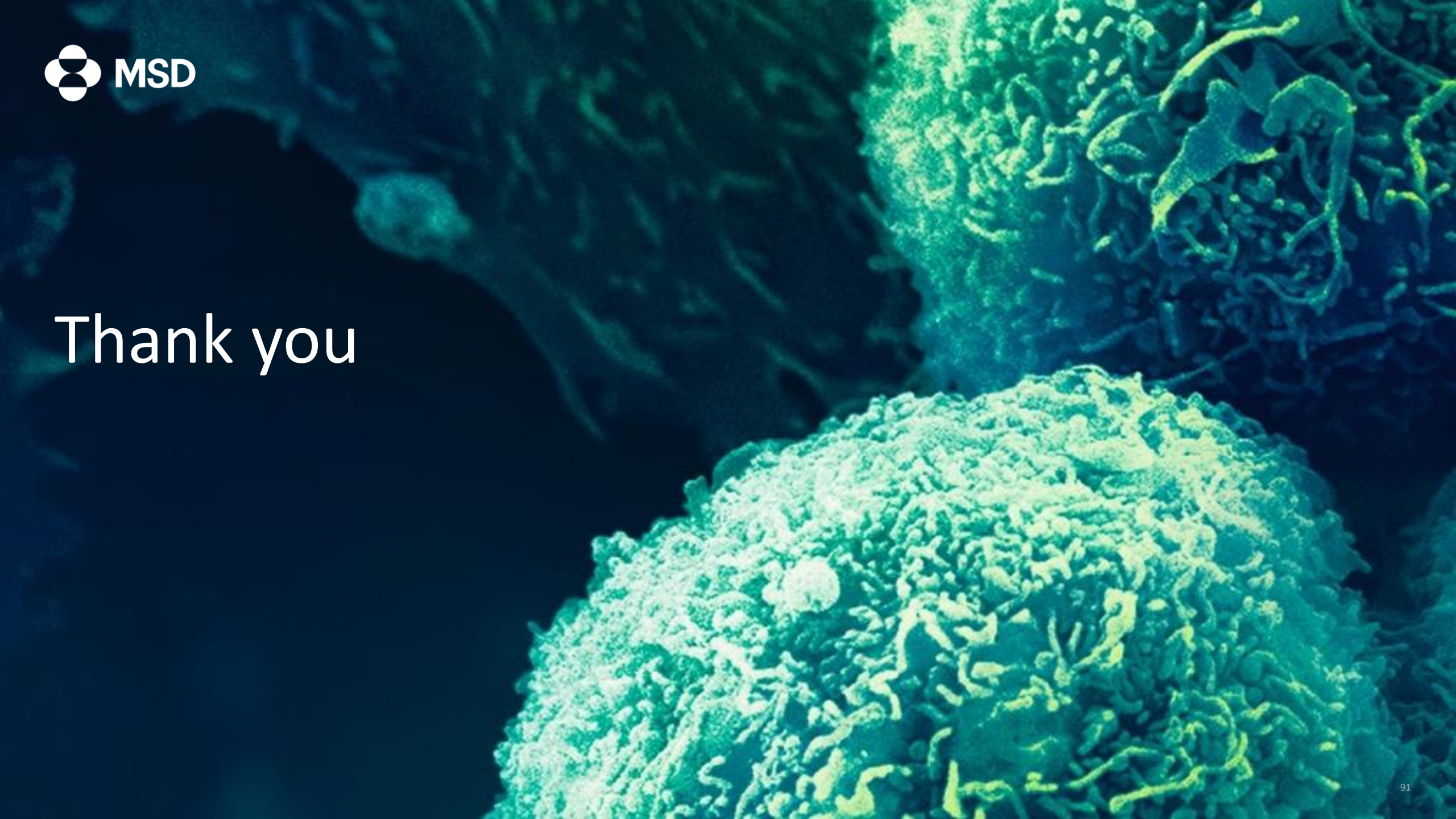
➔ Lost opportunity to enroll EU paediatric patients for 3 other tumor types

➔ Misalignment between PIP Key Binding Elements (KBEs) and EU trial participation

What would we recommend improving in the future?

rMS should rely on PDCO decision regarding the design of the paediatric study and timing for initiation	• A mechanism for the rMS to communicate with PDCO should be available in case of misalignment
Global mindset and risk-based approach to CTA review	• Focus on patient safety and data quality risks • Minimise number of questions and allow several rounds of RFI in case of remaining concerns
PDCO and CTA reviewers (NCAs and ECs) should align on minimum data requirements to open paediatric studies in EU	• Workshops / best-practice sharing sessions • Guidelines

CTA: clinical trial application, EC: ethics committee, NCA: National Competent Authority, PDCO: paediatric committee, rMS: reporting member state


MSD
Thank you

Academic perspective

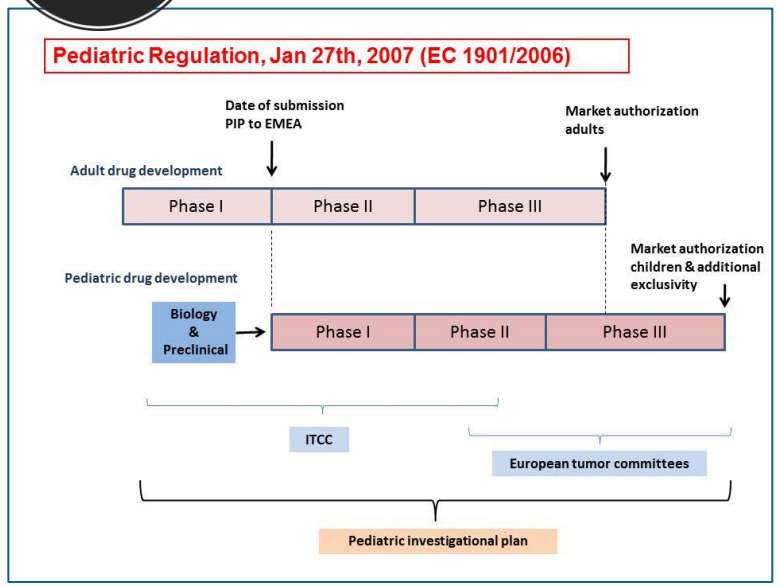
Prof. Michel Zwaan
Pediatric Oncologist

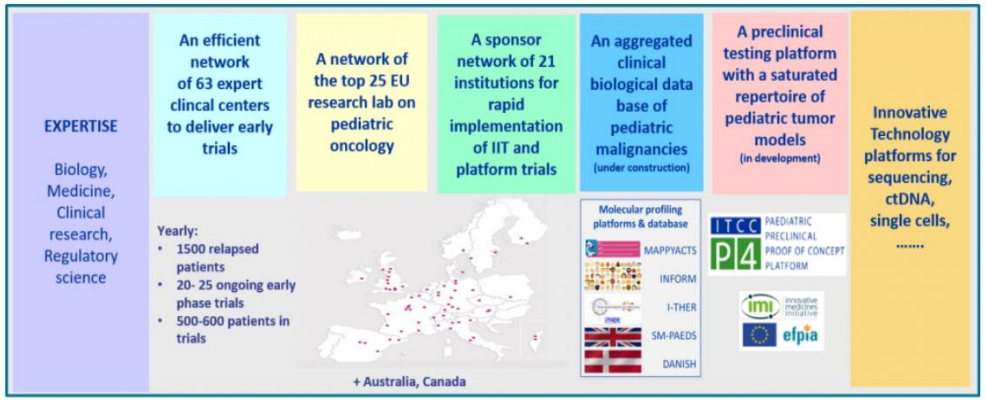
ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

ITCC (Innovative Therapies for Children with Cancer) 2003

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

Introduction of the pediatric regulation





>100 ITCC studies implemented

63 phase 1-2 clinical trial sites in 17 countries

- CRTCU, Birmingham, UK
- Gustave Roussy, Villejuif, France
- Centre Léon Bérard, Lyon, France
- Institut Curie, Paris, France
- CHU de Nantes, Nantes, France
- University of Munster, Munster, Germany
- Heidelberg University Hospital, Heidelberg, Germany
- Princess Maxima Center, Utrecht, NL

OVERARCHING GOAL : TO ACCELERATE THE INTRODUCTION OF NEW EFFECTIVE AND SAFE THERAPIES IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH CANCER

International coordinating sponsors network

www.itcc-consortium.org

	Active substance	Paediatric indication	Age range specified in the paediatric indication	Date of first paediatric indication	Orphan medicine status at time of paediatric approval	Paediatric Investigation Plan	Years since first marketing authorisation in adults	Marketing authorisation holder
New molecular entities								
Koselugo	Selumetinib	Plexiform neurofibroma	≥3 years	June 19, 2021	Yes	Yes	0	AstraZeneca
Retsevmo	Selpercatinib	RET-positive thyroid cancer	≥12 years	Feb 11, 2021	No	Yes	0	Eli Lilly Nederland
Rozlytrek	Entrectinib	NTRK-positive malignancies	≥12 years	July 31, 2020	No	Yes	0	Roche
MabThera	Rituximab	Mature B-cell non-Hodgkin lymphoma	≥6 months	March 15, 2020	No	Yes	21·5	Roche
Vitrakvi	Larotrectinib	NTRK-positive malignancies	Any	Sept 19, 2019	No	Yes	0	Bayer
Blincyto	Blinatumomab	CD19 acute lymphoblastic leukaemia	≥1 year	Aug 23, 2018	Yes	Yes	2·7	Amgen Europe
Kymriah	Tisagenlecleucel	CD19 acute lymphoblastic leukaemia	≤25 years	Aug 22, 2018	Yes	Yes	0	Novartis Europharm
Sprycel	Dasatinib	Chronic myeloid and Ph-positive acute lymphocytic leukaemias	Any	July 2, 2018	No	Yes	11·5	Bristol-Myers Squibb Pharma
Mylotarg	Gemtuzumab ozogamicin	CD33-positive acute myeloid leukaemia	≥15 years	April 19, 2018	Yes	Yes	0	Pfizer Europe
Yervoy	Ipilimumab	Melanoma	≥12 years	Jan 18, 2018	No	Yes	6·4	Bristol-Myers Squibb Pharma
Tasigna	Nilotinib	Chronic myeloid leukaemia	Any	Nov 15, 2017	Yes*	Yes	9·8	Novartis Europharm
Qarziba	Dinutuximab beta	Neuroblastoma	≥12 months	May 8, 2017	Yes	Yes	0	EUSA Pharma (Netherlands)
Caprelsa	Vandetanib	Thyroid cancer	≥5 years	Dec 20, 2016	No	Yes	4·8	Genzyme Europe
Keytruda	Pembrolizumab	Hodgkin lymphoma	≥3 years	Oct 13, 2016	No	Yes	1·2	Merck Sharp & Dohme
Votubia	Everolimus	Subependymal giant cell astrocytoma	Any	Sept 2, 2011	Yes	Yes	0	Novartis Europharm
Mepact	Mifamurtide	Osteosarcoma	≥2 years	March 6, 2009	Yes*	No	0	Takeda France
Atriance	Nelarabine	T-cell acute lymphoblastic leukaemia and lymphoma	Any	Aug 22, 2007	Yes*	No	0	Novartis Europharm
Evoltra	Clofarabine	Acute lymphoblastic leukaemia	Any	May 29, 2006	Yes*	No	0	Genzyme Europe
Lysodren	Mitotane	Adrenal cortical carcinoma	Any	April 28, 2004	Yes*	No	0	HRA Pharma Rare Diseases
Glivec	Imatinib	Chronic myeloid and Ph-positive acute lymphocytic leukaemias	Any	Dec 19, 2002	Yes*	No	1·1	Novartis Europharm
Temodal	Temozolomide	High-grade glioma	≥3 years	Jan 26, 1999	No	No	0	Merck Sharp & Dohme
Medicines already used in paediatric haemato-oncology								
Phelinun	Melphalan	Haematopoietic stem cell transplantation	Any	Nov 16, 2020	No	No	0	Adienne
Trecondi	Treosulfan	Haematopoietic stem cell transplantation	>1 month	June 20, 2019	Yes	Yes	0	Medac
Jylamvo	Methotrexate	Acute lymphocytic leukaemia	≥3 years	March 29, 2017	No	No	0	Therakind (Europe)
Oncaspar	Pegaspargase	Acute lymphocytic leukaemia	Any	Jan 14, 2016	No	No	0	Les Laboratoires Servier
Spectrila	Asparaginase	Acute lymphocytic leukaemia	Any	Jan 14, 2016	No	Yes	0	Medac
Xaluprine	6-mercaptopurine monohydrate	Acute lymphocytic leukaemia	Any	March 9, 2012	Yes*	Yes	0	Nova Laboratories Ireland
Tepadina	Thiotepa	Haematopoietic stem cell transplantation	Any	March 15, 2010	Yes*	No	0	Adienne
Busilvex	Busulfan	Haematopoietic stem cell transplantation	Any	Oct 31, 2005	Yes*	No	2·3	Pierre Fabre Médicament

NTRK=neutrotrophic tyrosine receptor kinase. RET=rearranged during transfection. *Lost orphan medicine status as of August, 2022.

Table: Anti-cancer medicines with a first paediatric indication in the EU since 1995

- Half of New Molecular Entities were authorised for the treatment of malignancies responsible for only 5·4% of all European childhood cancer deaths, including three medicines for melanoma and thyroid cancer—adult cancers occurring very rarely in children.
- Pediatric development of these drugs was driven by their adult market and did not address major unmet medical needs of children and adolescents with cancer

Impact of the EU Paediatric Medicine Regulation on new anti-cancer medicines for the treatment of children and adolescents

Gilles Vassal, Teresa de Rojas, Andrew D J Pearson

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Supported by

Pediatric Strategy Forums

Reference : Pearson et al. Eur J Cancer, 62:124, 2016

- **Objective** - provide a unique opportunity for interaction between *all stakeholders* (regulators, pharmaceutical companies, clinical and researcher academics and patient representatives) on topics requiring open discussion in drug development in children and adolescents with malignancy

- **Paediatric Strategy Forum** - scientific meeting to **share** information and advance learning which will inform a paediatric drug development strategy and subsequent decisions

- **Paediatric Strategy Forum** - introduce innovative treatments into the standard care of very rare children with cancer

Pediatric Strategy Forum meetings

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

• ALK inhibitors	30/31 Jan 2017
• Mature B-cell malignancies	13/14 Nov 2017 → GloBNHL master protocol
• Checkpoint inhibitors	5/6 Sept 2018
• AML	11/12 April 2019 (Rotterdam, NL) → Pedal ITCC101 master protocol & Scientific advice
• Epigenetics	23/24 Jan 2020 (1st time in NA)
• CAR-T cells	25/25/27 May 2021 (virtual) → Locatelli, anti-GD2 Prime designation
• Kinase inh in bone sarcoma	30 nov -1 dec 2021
• MAPK inh	28-29 March, 2022
• DNA damage pathways	27-28 Oct 2022
• PI3K, MTOR, AKT	3-4 April, 2023
• CDK inhibitors	26-27 Oct, 2023
• DMG	8-9 May 2024 (Toronto)
• Anti-GD2	24-25 Oct 2024 (Amsterdam)
• Antibody drug conjugates	June 2025 (Denver)

All published in Eur J Cancer

special articles

The Critical Role of Academic Clinical Trials in Pediatric Cancer Drug Approvals: Design, Conduct, and Fit for Purpose Data for Positive Regulatory Decisions

Bram De Wilde, MD[1,2]; Elly Barry, MD[3]; Elizabeth Fox, MD[4]; Dominik Karres, MD[5]; Mark Kieran, MD[3]; John Manlay, BA[6]; Donna Ludwinski, BSChE[7]; Gregory Reaman, MD[8]; and Pamela Kearns, MBChB, PhD[9]

TABLE 1. Knowledge and Expertise Gaps

Sponsor	Academic	Industry
Trials experience	Any, often phase III interventional or noninterventional, registry type trials. Limited, if any experience with intent to file trials	Phase I, II, III, and IV all conducted with an intent to file
Data management	Focus on data quality and integrity with data cleaning focused on primary analysis and publication. Monitoring strategies normally on the basis of the low-risk nature of the trials with limited source data verification	Clear and concise rigorous DMPs with full monitoring fixed data cleaning and data locking strategies
Documentation	Collects what is required to ensure data quality and quality of trial conduct	Documents anything and everything that ensures data quality, researcher qualification, and (financial) independence assuring objectively verifiable trial conduct
AE reporting	Often pragmatic with focus on unexpected or severe AEs	Complete, to meet filing requirement
Communication	Public presentation and publication	Filing application, with minor focus on public distribution of results

Abbreviations: AE, adverse event; DMP, data management plan.

ITCC-054 bosutinib study: EMA & FDA approval for a pediatric indication and a new formulation suitable for dosing children

Bosutinib phase 1-2 study planned as a registration study from the start (FPFV Nov 2016).

FDA and EMA approved bosutinib for CML in children based on data generated by the ITCC-054 study in collaboration with COG

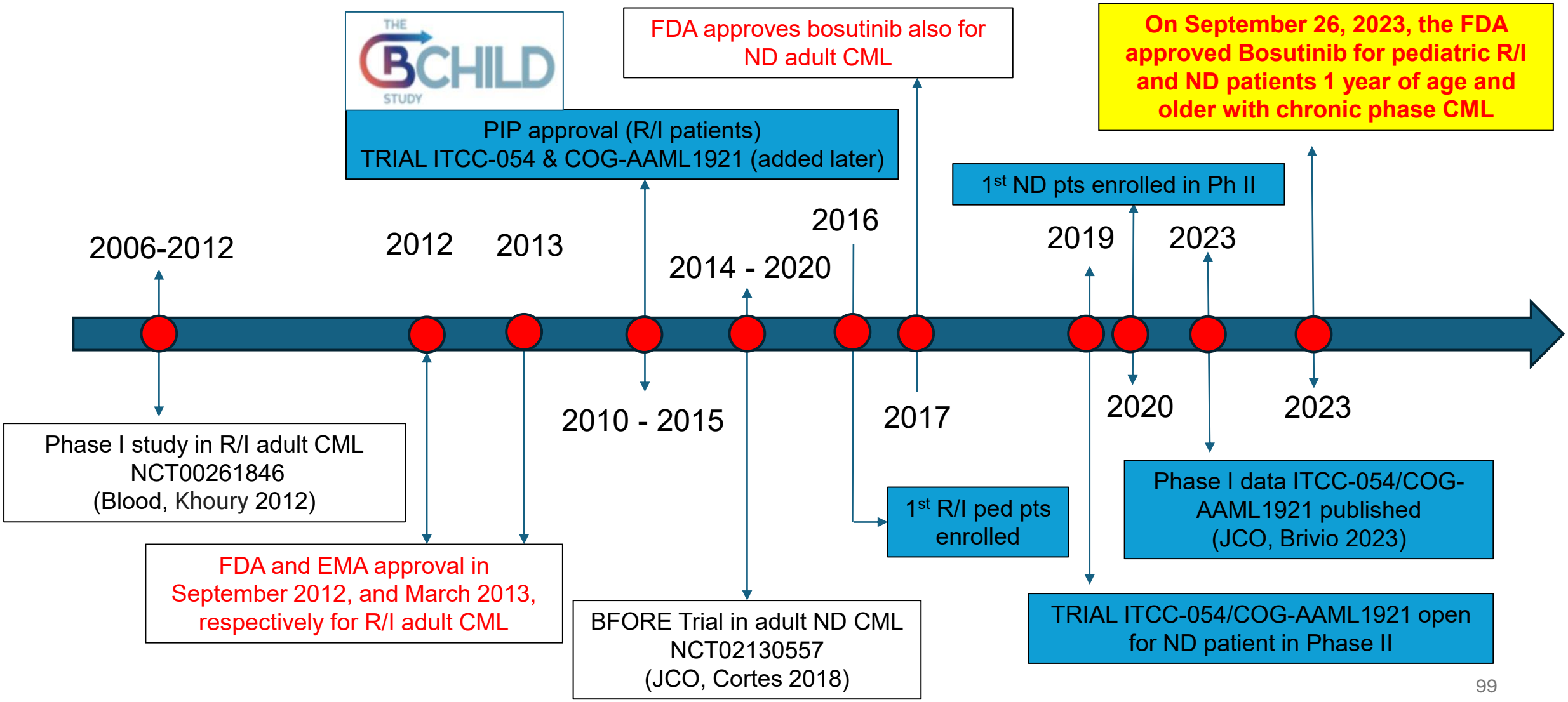
Study in the context of a Pediatric Investigational Plan (PIP) and Pediatric Written Request (PWR)

Started in 2016 – data transfer to MA holder and submission to FDA in 2023, submission to EMA in Q1 2024 as a PIP amendment needed to be approved

On 27 March 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending a change to the terms of the marketing authorisation for the medicinal product Bosulif.

The CHMP adopted a change to the existing indications to extend the use of Bosulif to children aged 6 years and older with certain types of chronic myelogenous leukaemia, along with a new pharmaceutical form, hard capsules, associated with two new strengths, 50 mg and 100 mg.

Bosutinib (pediatric) development milestones



- ITCC-059 Inotuzumab ozogamicin phase I/II study was specifically set up with intent to file (FPFV Jan 2017)
- Data ITCC studies transferred to regulatory authorities – this was done in 2023
- FDA approval March 6, 2024
- EMA accepted safety data for the label, but PIP2 study ongoing. After discussion with Pfizer data submitted for label extension as well (under review)
- PDMA approval obtained in March 2024

(EU CT number: 2023-504694-20-00)/
(EMEA-001429-PIP01-13-M07)

Drugs that are ***game changers*** need to be developed including a front-line study

This means we need to anticipate that the final PIP study should not be in 1st relapse but in newly diagnosed patients

....although not always easy to beforehand envision a drug will be a game changer

Mindset change needed in advice to companies and design, and re-evaluate (concept of 'living PIP')

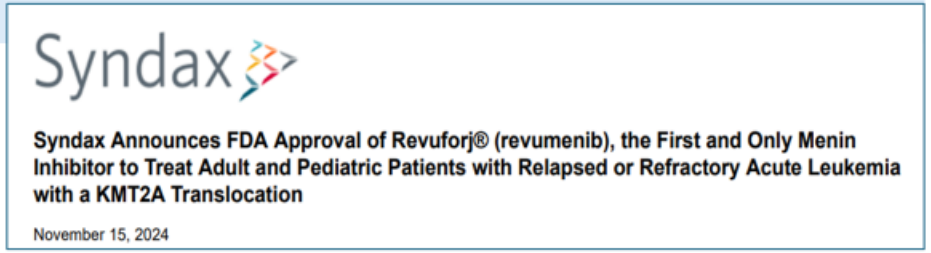
Accelerate meeting June 2022: prioritisation meeting 6 menin inhibitors

- Compounds
  - Revumenib [Syndax Pharmaceuticals],
  - Ziftomenib [Kura Oncology],
  - Bleximinib [Janssen],
  - BMF-219 [Biomea Fusion],
  - DS-1594 [Daiichi Sankyo],
  - DSP-5336 [Sumitomo Pharma Oncology].

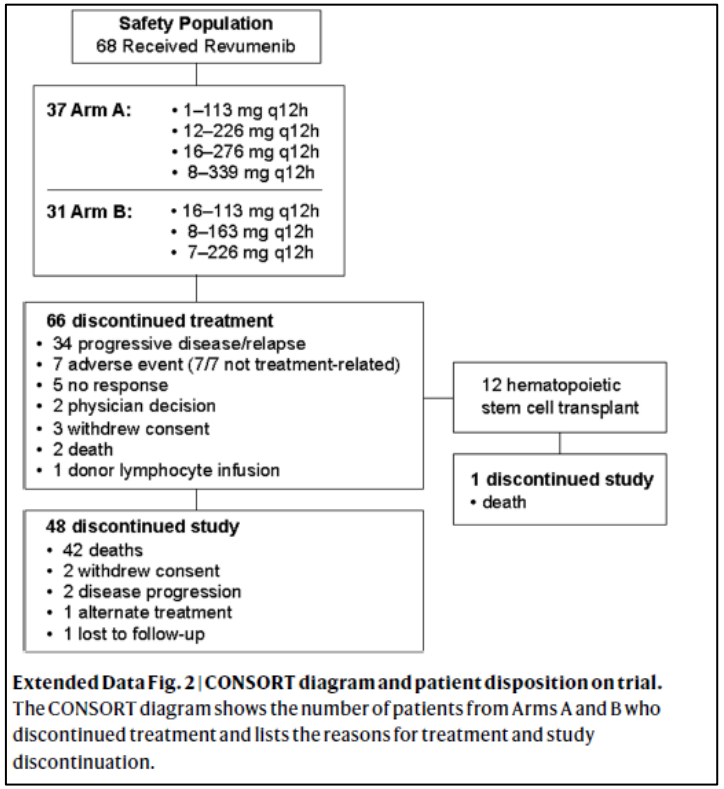
Revumenib will be added in the CHIP-AML study for newly diagnosed AML sponsored by Maxima

- Conclusion: As there are multiple products of the same class, a sequential approach is proposed. Menin inhibitors should move rapidly into front-line studies to be evaluated, especially infant leukaemia, as it is in this setting where there is the greatest unmet clinical need.

First approval Nov 24: Revuforj (revumenib) is an oral, first-in-class menin inhibitor that is **FDA approved** for the treatment of relapsed or refractory (R/R) acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients one year and older.



Augment-101 trial phase 1 study results Revumenib



Extended Data Fig. 2 | CONSORT diagram and patient disposition on trial. The CONSORT diagram shows the number of patients from Arms A and B who discontinued treatment and lists the reasons for treatment and study discontinuation.

Revumenib is a substrate of CYP3A4

Arm A without CYP3A4 inhibitor
Arm B with strong CYP3A4 inhibitors

Issa et al, Nature March 30, 2023

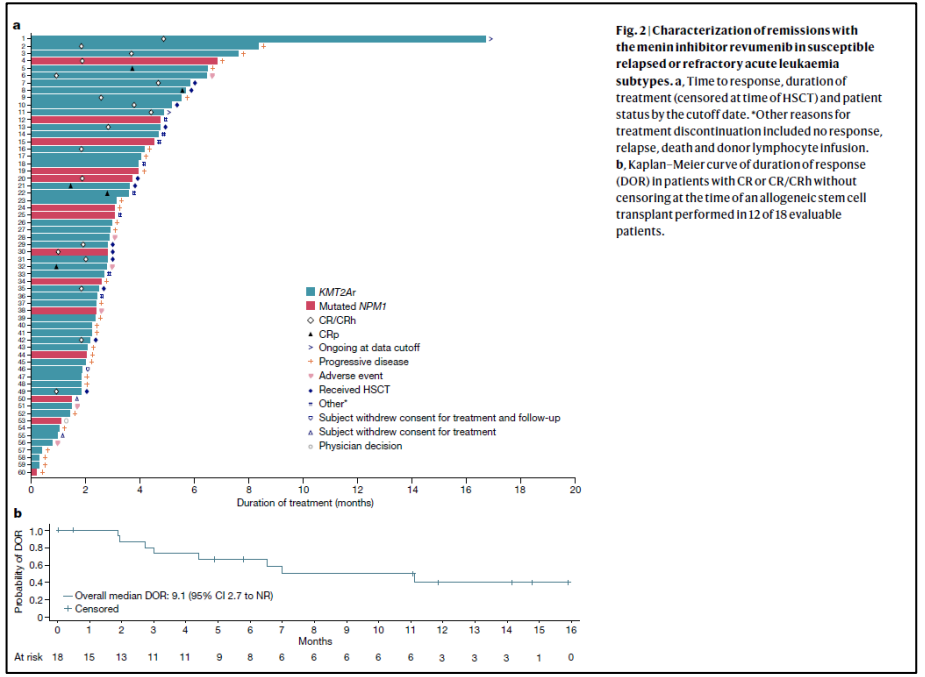


Fig. 2 | Characterization of remissions with the menin inhibitor revumenib in susceptible relapsed or refractory acute leukaemia subtypes. a, Time to response, duration of treatment (censored at time of HSCT) and patient status by the cutoff date. *Other reasons for treatment discontinuation included no response, relapse, death and donor lymphocyte infusion. **b**, Kaplan–Meier curve of duration of response (DOR) in patients with CR or CR/CRh without censoring at the time of an allogeneic stem cell transplant performed in 12 of 18 evaluable patients.

Table 1 | Any-grade treatment-related and TEAEs, regardless of causality

Event	Overall population (*n*=68)
Any-grade TRAE (5% or over)	53 (77.9%)
ECG QT prolonged	36 (52.9%)
Nausea	18 (26.5%)
Differentiation syndrome	11 (16.2%)
Vomiting	11 (16.2%)
Diarrhoea	7 (10.3%)
Decreased appetite	5 (7.4%)
Dysgeusia	5 (7.4%)
Any-grade TEAE (20% or over)	67 (98.5%)
ECG QT prolonged	38 (55.9%)
Nausea	34 (50.0%)
Vomiting	27 (39.7%)
Febrile neutropenia	21 (30.9%)
Diarrhoea	20 (29.4%)
Fatigue	18 (26.5%)
ALT increased	17 (25.0%)
Headache	16 (23.5%)
Hyperphosphataemia	16 (23.5%)
Hypokalaemia	15 (22.1%)
Hyponatraemia	15 (22.1%)
Thrombocytopenia	15 (22.1%)
Epistaxis	14 (20.6%)
Peripheral oedema	14 (20.6%)

All AEs shown as *n* (%).
ALT, alanine aminotransferase.

Sixty patients were adults (at least 18 years old) and eight were children (under 18 years of age).

Table 2 | Responses to treatment

Response	Efficacy population (*n*=60)	*KMT2Ar* (*n*=46)	Mutated *NPM1* (*n*=14)
Overall response*	32 (53%)	27 (59%)	5 (36%)
Median time to first morphologic response (range), months	0.95 (0.9–3.7)	0.95 (0.9–3.7)	0.99 (1.0–1.9)
Best response*			
CR/CRh	18 (30%)	15 (33%)	3 (21%)
CR	12 (20%)	9 (20%)	3 (21%)
CRh	6 (10%)	6 (13%)	0
Median time to CR or CRh (range), months	1.9 (0.9–4.9)	2.0 (0.9–4.9)	1.9 (1.0–1.9)
CRi	0	0	0
CRp	5 (8%)	5 (11%)	0
MLFS	9 (15%)	7 (15%)	2 (14%)
Partial remission	0	0	0
No response	19 (32%)	12 (26%)	7 (50)
Progressive disease	7 (12%)	6 (13%)	1 (7%)
Missing	2 (3%)	1 (2%)	1 (7%)
MRD' neg. rate within CR/CRh	14/18 (78%)	11/15 (73%)	3/3 (100%)
Median time to MRD' neg. among patients with CR/CRh (range), months	1.9 (0.9–4.9)	1.9 (0.9–4.9)	1.9 (1.0–2.8)

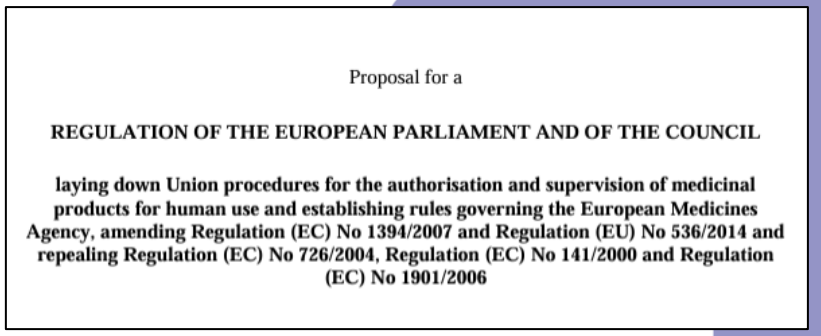
*Responses were assessed by the investigators; responses and MRD-negative rates are shown as *n* (%).
'MRD, minimal or measurable residual disease assessed at participating sites by either multicolour flow cytometry or PCR; MRD status percentage based on patients with non-missing MRD status out of all responders.
MLFS, morphologic leukaemia-free state.

To accelerate in the targeted therapy area

- Drop the age on adult phase 1 (stepwise)
- In case similar target in adult and children
- Generate early PK-data
- Only when Recommended Phase 2 Dose in adults is known ?

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

New EU Pharmaceutical Strategy



Proposal for a

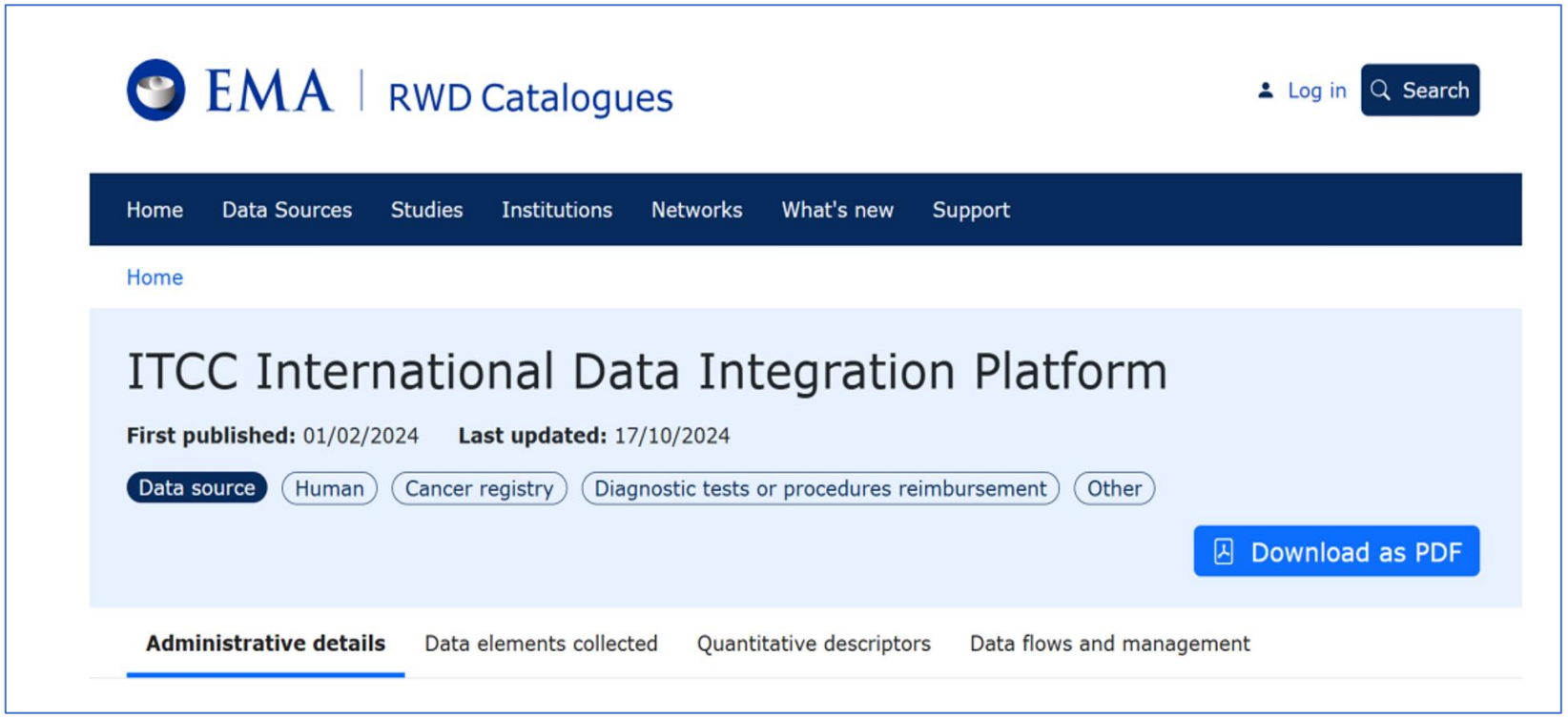
REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

- Science-driven, mechanism-of-action-based approach both in Europe and US
- Addressing unmet needs - a priority
- Multi-stakeholder meetings - critical
- Unmet needs Step-wise PIP
  - Pre-clinical evaluation consensus
  - EMA wants academic opinion on go / no go decisions
  - Academic capacity building to support EMA
- EMA encourage academic development (collaborative intent to file studies)
- Very early involvement of regulators and patient advocates is crucial when devising a clinical trial
- Clinical trials should benefit science & children **and** fulfil regulatory requirements
- Filing options for non-MAH ?

Pediatric precision oncology registry

(real world data collection to support intent to file trials)



For example in Máxima:

- Wilms tumor registry (>30 years)
- NOPHO relapsed AML

Other examples:

- NBL SIOPEN Bioportal
- IntReALL (1st relapse ALL)

New challenges

- From “repurposing drugs developed for adults”
- To “developing drugs against pediatric-specific targets”
- ATMP development
- But also molecular glues (small molecules targeting protein degradation) and PROTACS (degrading proteins via the proteasome)
- Examples
  - ARA-0001 anti-CD19 CART study (Prime designation) Barcelona
  - Anti-GD2 CART study Neuroblastoma (Prime designation) Rome
- Challenges: academia acting as MA holder in the intent-to-file process and sustainability of production in the future

Conclusions

- Intensive collaboration between the stakeholders is needed to drive innovation
- Academia can pay a major role not only in prioritiziation but also in study execution
- We need Living PIPs that are regularly re-assessed if they are fit for purpose (treatment may rapidly change), especially if a ‘game changer’ is identified
- New developments need reconsideration also of the assessment procedures
  - Pediatric specific targets and drugs
  - Dropping the age early on adult clinical trials
- Is there a need for other pediatric subspecialties to follow the ‘ped oncology’ model and not re-invent the wheel
- Better collection of SOC data is needed as real-world control data

Questions?

ACT EU Paediatrics Trials in EU/EEA

Patient perspective

14th – 15th July 2025, EMA, Amsterdam

Workshop on the Assessment of Clinical Trials Applications involving Paediatric Patients

Tomasz Grybek, Board Member of EURORDIS-Rare Diseases Europe

Disclaimer

The views expressed in this presentation **are the personal views of the author** and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency and Paediatric Committee nor the EURORDIS – Rare Diseases Europe.

Our mission

EURORDIS works across borders and diseases to improve the lives of all people living with rare diseases.

OVER

1000

MEMBER PATIENT ORGANISATIONS

74 COUNTRIES (27 EU COUNTRIES)

57 NATIONAL ALLIANCES OF RARE DISEASE PATIENT ORGANISATIONS

84 EUROPEAN & INTERNATIONAL FEDERATIONS OF SPECIFIC RARE DISEASES

FOUNDED IN

1997

5.5 MILLION EURO BUDGET

OUTREACH TO OVER

2500

PATIENT GROUPS

OVER

65

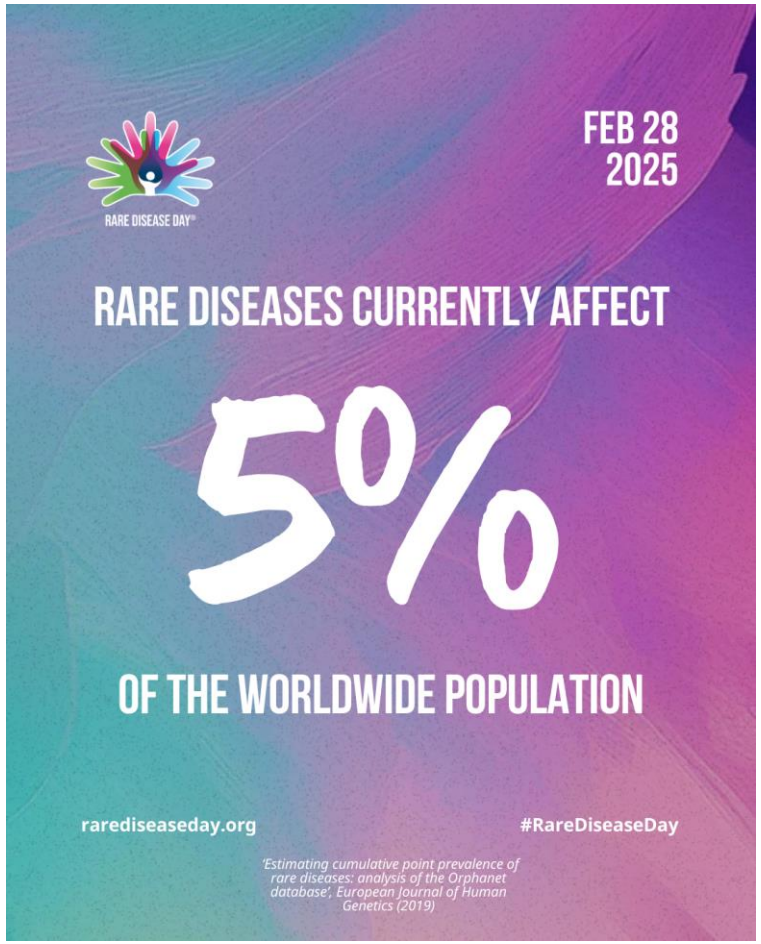
VOLUNTEER PATIENT ADVOCATES

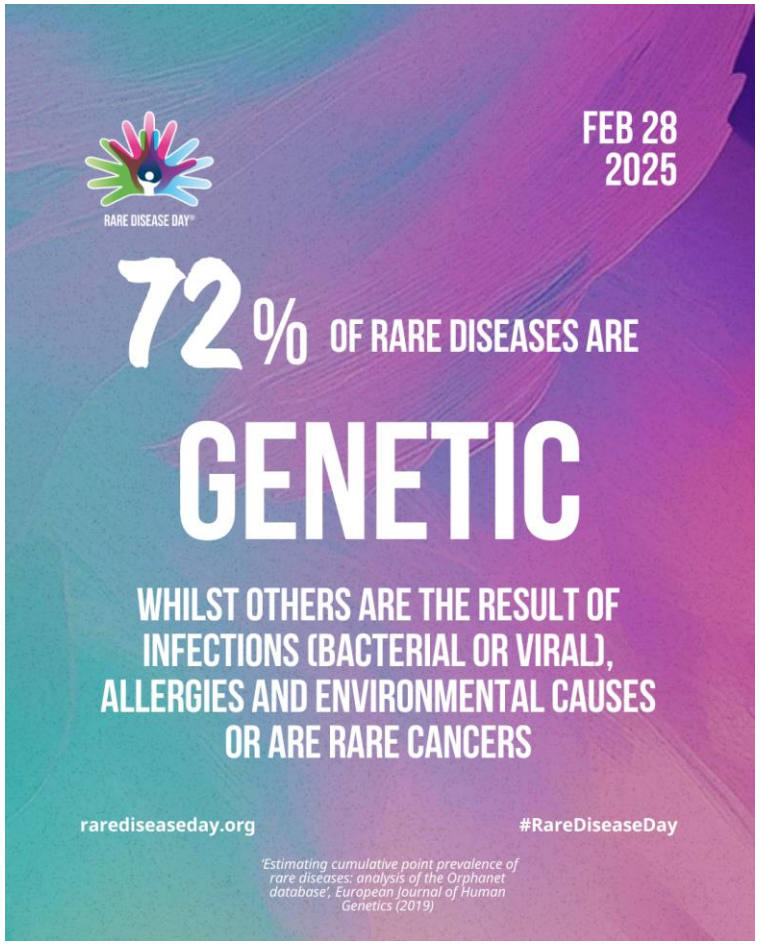
40

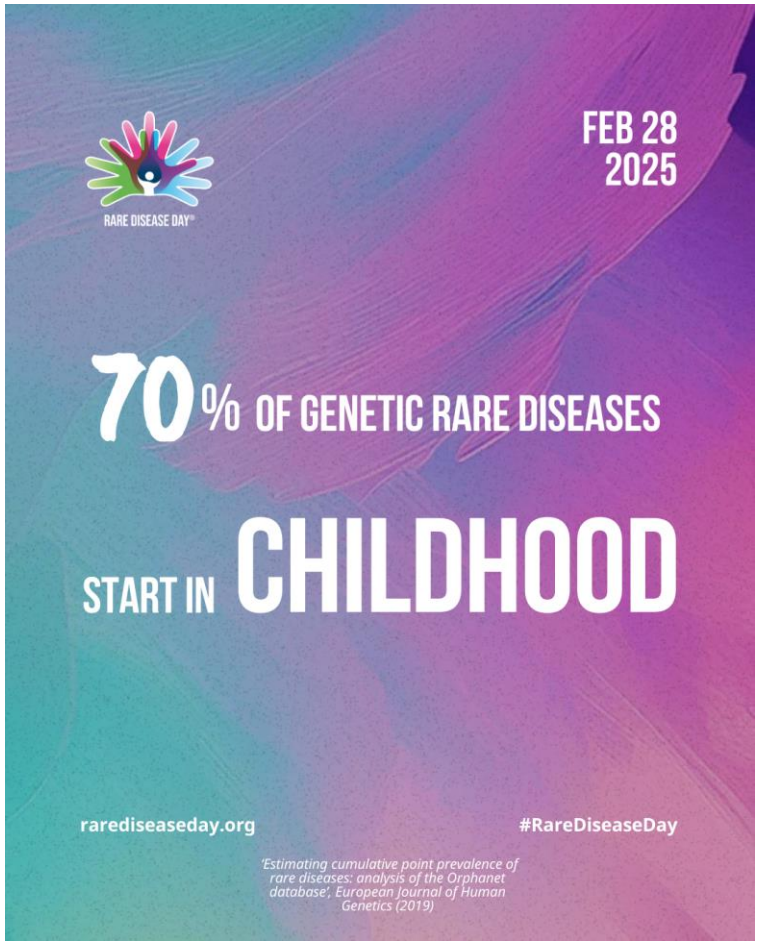
TEAM MEMBERS, WITH OFFICES IN PARIS, BRUSSELS, BARCELONA

EURORDIS.ORG

Rare disease facts







Source: rarediseaseday.org

An insight into the participation of rare disease patients in research

30 million people are living with a rare disease in Europe and 300 million worldwide

No cure for the vast majority of diseases and few treatments available

3213 rare disease patients and their families responded to the survey, conducted in 23 languages across 42 countries worldwide

Key findings of a Rare Barometer Voices survey on the participation of rare disease patients in research:

Top 3 obstacles to rare disease research

1. Lack of public funding
2. Lack of private funding
3. Small patient population

Top 3 priorities for patients

1. Develop therapies
2. Improve diagnosis
3. Identify mechanisms & causes of rare diseases

What type of research do patients participate in?

1/3 of rare disease patients have participated in medical research, among them:

- **59%** to develop treatments & therapies
- **52%** in research on quality of life
- **16%** to develop genetic therapies

What matters to patients?

Rare Barometer Voices is a EURORDIS-Rare Diseases Europe online survey initiative. It brings together over 8,000 patients, carers and family members to make the voice of the rare disease community stronger.

Thank you to all Rare Barometer Voices participants and partners! To read the full report, register to participate in future surveys or for more information, visit: eurordis.org/voices.

Reported barriers

Barrier
Insufficient benefits and/or concern over worrisome risks or management of risks
Initial contact by the study team was not effective
Study logistics were too complicated or difficult
The child did not want to participate
The child's own doctor did not recommend participation

Source: Greenberg, R. G., et al. (2017). Parents' perceived obstacles to pediatric clinical trial participation: Findings from the clinical trials transformation initiative. Contemporary clinical trials communications, 9, 33–39. https://doi.org/10.1016/j.conctc.2017.11.005

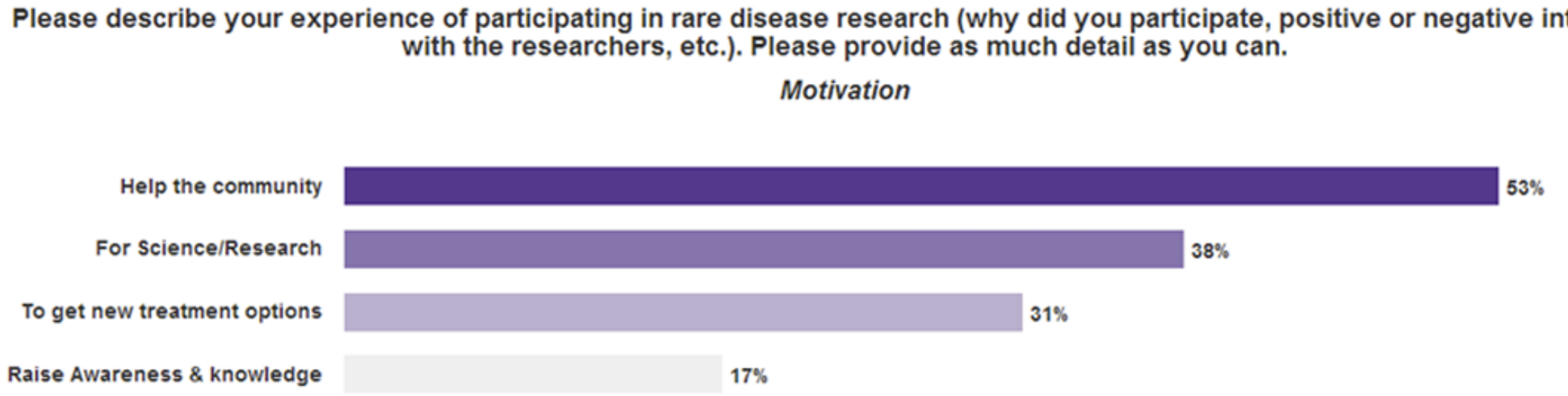
Reported barriers

Barrier	
Insufficient benefits and/or concern over worrisome risks or management of risks	Reassurance that there is a “safety net” should the child experience an adverse effect
	Reassurance that there is access to a responsible person 24/7
	Reassurance that signing a consent form does not mean signing away legal rights if the child is harmed
	Familiarity of study team with child's medical condition
The child did not want to participate	Include the child in the discussion of the trial and explain to them at their level
	Have a “kid friendly” place to explain and conduct the study (brightly colored, video games, toys, kid-sized furniture)

Source: Greenberg, R. G., et al. (2017). Parents' perceived obstacles to pediatric clinical trial participation: Findings from the clinical trials transformation initiative. Contemporary clinical trials communications, 9, 33–39. https://doi.org/10.1016/j.conctc.2017.11.005

Motivation

Graph. 6



The reasons why patients participate are very often altruistic. Most of the time, **patients acknowledge that their participation will result in new treatment options only for future patients affected by the same disease** and they want to contribute to this change for the community (53%) and help science to progress (38%). Ranking altruistic reasons

Testimonies

> Initially I participated because there were no treatment options for me and I nearly died several times. I started as a child and my parents saw the clinical trials as a way to keep me alive. It worked, I'm still alive! » **United States**

> I will always participate no matter what it costs me. I believe that not enough is being done in South Africa regarding (disease) research and treatment! » **South Africa**

> A significant amount of tissue was taken for biopsy and research purposes. The researcher was very thorough on explaining things to me. He was kind and respectful. It was a very positive experience for me. » **United States**

Testimonies

> It was very positive. Besides obtaining important information on the disease I am affected with, I have learnt to listen to my body, discovered beneficial activities to carry out to maintain my muscles and the experience in general appeared to be psychological and moral support. » **France**

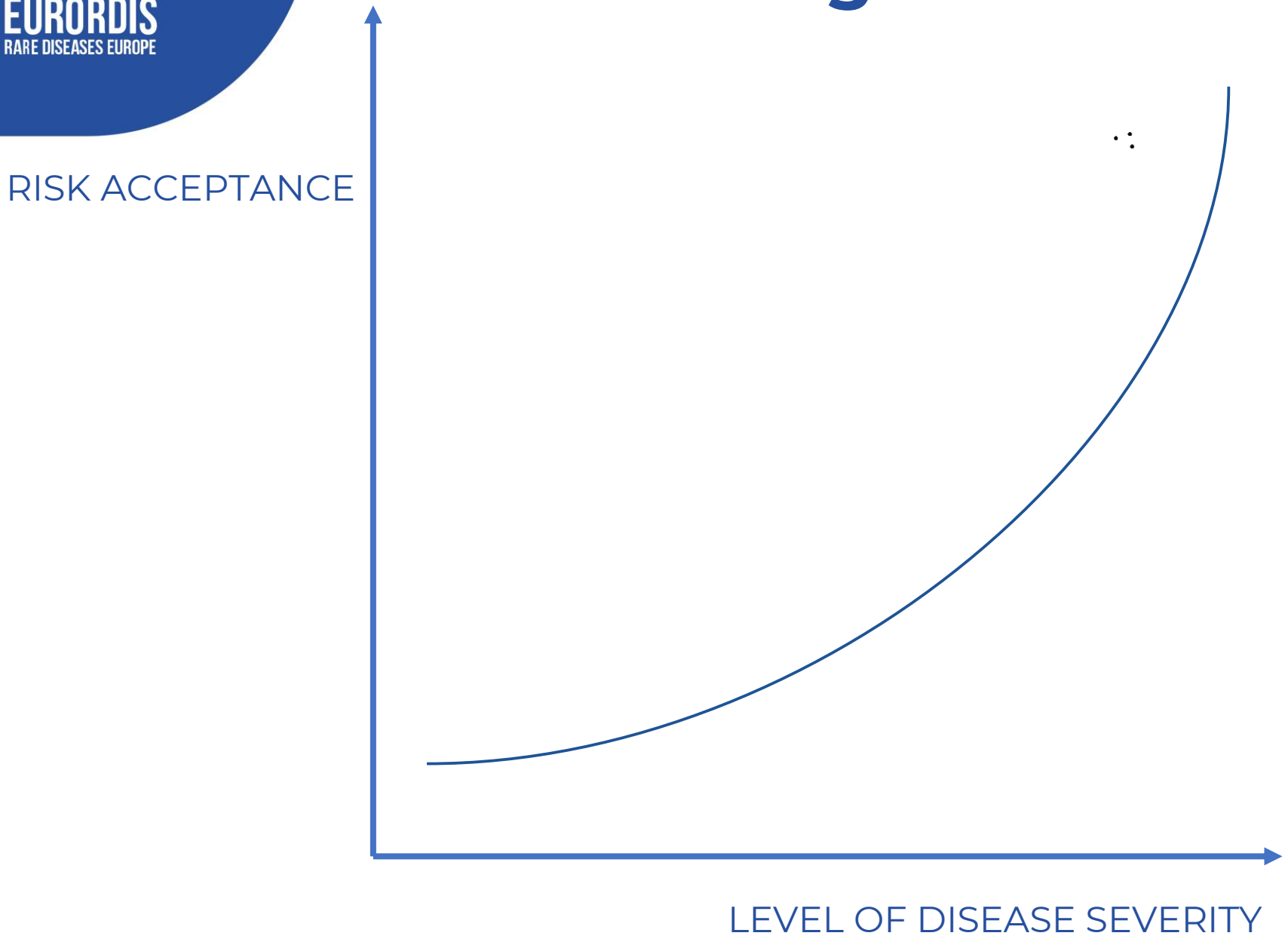
> It was interesting to see the results after the conducted surveys » **Croatia**

> In my country, it enabled frequent check-ups and follow-up about the disease. » **Macedonia**

Testimonies

> “We gave permission to use our information and felt like we were being used by the researchers for THEIR benefit, there was absolutely no benefit for us as patients. All the benefit was fame and recognition for the research team. They used us and then treated us like disposable lab rats when they were done with us. » **Canada**

Risk management?

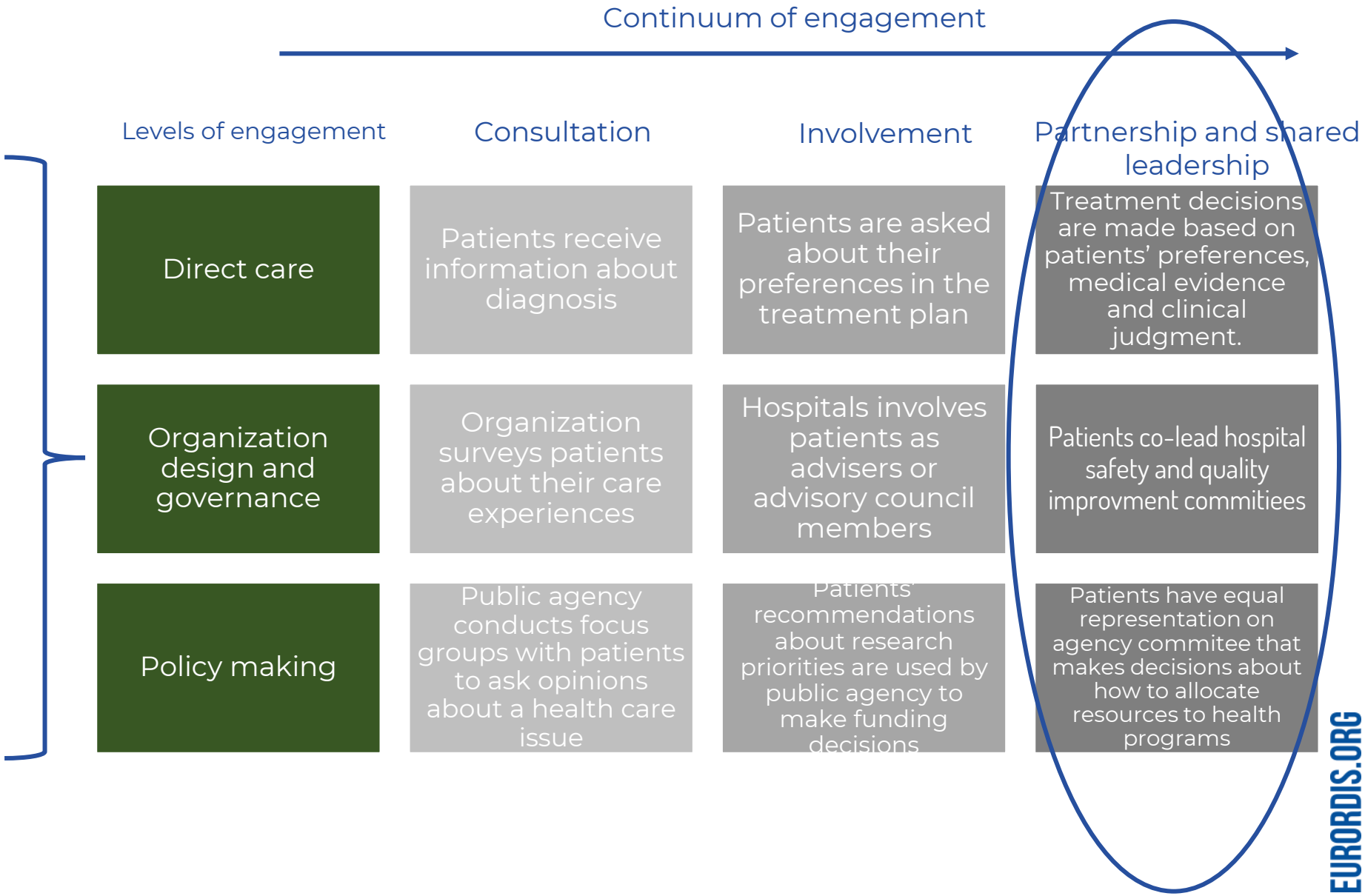


Factors influencing engagement:

Patient (beliefs about patient role, health literacy, education)

Organization (policies and practicies, culture)

Society (social norms, regulations, policy)



K. L. Carman *et. al.,* "Patient And Family Engagement: A Framework For Understanding The Elements And Developing Interventions And Policies, Health Affairs 32, no.2, 2013

Conclusions

- **Lived experience is a valuable form of knowledge** and a critical asset in decision-making processes.
- **Risk perception varies across individuals and communities** and must be acknowledged in regulatory and policy frameworks.
- **Meaningful patient involvement is essential** to ensure relevance, trust, and impact across all stages of healthcare and research.

Borys, metachromatic leukodystrophy

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RARE DISEASES EUROPE

Thank you for your attention

Questions?

Panel discussion

Moderated by Anette Solli Karlsen (*PDCO member, NOMA*)

14 July 2025

Thank you