EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European perspective on complementary US and EU regulations in support of global development

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Disclaimer

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

Overview

Background, impact and general considerations

Reflections on mode of action developments

Conclusions

EU Paediatric Regulation - Paediatric Investigation Plan (PIP)

Research and development programme framed around concept of **condition* -** proposal to **take mode/ mechanism of action (MoA) into account#**

Quality
Pre-clinical (safety and proof of concept)
Clinical

} **Marketing Authorisation**

Tools like **deferrals, modifications** and **waivers** in place, intended to ensuring:

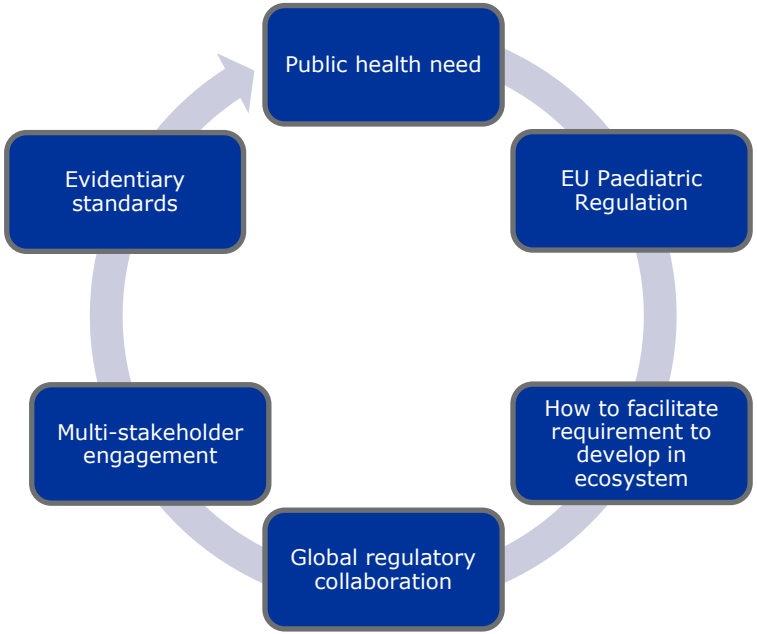
- timely evidence generation

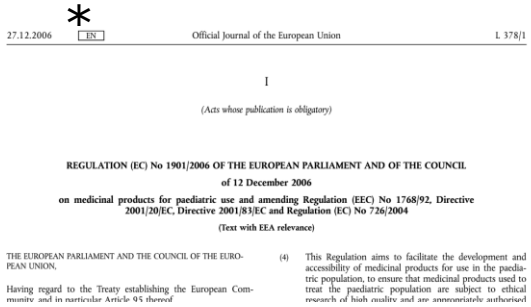
while allowing:

- (re) focus of development efforts based on emerging evidence and potential changing needs over time

* https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32006R1902&qid=1621344480633
# https://eur-lex.europa.eu/resource.html?uri=cellar:e3f40e76-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF

Background





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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)

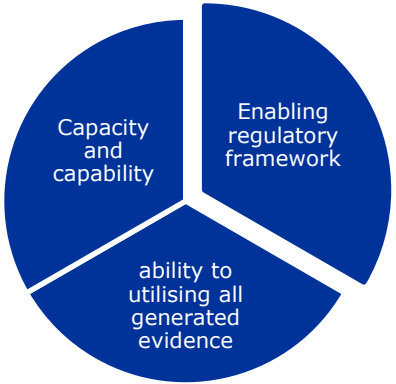
THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Research and Development (R&D)

To pivotal evidence



* https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32006R1902&qid=1621344480633

EU Paediatric Regulation – Complementation and impact

Paediatric oncology drug development takes place in the **rare disease space**, and is a **global enterprise**

- Strong regulatory collaboration [1, 2, 3]

Since **implementation** of US legislation

- **Increase in 'voluntary' PIPs**

1. 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-plans-paediatric-investigation-plans-pips_en.pdf
2. J Clin Oncol. 2020 Dec 20;38(36):4227-4230
3. Ther Innov Regul Sci. 2021 Nov;55(6):1109-1110

How to facilitate requirement to develop

- **Growing pipelines of new products**: based on the mode of action, how to identify and support completion of development efforts in children for products likely to address existing unmet medical needs

  - a regulatory framework that fosters a R&D environment allowing for evolution of scientific knowledge [1], also related to relevance of a products mode of action

  - need to move from 'product to population' focused discussions
    - based on the products **mode of action,**
    - what is the **target population**
    - for which the product is **able to offer significant therapeutic benefits**
    - in **context of existing treatments and the wider R&D landscape**
    - such **that (clinical) development is feasible and generates meaningful evidence timely**

1. Eur J Cancer. 2022 Dec:177:25-29

Multistakeholder engagement

- Engagement with patients, parents, academic researchers, clinicians, investigators, industry via
  - e.g. Paediatric Strategy Forums and other initiatives
- Utilising data from academic sponsored studies
- Early regulatory interaction remains key

Reflections on mode of action developments

Paediatric investigation plans for medicinal products for children, based on a medicinal product's mechanism of action

Currently, the obligation to conduct a paediatric investigation plan (PIP) for studies in children is waived in certain situations, for example when an adult product is intended for a disease not existing in children. However, in certain cases the molecule in question, due to its molecular mechanism of action, may be efficacious against a disease in children that is different from the one for which it was initially designed for use in adults.

The proposal envisages that in such cases, the product will have to be studied for use in children too. This requirement, apart from increasing the number of medicinal products adequately studied for use in children, is also expected to promote innovation and research.

Recital out of the explanatory memorandum in the current EC legislative proposal:
https://eur-lex.europa.eu/resource.html?uri=cellar:e3f40e76-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF

Impact

Mode of action-based developments increasingly proposed already

→ Translating into increasing 'voluntary' PIP proposals – and requests to EMAs Non-clinical Working Party (NcWP) to discuss needs for additional proof of concept data

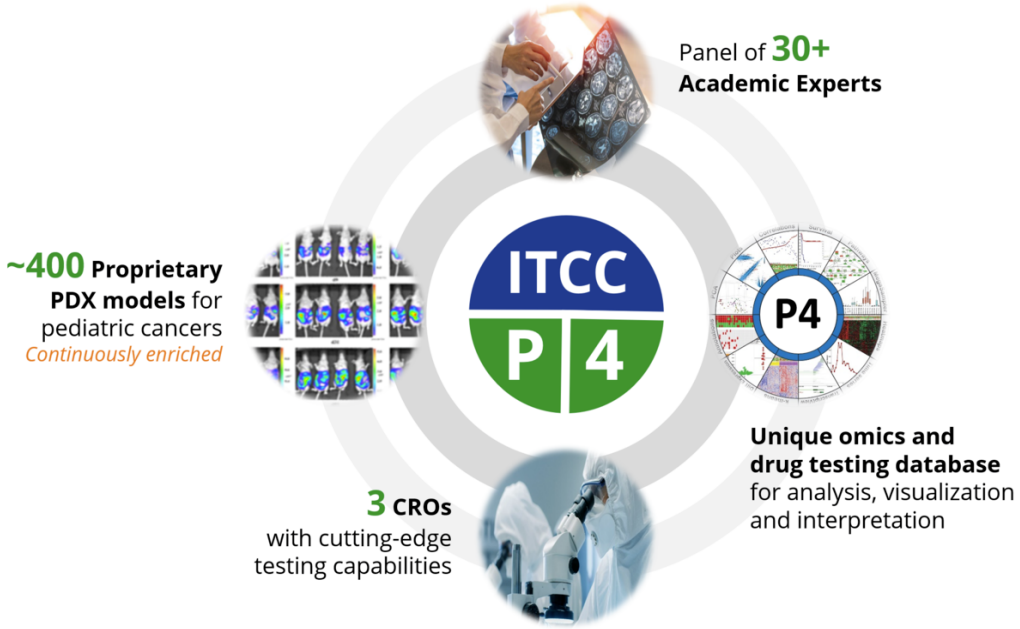
→ Will come with the revised pharma legislation in Europe

This means:

- Need to understand target relevance
- Need for sufficiently robust non-clinical proof of concept data before moving a novel agent into first in child studies – particularly if the adult development is in a different disease as compared to children

→ Focus on non-clinical space

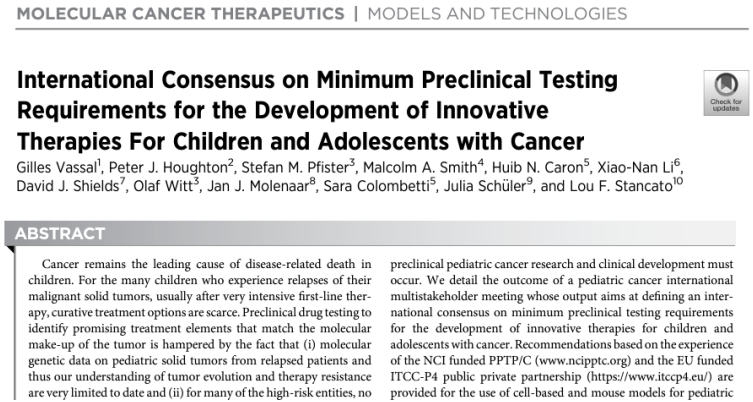
Academic capacity building to address the need for non-clinical proof-of-concept data – Europe



https://www.itccp4.eu/

Pre-clinical requirements

→ academic consensus on minimum preclinical requirements



MOLECULAR CANCER THERAPEUTICS | MODELS AND TECHNOLOGIES

International Consensus on Minimum Preclinical Testing Requirements for the Development of Innovative Therapies For Children and Adolescents with Cancer

Gilles Vassal[1], Peter J. Houghton[2], Stefan M. Pfister[3], Malcolm A. Smith[4], Huib N. Caron[5], Xiao-Nan Li[6], David J. Shields[7], Olaf Witt[3], Jan J. Molenaar[8], Sara Colombetti[5], Julia Schüler[9], and Lou F. Stancato[10]

ABSTRACT

Cancer remains the leading cause of disease-related death in children. For the many children who experience relapses of their malignant solid tumors, usually after very intensive first-line therapy, curative treatment options are scarce. Preclinical drug testing to identify promising treatment elements that match the molecular make-up of the tumor is hampered by the fact that (i) molecular genetic data on pediatric solid tumors from relapsed patients and thus our understanding of tumor evolution and therapy resistance are very limited to date and (ii) for many of the high-risk entities, no preclinical pediatric cancer research and clinical development must occur. We detail the outcome of a pediatric cancer international multistakeholder meeting whose output aims at defining an international consensus on minimum preclinical testing requirements for the development of innovative therapies for children and adolescents with cancer. Recommendations based on the experience of the NCI funded PPTP/C (www.ncipptc.org) and the EU funded ITCC-P4 public private partnership (https://www.itccp4.eu/) are provided for the use of cell-based and mouse models for pediatric

11 Mol Cancer Ther (2021) 20 (8): 1462–1468.

Academic capacity building to address the need for pre-clinical proof-of-concept data – US – PIVOT consortium/ NCI funded

PIVOT
Pediatric Preclinical In Vivo Testing

PIVOT Consortium Members

Coordinating Center	Sarcomas, Kidney, Liver	Neuroblastoma	Childhood Leukemia
The Jackson Laboratory; Seven Bridges	UT Health San Antonio; Greehey Children's Cancer Research Institute	The Children's Hospital of Philadelphia	Children's Cancer Institute
Carol J. Bult, PhD Jeff H. Chuang, PhD Emily Jocoy, PhD Dennis Dean, PhD	Peter J. Houghton, PhD Raushan Kurmasheva, PhD	Yael Mossé, MD John M. Maris, MD	Richard Lock, PhD
Brain Tumors	**Osteosarcoma**	**Soft Tissue Sarcomas**	**Sarcomas, Kidney, Rare Tumors**
Ann & Robert H. Lurie Children's Hospital of Chicago	The University of Texas MD Anderson Cancer Center Children's Cancer Hospital	St. Jude Children's Research Hospital	Memorial Sloan Kettering Cancer Center
Xiao-Nan Li, MD, PhD	Richard G. Gorlick, MD	Michael A. Dyer, PhD Elizabeth Stewart, MD	Andrew Kung, MD, PhD Filemon Dela Cruz, MD

https://ctep.cancer.gov/MajorInitiatives/Pediatric_PIVOT_Program.htm

Building regulatory capacity at EMA

1) Proof-of-concept data in oncology PIPs are discussed in a dedicated Non-clinical Working Party session involving a **multidisciplinary** group of colleagues with participation of FDA expert observers
2) Activities related to building preparedness for the new legislation will be captured in the EMA Non-clinical Domain **Workplan** for 2025-2027
3) Initiated engagement with the **industry** during the annual Preclinical Assessors Meeting (PAM) with European Federation of Pharmaceutical Industries and Associations (EFPIA)
4) Dedicated meetings to engage with **academics** are being organised

Multidisciplinary work

Drafting Group of the Non-clinical Working Party to work on a reflection paper on the MoA driven assessments in paediatric oncology covering:

- **the process** - encouraging routine multistakeholder engagement and discussions, including FDA and academics as appropriate

- **the methodology** of such assessments, utilising a weight of evidence approach, involving clinical and non-clinical expertise

Conclusion

- Increase in products proposed for paediatric development in oncology - driven by US regulation – legislation proposal formalising similar approach in EU
- Need for robust non-clinical data to support go/ no go decisions on which product based on its MoA should move into the clinical
- Importance of non-clinical data to balance (lack of) efficacy versus safety
- Academia has started to explore concepts and to build capacity in that regard
- Regulators are asked to regulate data requirements (as part of a PIP)

Future perspective

- Capacity building & dialogue with stakeholders
- Using the oncology space as a learning platform for regulators
- Plan a reflection paper in the implementation of the MoA based assessments
- No plans for guideline on minimum requirements
- Commitment for continuous collaboration with FDA

Acknowledgments

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Giovanni Lesa

Any questions?

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Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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Impact of RACE Act: COG Perspective

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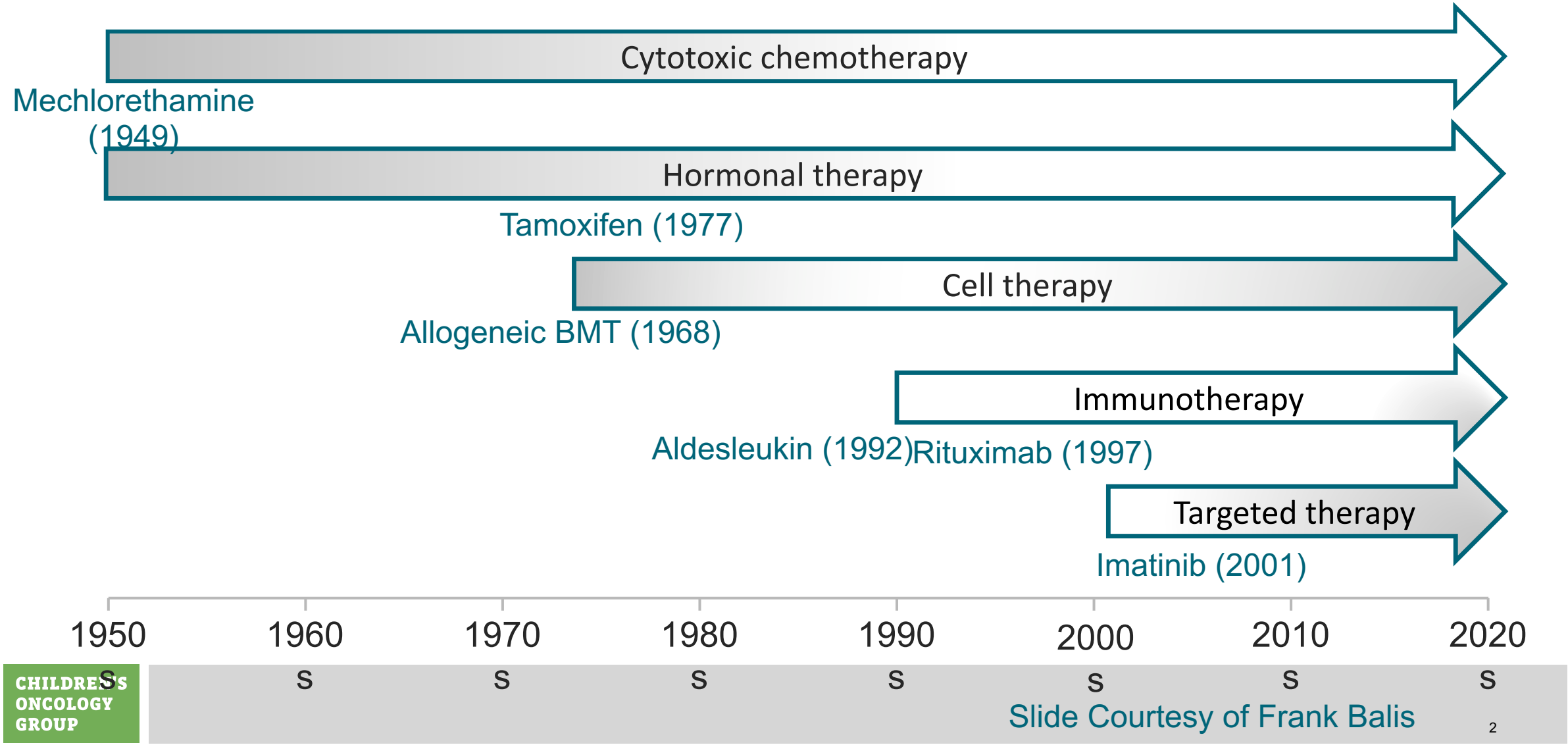
Professor and Division Director
Pediatric Hematology/Oncology
University of Minnesota

Chair, Developmental Therapeutics COG

CHILDREN'S ONCOLOGY GROUP

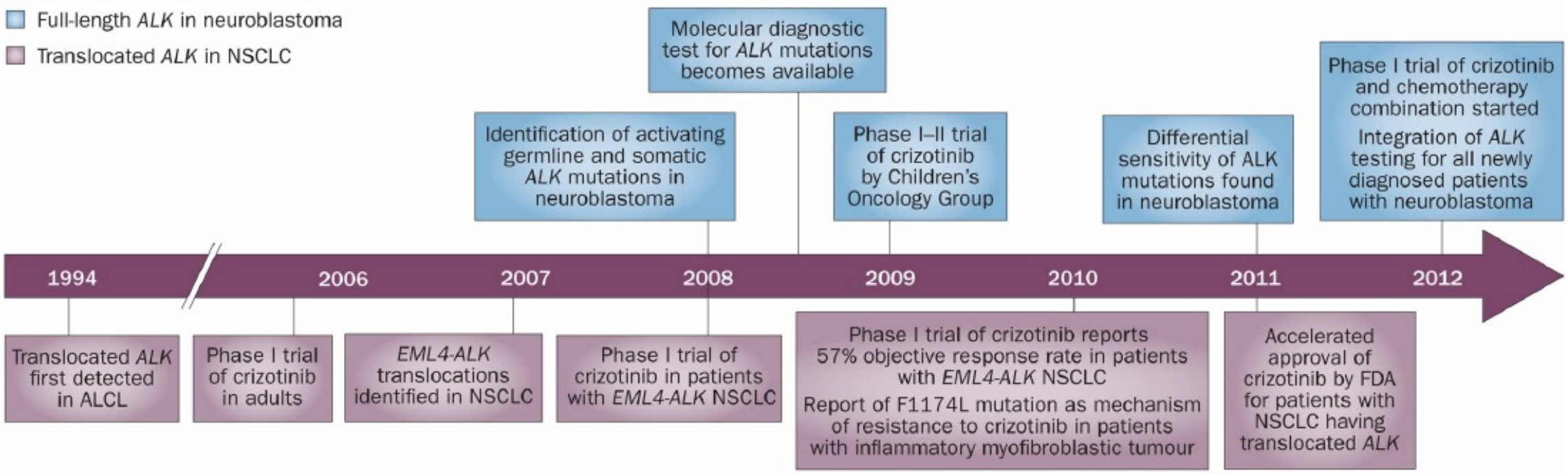
Evolution of Anticancer Drugs



CHILDREN'S ONCOLOGY GROUP

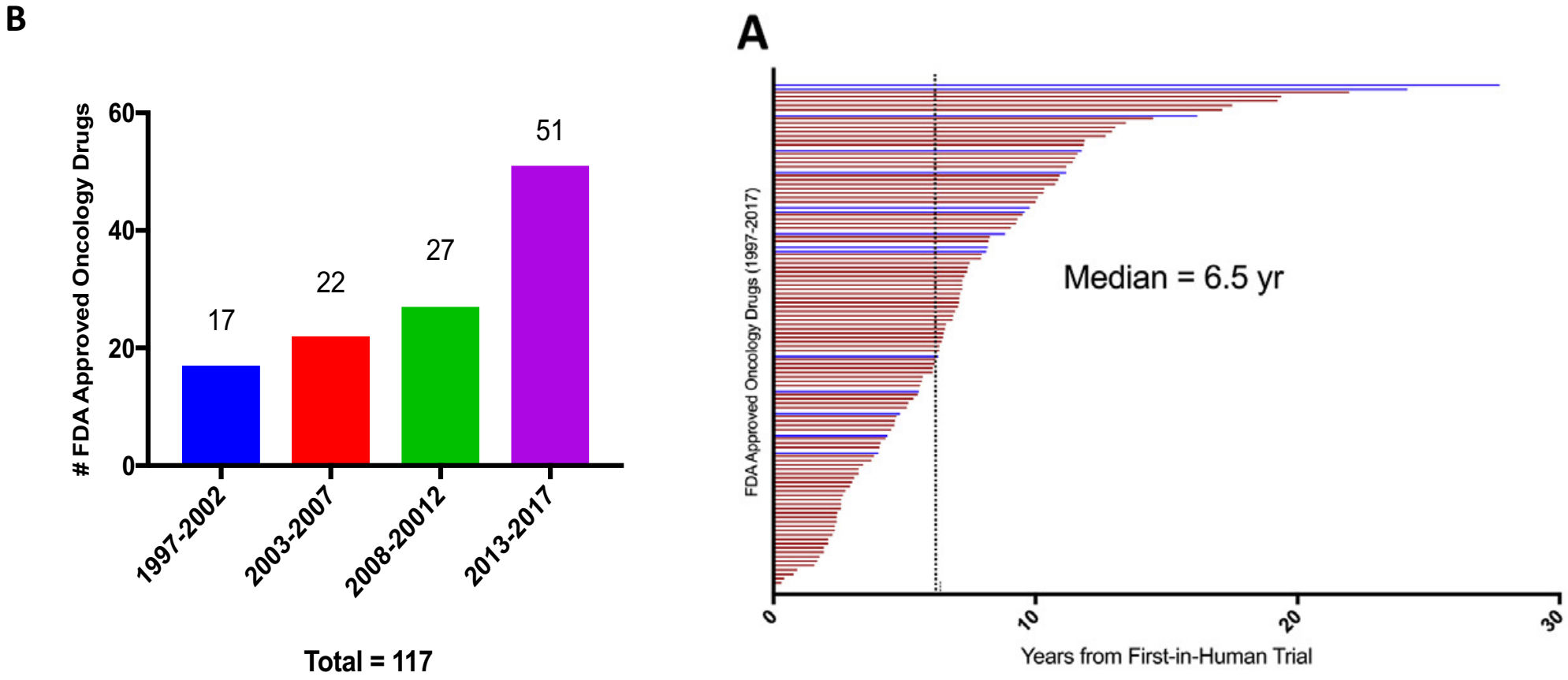
Slide Courtesy of Frank Balis

Crizotinib Development Timeline



Nat Rev Clin Oncol:9(7):391-399,2012

Average of 6.5 yrs to Start Pediatric Trial



Neel DV et al. *Eur J Cancer*. 2019

Historically Pediatric Indications of Oncology Drugs is Significantly Delayed over Adult Approvals

- In the era of Novel Trial Designs, is there a way to incorporate pediatric investigation early to accelerate pediatric investigation and define relevant pediatric dose?

RACE for Children Act

- Incorporated as Title V of the **FDA Reauthorization Act (FDARA),** enacted August 18, 2017; required August 18, 2020
- **Requires** evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer."
- **Molecularly targeted pediatric cancer investigation**: clinically meaningful study data, "using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling." [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Factors Related to Relevance

- Identification of the target in a pediatric cancer
- Target function related to etiology or resistance
- Effect of target modulation- *in vivo, in vitro;* synergy in biologic/rational combination
- Clinical experience: adult and pediatric
- Availability of predictive and response biomarkers

Biology and Pre-clinical Data

- Valid and relevant cell lines and models limited in pediatric oncology
- Many ‘targets’ evaluated late
  - eg Alk and crizotinib
- Limited relevant human tumor data
  - Different tumors
  - Relative rarity

Drug Formulation

- IV is easy
  - All ages eligible
- Oral
  - May limit based on size to allow for dosing in pediatrics
  - Don’t base on age but size and the available strengths/formulation
  - Currently most companies delay development of pediatric formulation until an adult indication is clear: RACE Act may help change this

Key Considerations

- Pediatric formulation requirement
  - Molecularly targeted pediatric cancer investigation: clinically meaningful study data, **“using appropriate formulations, regarding dosing, safety and preliminary efficacy** to inform potential pediatric labeling.” [FDARA Title V Sec 504 (a)(3)(A) or FD&C Act Sec. 505B (a)(3)(A)].

- Importance and timing of development of these pediatric formulations (early):
  - eg: larotrectinib and NTRK fusions

- Impact on administration to children
  - Phased formulation development
    - Start with existing formulation and concurrently develop pediatric appropriate formulation as data emerge

Key Considerations

- Clinical benefit: risk analysis
  - Safety and toxicity profile
    - Pre-clinical
      - Growth and development
    - Clinical
      - Toxicities from adults

Key Considerations

- Rare target patient populations require collaboration
  - International clinical trial collaboration
  - Coordination of regulatory requirements
- Adequate safety and dosing data in children and adolescents
  - Age of eligibility and appropriate formulations
  - FDA recommendation on adolescent cohorts *Chuk et al Clin Cancer Res 2017 23:9-12*
- Impact on trial design
  - Master/Platform protocols
  - Rolling 6 design with expansions to ensure adequate toxicity and PK data
  - Starting dose based on adult recommended phase 2 dose
  - Limit pediatric dose finding

Types of COG Industry Collaborations

NCI-Sponsored Trials	Hybrid Trials	Industry-Sponsored Trials
• NCI & Drug Company Contract Only • Standard NCI Support Only • NCI held IND	• NCI Trial with COG & Drug Company Contract • Drug Supply, Additional Data, and/or Funding • COG or Company held IND	• COG & Drug Company Contract, without NCI Involvement • Fully Sponsored by Industry • Company held IND

Beginning the Discussion with Industry Collaborator

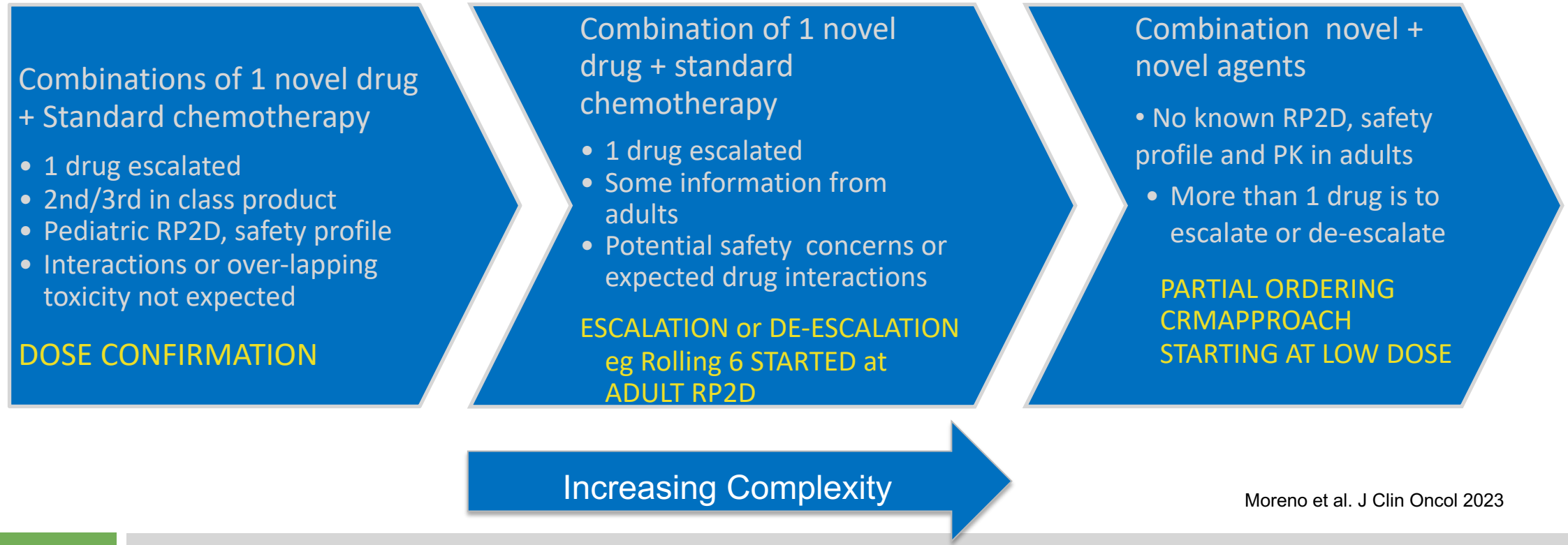
- The idea – investigator or industry initiated
- Key Considerations
  - Business and Regulatory strategy
  - How does the drug work, mechanisms of action
  - Drug formulations and sizes
  - Studies underway in the adult and/or pediatric population
  - Drug safety concerns

Selection of Combination Regimens

	Cytotoxic	Molecular Target	Immune Check Point Inhibitors (ICI)
Activity in advanced disease	+	±	-
Non-cross resistant	+	±	±
Mechanism of Action Additive or Synergistic	+	+	+
Non-overlapping Toxicity	±	±	-

Combination Strategies

Spectrum of designs and starting doses for pediatric combination trials



Moreno et al. J Clin Oncol 2023

Conclusions to Date

- Too soon to truly understand the impact of the RACE Act
- Has seemed to shift the industry pendulum to earlier discussions regarding potential pediatric trials for targeted therapies but not clear that this has yet translated into more clinical trials or ultimately approvals
- Focused on molecular targets and does not take into account cellular therapy or combination therapy
- Need a quick process for no go decisions in the pediatric space

Points to Consider

- How to engage pediatric hematology/oncology experts as early as possible in the regulatory process?
  - iPSP required at the end of phase 2 testing in adults: need earlier engagement
  - Are there ways to accelerate the process?
- How do we include and address issues of cellular therapy?
- How do we move forward new agents that are not molecularly targeted by may have relevance eg tumor microenvironment?
- How do we address combinations?

Points to Consider

- What are regulatory considerations for trial designs that accommodate new agent monotherapy safety and PK prior to evaluation of safety and activity in combination with other agent(s)?
  - · Pre-clinical data requirements
  - · No adult data on combination?
  - · Combination with cytotoxic vs novel agents?
  - · Designs to evaluate safety throughout therapy
- What circumstances require demonstration of single agent activity prior to incorporation into a clinical trial?

Points to Consider

- How do we address multiple agents in class in a limited patient population?
  - Issues of efficacy
  - Issues of toxicity, short vs longterm

- International collaboration is key!

QUESTIONS?
And
DISCUSSION

CHILDREN'S ONCOLOGY GROUP

Research to Accelerate Cures and Equity for Children Act (RACE Act) Implementation and Impact Industry Perspective

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

May 22, 2024

Ruchi Gupta, M.S.
Program Director, Regulatory Affairs
Genentech, a member of the Roche Group
South San Francisco

Disclosure Information

The presenter Ruchi Gupta is an Employee of Genentech, Inc and a Stock Holder of Hoffmann-La Roche, Inc

The presentation describes the Roche/Genentech perspective on industry challenges associated with implementation of RACE Act under Food and Drug Administration Reauthorization Act (FDARA 2017)

Outline

- Introduction to Pediatric Research Equity Act (PREA) and Challenges associated with it
- RACE Act under FDARA 2017
  - Changing landscape and shifting paradigm of pediatric oncology ddrug development
  - Impact on the industry and its challenges
  - Roche's best practices
  - How can FDARA 2017 be made more effective
- Key Messages

Pediatric Research Equity Act (PREA)

Regulatory Requirements pre-FDARA 2017

- Applicable to both drugs and biologics and all therapeutic areas
- Pediatric studies are **mandatory**
- Requires pediatric studies **only on adult indication(s) under review**
- **Orphan indications exempt** from conducting pediatric studies
- Once completed, pediatric studies must inform the product label

Challenges Implementing PREA in Oncology

pre-FDARA 2017

- **Pediatric oncology drug development is largely based on adult programs.**
  - The majority of pediatric tumors are rare and distinct entities from those seen in adults
- **Reactive obligatory vs proactive voluntary approach:**
  - PREA not applicable to vast majority of pediatric cancers
  - Orphan Drug Designation exempted molecules from pediatric obligations
  - Limited patient pool
  - Limited market incentives
- **Outcome: Children with Cancer Do Not Have Timely Access to Safe and Efficacious Drugs**
  - Pediatric oncology labeling lags other therapeutic areas

Pediatric Research Equity Act

What it meant post-FDARA 2017?

- Implemented on both drugs & biologics being studied in Oncology
- **Requires molecularly targeted pediatric cancer investigation** of new molecular entities (drugs and biologics) “intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer.”
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets
- Once completed, pediatric studies must inform the product label

Changing Landscape

Industry-Sponsored Pediatric Oncology Drug Development Needs Innovation

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- Sponsors are required to submit iPSPs for marketing applications for **new molecular entities** submitted after **August 2020** unless the PREA requirement is waived.
- Submitting a pediatric study plan outlining the clinical study design to evaluate dose, safety and preliminary efficacy of the drug would require early evaluation and availability of:
  - Adult safety and efficacy data (if available)
  - Pre-clinical data supporting molecular target relevance in pediatric tumors and evidence of pre-clinical anti-tumor activity
  - Pediatric formulation and starting dose for pediatric study
  - Feasibility of conducting a clinical trial (population, route to clinical adoption, competitors)

Shifted the Paradigm of Pediatric Drug Development

- Increased interest in pediatric cancer drug development (internally, and externally) with large academic institutions and consortiums
- Increased visibility to unmet clinical pediatric cancer needs
- Potential for increased treatment options for pediatric population due to the increase in pediatric clinical trials being initiated across the U.S.
- Impact on adult drug development is yet to be assessed

Challenges of Obligatory Pediatric Oncology Drug Development

- Harmonization between Health Authorities, Institutional Review Boards (IRBs)/ Ethics Committees (ECs) on the study design
- Study Design challenges
  - Assessment (predictive of safety and efficacy) of preclinical data or early clinical data in adult vs pediatric models
  - Alignment on proposed pediatric cancer types
  - Starting dose in pediatrics
  - Selection of patient population/ Size of the trial
  - Choice of Single agent vs combinations

Challenges of Obligatory Pediatric Oncology Drug Development (contd.)

- Operational challenges
  - Feasibility – Prioritization of molecules within same class and similar MoA and of molecules within the same disease area in rare diseases leading to enrollment challenges delaying overall study completion
  - Timelines and procedure for submission and reviews of Pediatric Study Plans (PSPs), Paediatric Investigational Plans (PIPs) and Investigational New Drug (INDs) applications and Clinical Trial Applications (CTAs)

Roche's Best Practices

How pediatric studies are designed at Roche

To determine the relevant cancer types for pediatric investigation based on the Mechanism of Action (MoA) of a new molecular entity, Genentech/ Roche assesses a number of things:

- Reference to FDA's Published List of Molecular Targets for the Growth and Development of Pediatric Cancers
- Any available safety, pharmacokinetics and efficacy data in adult trials
- Nonclinical data (juvenile toxicity data, etc.)
- Relevant biomarker expression across pediatric cancers
- Feasibility assessments
  - Incidence/prevalence of relevant cancer types in the pediatric population
  - Internal/external pediatric trials that may be competing within the same disease area
- Unmet medical need
- Age-Appropriate Formulation feasibility
- Regulatory Obligations - Drug development milestones that trigger PREA requirements and the associated timing

How Can FDARA 2017 Be Made More Effective?

- Develop a process for molecule prioritization across industry
  - Have specific procedures that would streamline the review of PSPs that are competing with same in class molecules and a more defined approach and timelines for deferral processes
  - Realistic approach about the number of pediatric indications that could be investigated for a given program recognizing the challenges associated with competition and prioritization internally and externally
  - Set practical targets in order to define minimum patient numbers required for conducting pediatric studies, taking incidence and prevalence data into consideration
- Provide guidance on evidence collection or willingness to accept alternatives in lieu of appropriate animal models to establish safety, efficacy and dose in rare pediatric indications

Key Messages

- Requirement for Mechanism of Action (MOA) based pediatric drug development under FDARA 2017:
  - Has enforced the proactive and early consideration of integrating pediatric development as part of overall clinical development plan for the molecule.
  - Encouraged collaboration among regulators, sponsors and academic partners to share best practices
  - Presents the opportunity for additional global harmonization of study designs
- Innovative trial designs, establishing clinical development matching pediatric potential and molecule developability and shifting mindsets to take a portfolio approach has the potential to be an effective way to address some of the challenges posed by the changes in regulation and benefit children in need.

THANK YOU

European academic perspectives on international trial collaboration in paediatric oncology

Professor Pamela Kearns
Director, Institute of Cancer and Genomic Sciences
University of Birmingham
President of ITCC

UNIVERSITY OF BIRMINGHAM

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

SIOP Europe
the European Society for Paediatric Oncology

Clinical Research Infrastructure in Europe

SIOP Europe
the European Society for Paediatric Oncology

Childhood Cancer International EUROPE

European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

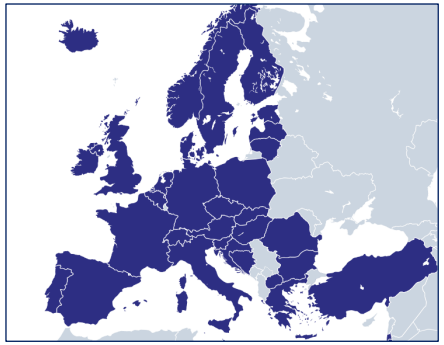
All European Clinical Trial Groups (**ECTGs**)

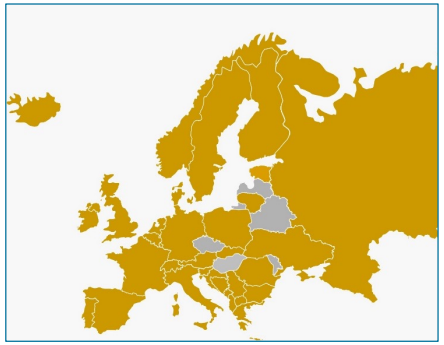
National Paediatric Haemato-Oncology Societies (**NaPHOS**) or paediatric oncology centres

35 countries incl. all EU Member States

67 **Patient**, **Parent** and **Survivor Organisations**

34 countries incl. most EU Member States





SIOP Europe
Clinical Research **Council**

- Memorandum-based core partnerships
- Cooperation with industry
- EU projects and platforms
- Joint Strategy

JARC JOINT ACTION ON RARE CANCERS

European Commission

Europe's Early Phase Clinical Trials Network for Children and Adolescents

GOAL: To develop novel therapies for the treatment of paediatric and adolescent cancers in cooperation with regulatory bodies, pharmaceutical enterprises, parents and patients.

COMPRISES:

- **62 European Paediatric Oncology clinical trial centres in 17 countries** with expertise in conducting early phase trials in children and adolescents
- **25 European research laboratories engaged in genomic and translational research**
- Recognised as a European Category 1 Network for Paediatric Research at the European Medicines Agency (**EnprEMA**).

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

An integrated and coordinated approach

EXPERTISE

Biology, Medicine, Clinical research, Regulatory science

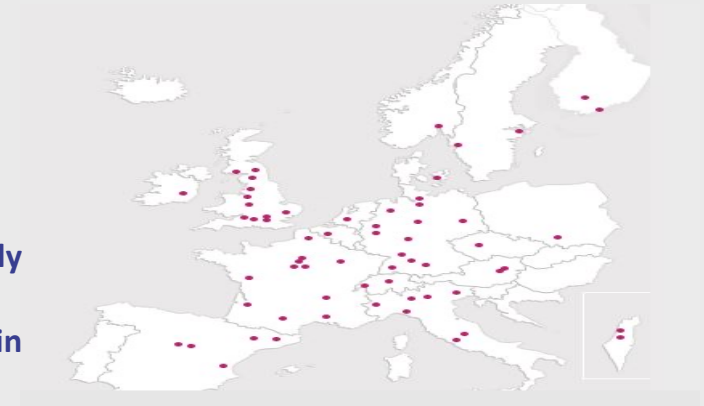
An efficient network of 62 expert clinical centers to deliver early trials in 16 countries

ITCC institutions

Yearly:

- 1500 relapsed patients
- 20- 25 ongoing early phase trials
- 400 - 500 patients in trials

A network of the top 25 EU research labs on pediatric oncology



+ association with ANZCHOG, C17

An academic sponsor network of institutions for implementation of IIT and platform trials

An aggregated clinical biological data base of pediatric malignancies
(under construction)

Molecular data input

Molecular profiling platforms

- MAPPYACTS/ MICCHADO
- INFORM
- I-THER
- SM-PAEDS
- DANISH
- ZERO
- PROFYLE

A preclinical testing platform with a saturated repertoire of pediatric tumor models
(in development)

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

imi innovative medicines initiative
efpia

Innovative Technology platforms for sequencing, ctDNA, single cells, etc

FOUNDER MEMBER OF ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Types of Trials

Trial type	Sponsor	Funding	Intended use	Industry role	Filing intent
Academic trial		**Non industry** * charity, government	**Publication clinical practice guidance**	**None**	
Investigator-Initiated trial		**Mixed**	**Publication clinical practice guidance**	**Drug provisioning** Funding	 * exceptions exist
Academic-Industry Collaborative trial		**Industry**	**Licensing** Publication	**Full funding** Drug provisioning	
Industry Trial		**Industry**	**Licensing**	**Full responsibility** Ownership of the trial	

Innovative approach to Industry Collaboration: making the data count

Outcomes from academic trials rarely inform the drug label /marketing authorization

‘Fit for Filing’: a paradigm shift in Academia –Industry collaborative trials

Journal of Clinical Oncology 2022 40:29, 3456

SPECIAL ARTICLE

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]

Childhood Cancer International EUROPE

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

FDA

Academics

Pharma

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Paediatric Strategy Forum for B-NHL

European Journal of Cancer 110 (2019) 74–85

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

ACCELERATE and European Medicine Agency Paediatric Strategy Forum for medicinal product development for mature B-cell malignancies in children

"In addition to industry-initiated drug development, there are many benefits of conducting industry-supported, academic-sponsored studies with compounds from different pharmaceutical companies and different mechanisms of action using an adaptive design; however, academic clinical trials supported by industry should be designed and conducted to a very high quality standard with 'intent to file', in order that clinical trial data can be used for licensing purposes, and early input should be sought from regulators (through available procedures with the EMA's PDCO and/or SAWP and FDA)."

GIO-BNHL

Platform trial for paediatric **relapsed & refractory B-cell NHL**

Challenge: small population

Approach: Bayesian statistics

Bayesian approach

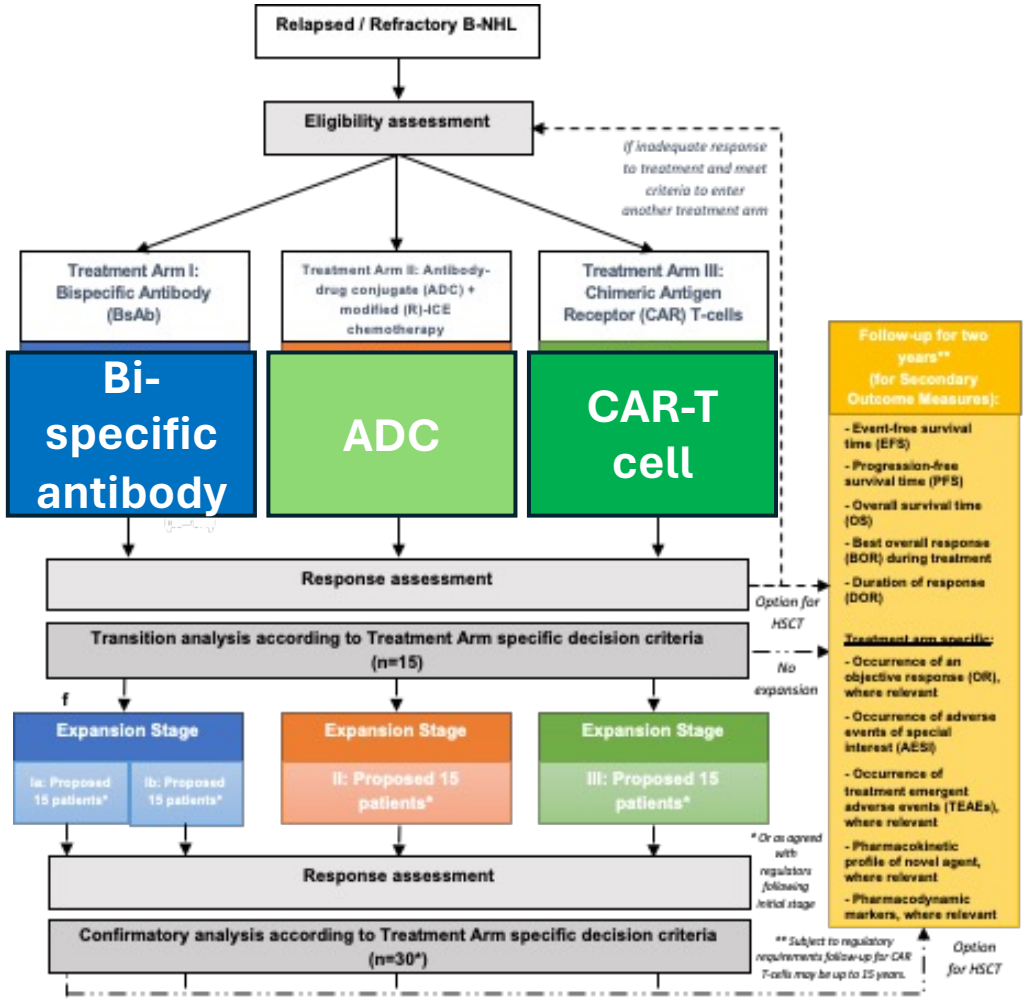
- **for estimation & decision-making in each treatment arm**

Credible and feasible trial design

- **EMA Qualification Advice and Support** (PIP compliance)
- **FDA –Pre-IND support**

Academic 'Fit for Filing' capability

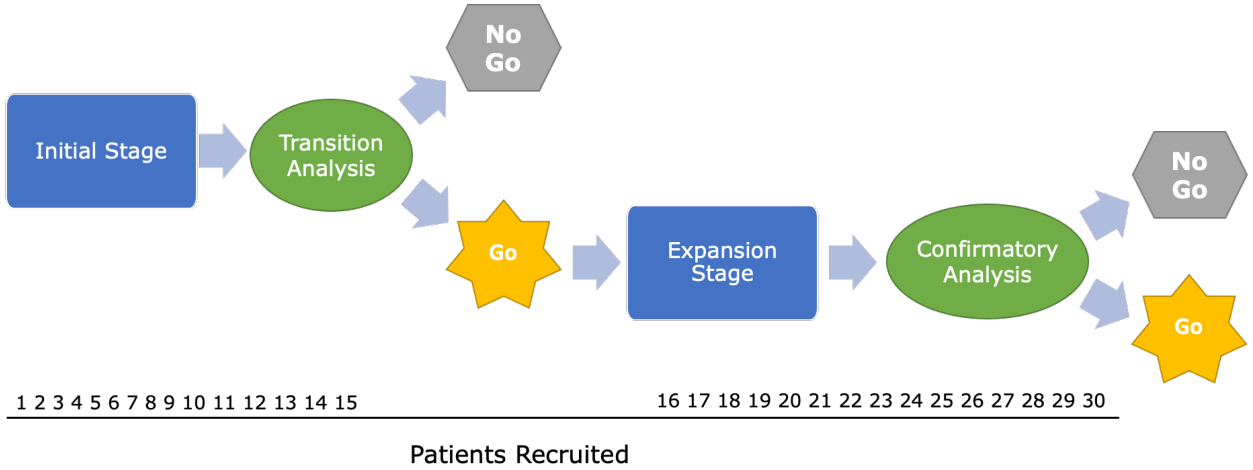
- ICH-GCP compliance from design to clinical study report
- **Accelerated and Cost-Effective Delivery**



CANCER RESEARCH UK | BIRMINGHAM CANCER RESEARCH UK CLINICAL TRIALS UNIT | UNIVERSITY OF BIRMINGHAM

FIGHT KIDS CANCER | eicnhl | CHILDREN'S ONCOLOGY GROUP | ITCC INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

Glo-BNHL Statistical Design, Interventions and outcome measures



	Treatment Arm Ia	Treatment Arm Ib	Treatment Arm II	Treatment Arm III
Primary Outcome Measure	Objective response rate	Objective response rate	Complete response rate	Objective response rate
Clinically relevant target response rate	40%	10%	20%	10%
Transition Analysis: responses required for Go decision	8/15	3/15	5/15	3/15
Confirmatory Analysis: responses required for Go decision	17/30	6/30	10/30	6/30

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2022
EMADOC-1700519818-746444
Executive Director

Letter of support for the Global Platform Study of Novel Medicines in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (Glo-BNHL platform)

- **Decisions based on probabilities:**

  Prob (True response rate > Target)
- **Transition analysis**
  - 15 patients
  - Required certainty of 0.8 for 'Go'
- **Confirmatory analysis**
  - 30 patients
  - Required certainty 0.95 for 'Go'

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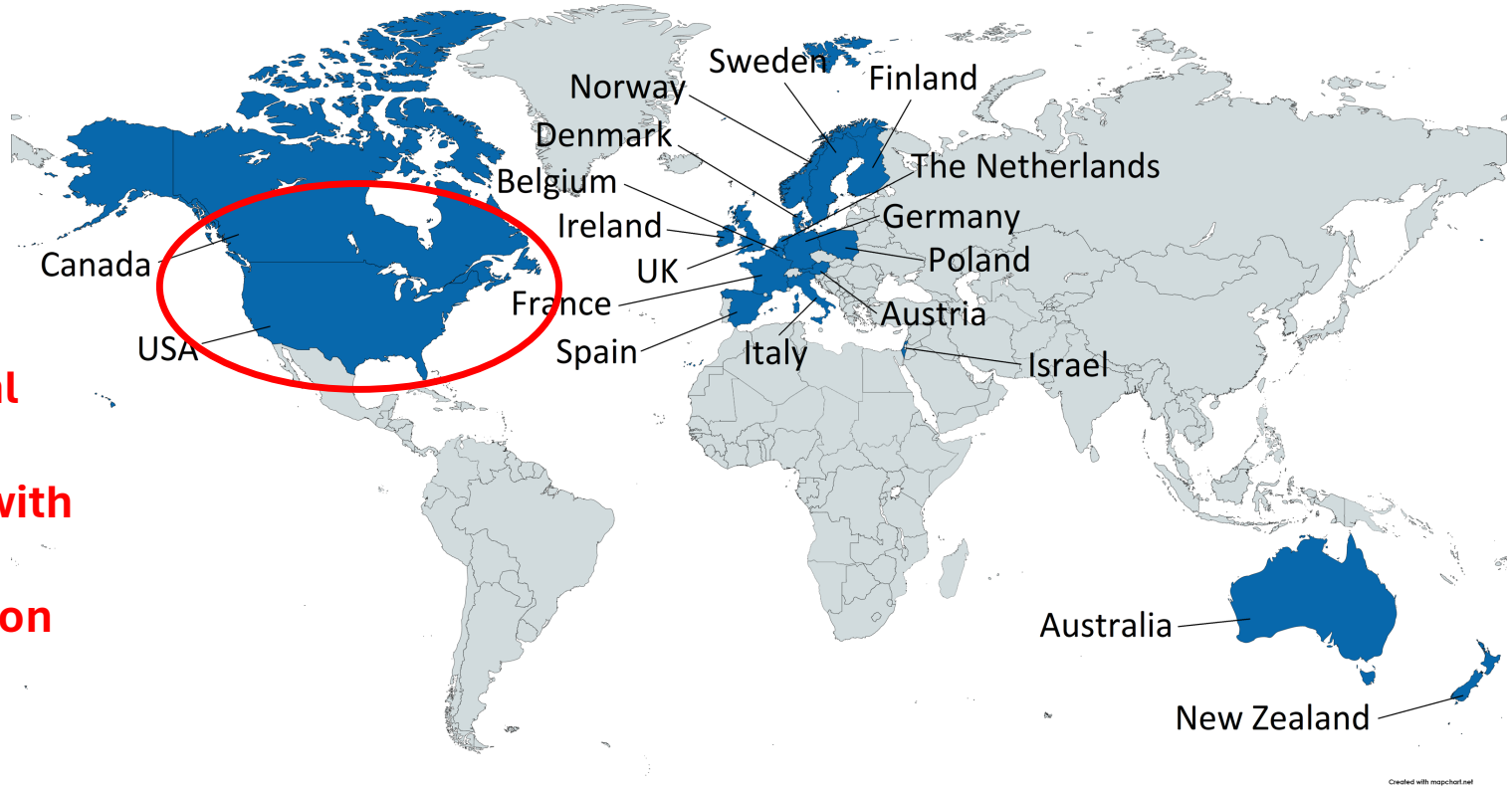
GIO-BNHL An international collaboration



Operational challenges identified with the US collaboration

<u>Note</u>: other collaborators are in discussion including Switzerland

ITCC/COG/CTEP INTERNATIONAL TRIALS PROJECT

Improving collaborations in transatlantic academic trials in paediatric oncology

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

CHILDREN'S ONCOLOGY GROUP

NIH NATIONAL CANCER INSTITUTE

Shared **DESIRE** for transatlantic collaboration in childhood cancer trials
Shared **NEED** to collaborate as we move towards increased patient stratification based on biology
Shared **FRUSTRATION** with the delays in achieving the collaborations
Shared **LACK OF UNDERSTANDING** of each others' processes

ITCC/COG/CTEP INTERNATIONAL TRIALS PROJECT

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

CHILDREN'S ONCOLOGY GROUP

NIH NATIONAL CANCER INSTITUTE

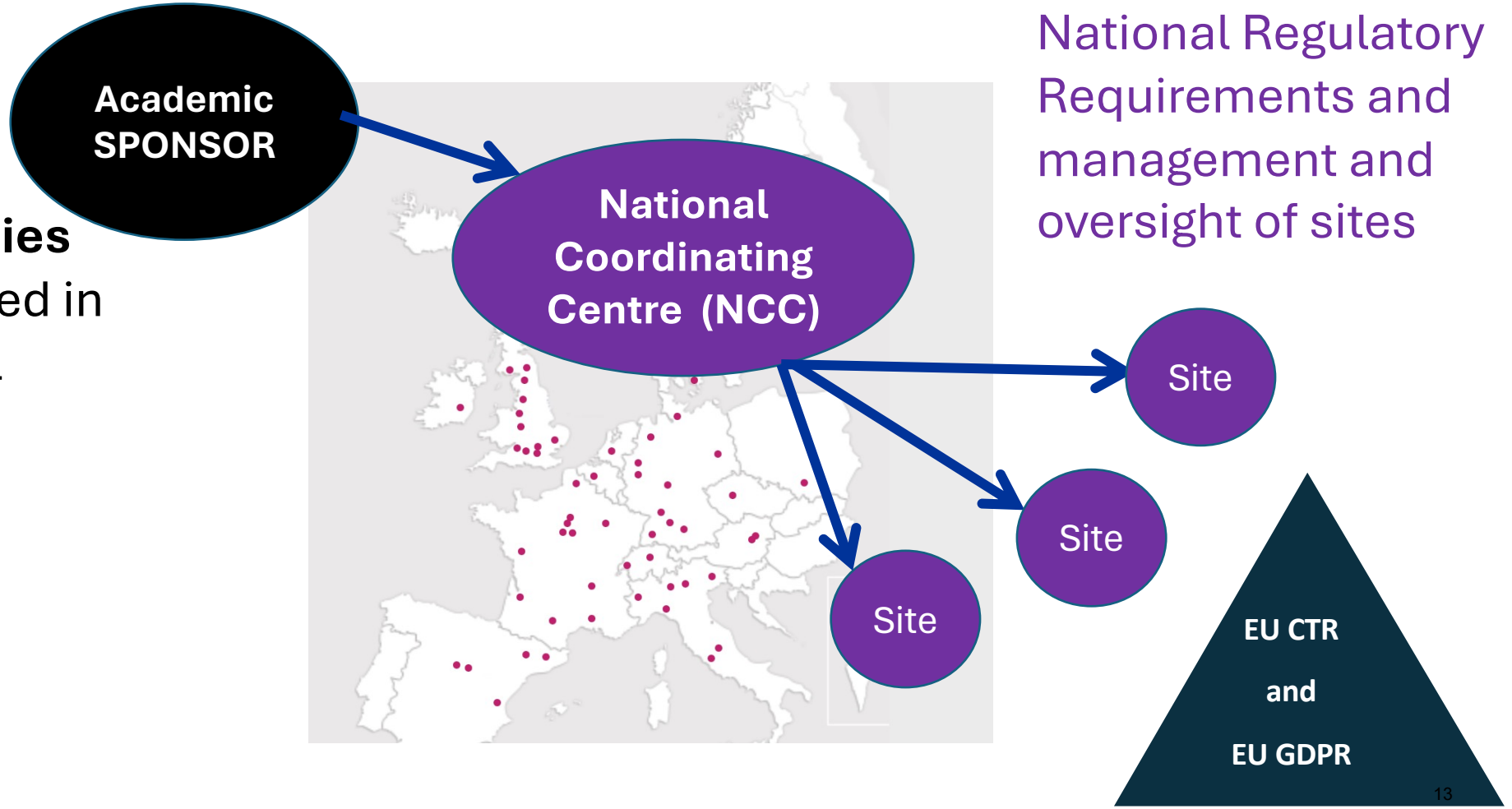
Aim

- Effective transatlantic collaboration to deliver rare small population academic clinical trials

- **Objectives**
- To develop a better shared understanding of the differences between delivery of internationally collaborative trials in Europe compared to the US COG system
- To develop a framework to achieve accelerated transatlantic academic clinical trial delivery

ITCC international trials framework

Delegate responsibilities to **NCC** defined in a clinical trial agreement



Responsible for National Regulatory Requirements and management and oversight of sites

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

ITCC international trials framework

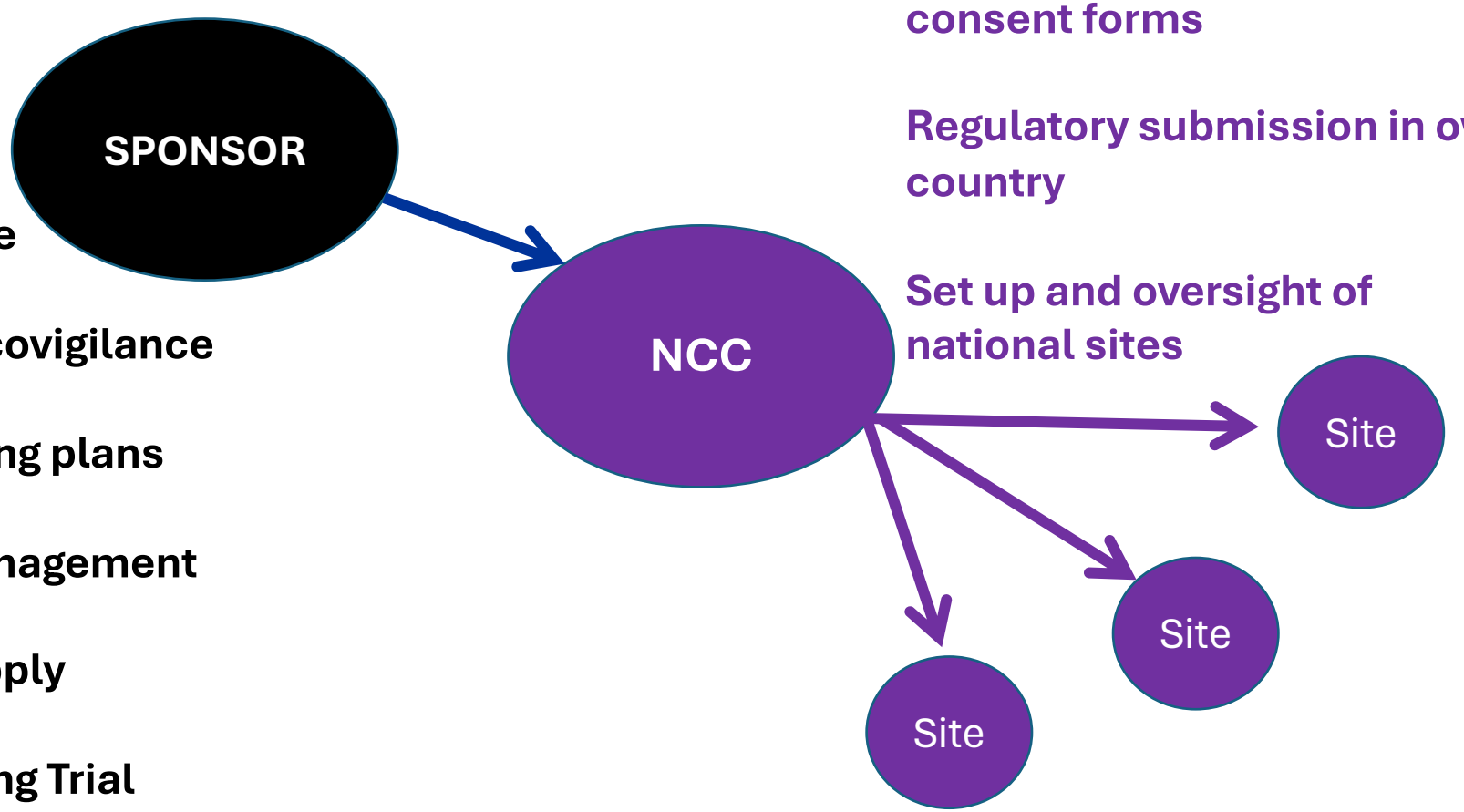
Trial design in collaboration with CI and clinical network

Coordination funding

Protocol and trial document preparation

Regulatory submission in own country

Trial Insurance



Database

Pharmacovigilance

Monitoring plans

Data management

Drug supply

Convening Trial Committees

Trial analyses & Publication

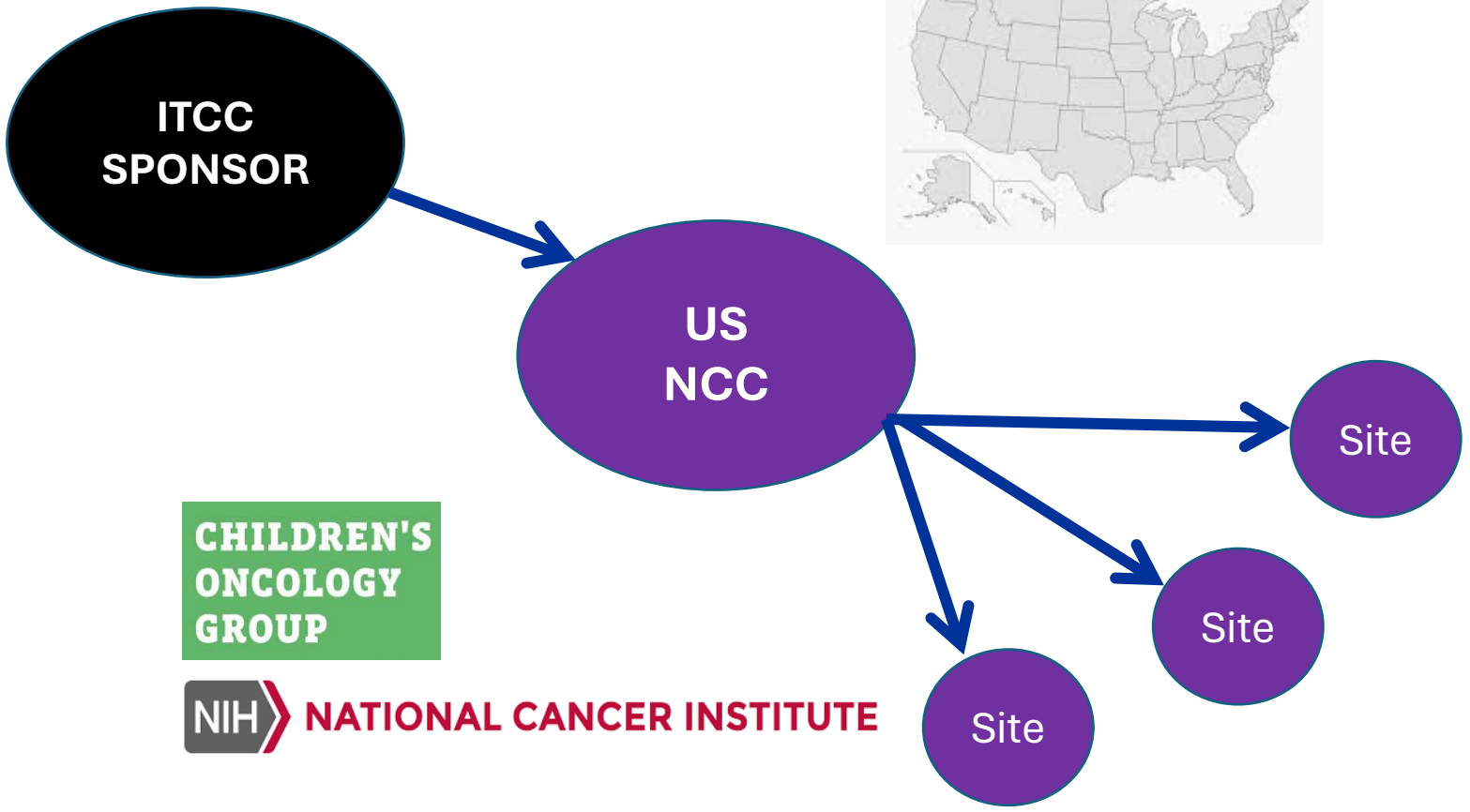
Patient Information and consent forms

Regulatory submission in own country

Set up and oversight of national sites

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

Applying the Framework outside the ITCC Network?



ITCC participation in a US led Trial

CHILDREN'S ONCOLOGY GROUP

NIH NATIONAL CANCER INSTITUTE

US SPONSOR

ITCC Sponsor

NCC

Site

NCC

Site

NCC

Site

ITCC International Sponsor would act as European delegated Sponsor

What are the problems?

Workshops to Define the Roadblocks with

3 case studies & considered potential solutions

COG sponsored, with coordination in Europe and European database (**ACNS1831**)

European sponsored, COG participation using Europe based database (**GLO-B-NHL**)

COG sponsored, European coordination with direct access to COG database (**AGCT1531**)

Four Main Roadblocks

1. Lack of **transatlantic understanding** of each others' processes
2. **Database access**; incompatibility in clinical trial infrastructure and processes
3. Differences in **Data Protection** Legislation and its interpretation
4. Regulatory differences: **Pharmacovigilance**

4 Working Groups to propose solutions

ITCC
INNOVATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH CANCER

CHILDREN'S ONCOLOGY GROUP

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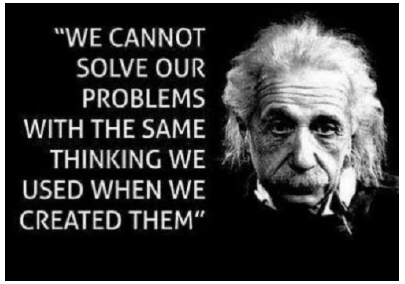
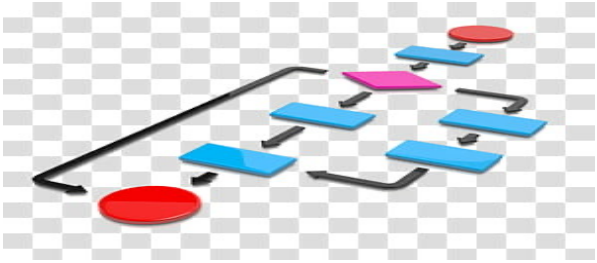


WG 1: Process Mapping



Idea

COG Disease specific Committee

Study development group

- Disease specific group
- ITCC/SIOPE
- National clinical study group

Concept with broad aims and treatment questions defined

COG Operations*

Sponsor/Clinical trials unit

Trial Management Group formed:

- statistical design
- Funding strategy
- PPI
- Feasibility
- Collaboration explored (recruitment/pharma involvement etc)

ications ajoutées

Model for collaboration agreed
(process map splits)

Solution:
Guidance documents to detail US /European/UK trial development and set up processes

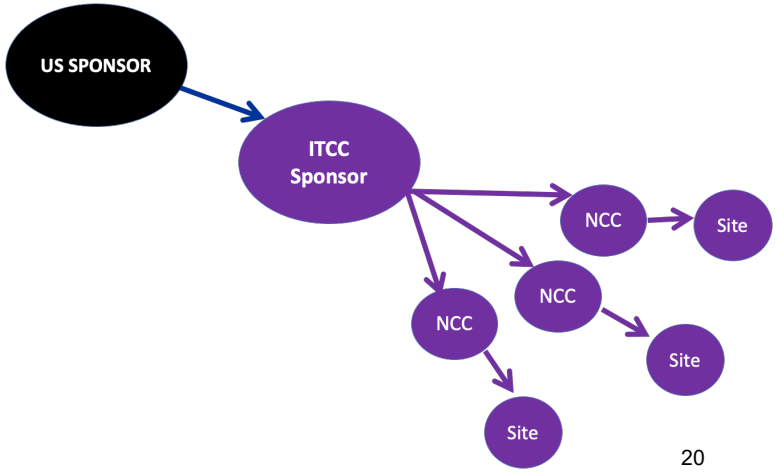
WG 2: Databases (accessing clinical trial infrastructure)

Aims

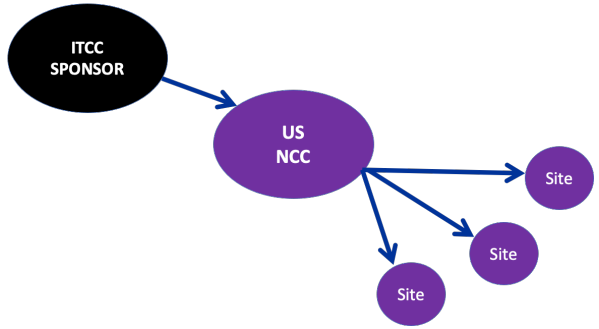
- To understand the regulatory issues of access in the clinical trials infrastructure whether the US NCI as a sponsor or a European academic organisation as as sponsor
- Agree on the ideal scenario with a **single database as the preferred option**

WG 2: Databases (accessing clinical trial infrastructure)

- **Accessing NCI/COG databases**:
  - **FWA** (Federal Wide Assurance)
    - The rules is that the site should have FWA in order to be able to access the NCI database because it is part of compliance with the organisation using an infrastructure that uses federal funding
    - **A proposed workable model** by which only the coordinating centre has a FWA without the individual sites needing to have FWA in place
      - Awaiting to hear of this can be taken forward
  - **Investigator registration process** (in NCI RCR system)
    - Largely resolved !!



WG 2: Databases (accessing clinical trial infrastructure)



COG sites to enter data into a ITCC –led trial (European database)

- Prior to being able to participate in the study, COG sites need to have all regulatory approval documents and SIV in place in accordance with FDA requirements
- Question around who takes responsibility for this in a European (non-NCI) sponsored study
  - European Sponsor/CTU
  - Responsibilities delegated to COG i.e., NCC as per ITCC international collaboration model
  - Hired CRO
- **Proposed solution for COG to develop capacity to act as an NCC**
  - **Personnel and Expertise needed under discussion**

- **Solution**
  - **COG to use Glo-B-NHL as the case study to develop the capacity to serve as an NCC**

WG 3: Data Protection Legislation

The challenge is entering or transferring study data to the US: considered under EU law to be a country which does not provide GDPR adequate protection

Objective: To define how a European sponsors could agree data transfer without breaching GDPR

Proposed Solution:

Art. 49 GDPR

Derogations for specific situations

WG 3: Data Protection Legislation

- **The Article 49 derogation** *does* seem to be a way forward but
  - it needs to be applied for on a study by study basis
  - some countries may locally require this to be reviewed and may not approve
  - Does not address the Subject's right to withdraw data and right to erasure
  - *It is known that the right to withdraw from trial participation is a standard procedure for clinical trials, however the right of data erasure is extremely problematic for clinical trial data*
- Other case studies to be reviewed:
  - . the use of DPIA to address explicit consent
- Monitor European Commission's review of GDPR
  - Note NCI are leading on policy discussion with European Commission on GDPR items
- **Survey the ITCC European NCCs for acceptability of Article 49 exemption language**

WG 4: Pharmacovigilance

- The group undertook a mapping across US, UK and EU
- Focus on
  - phase 2+ drug trials; not earlier phase trials or devices
  - Regulatory approval bodies:
    - FDA for the US,
    - EMA Scientific and Marketing for the EU,
    - MHRA for the UK

Ethics Authority	Institutional Review Board (Central)	CTIS Part 2 – per country	Research Ethics Committees (Central)
Investigational products	Investigational New Drug (IND) as defined in the US Code of Federal Regulations (CFR)	Investigational medicinal products (IMP) – as defined by EU regulation (Appendix I) IMPs are not necessarily unauthorized. Auxiliary medicinal product (AxMP) Minimal Intervention Clinical Trial	Investigational medicinal products (IMP) – as defined by UK regulation (Appendix I) IMPs are not necessarily unauthorized. Note: UK regulation will be changing at the end of 2023

	USA	EU	UK
Regulatory Approval (medication authorization, Pediatric Investigational Plan)	FDA	EMA - Scientific and marketing	MHRA
Regulatory Protocol Approval	FDA	Country specific regulatory authorities via Clinical Trial Information System (CTIS) (centralized procedure)	MHRA
Regulatory/Competent Authority Application	Investigational New Drug (IND) – only for studies with investigational agents that require IND application	Clinical Trial Application (CTA) via CTIS Part 1 – competent authority	Clinical Trial Application (CTA) Note: UK can use CTIS for a European application. Uses UK specific platform for member state applications

WG 4: Pharmacovigilance

Key differences:

- The definition of **Investigational products**:
  - Very different in the US vs the EU and the UK
  - US Investigational New Drug definition **(IND)** narrower compared to the UK and the EU definition of an investigational medicinal product **(IMP)**

- **Exemption criteria**:
  - the FDA does have IND exemption criteria; not every trial would be an investigational new drug trial;
  - no equivalent exemption criteria in the EU or the UK.

  There are a number of trials in the US that are not considered to be IND but in EU countries and the UK they are considered as investigational medicinal product trials (CTIMPs).

WG 4: Pharmacovigilance

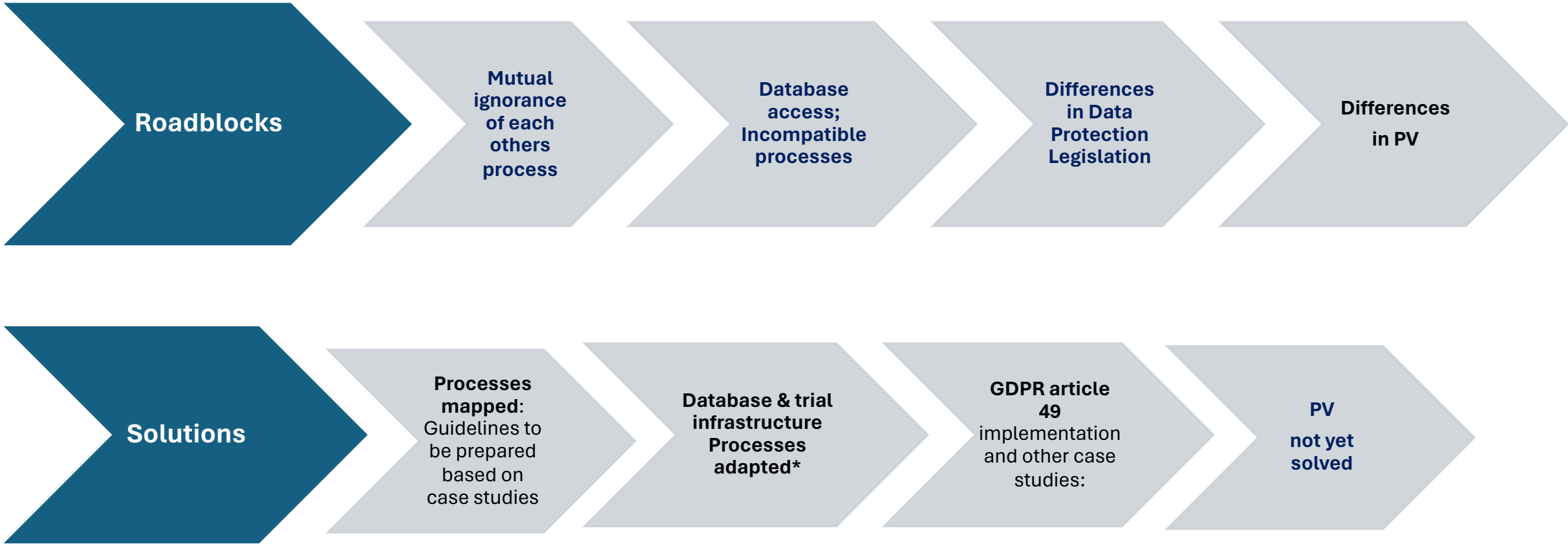
Key differences:

- **AE reporting** requirements **:**
  - for the investigational agents, all reasonably similar on SAE reporting timelines but:
    - For **commercially available agents** or **non-IMPs,**
      - US: the reporting required **is minimal.**
      - EU/UK the reporting is similar to the investigational agent
- **Causality**:
  - In the US the reporting investigator provides initial causality assessment but the sponsor makes the final decision
  - In the EU/UK, the investigator makes the decision and the sponsor can upgrade but not downgrade
- **Expectedness**:
- the US, the reference safety information and protocol specific exclusions are used.
- In the EU and the UK, there are no protocol specific exclusions;

Outcome is key difference in what needs to be reported to US vs EU/UK regulators

NOT YET RESOLVED

In Summary



*FWA requirement changes awaited

*NCI and EC discussions to overcome the data legislation anomalies

Conclusions

Academic cooperative groups can deliver trials of the design and data quality for filing BUT transatlantic collaboration needed *BUT*

- ***We need to help to enable the collaborations in transatlantic academic trials in paediatric oncology***
  - **It is resource intensive**
  - **Guidance documents need to be developed**
  - **Exemplar cases need to implement proposed solutions (i.e., GLO-B-NHL)**
  - **Need for on-going ITCC-COG-NCI-CTEP Working Group to continue to develop and test solutions**

- **Some problems need transatlantic/international consideration of how to achieve alignment of clinical trial legislation**

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Robert McLaughlin

Marieke Willemse

Stephanie Waldron

Jonathan Rubino

Rodney Howells

Emily Meier

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Jean-Luc Joannic

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Leah Williams

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Carole Lecinse

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