Introducing the Principle of Responsible Inclusion of Children in the Declaration of Helsinki (2024)

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Children's Oncology Group (COG) *Yu Alice et al, N Engl J Med 2010;363:1324-34.*

Research and studies preceeding the phase III trial

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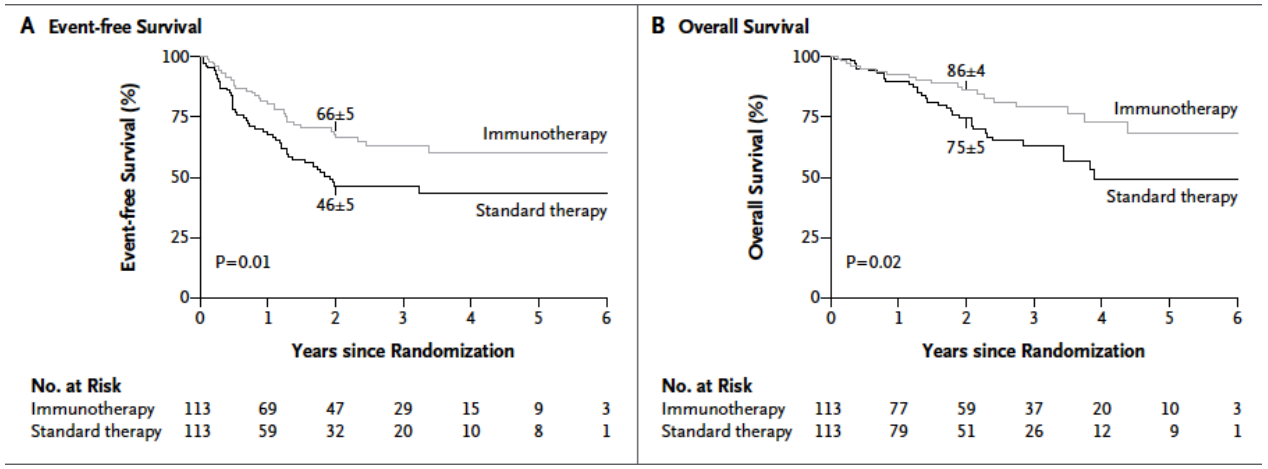


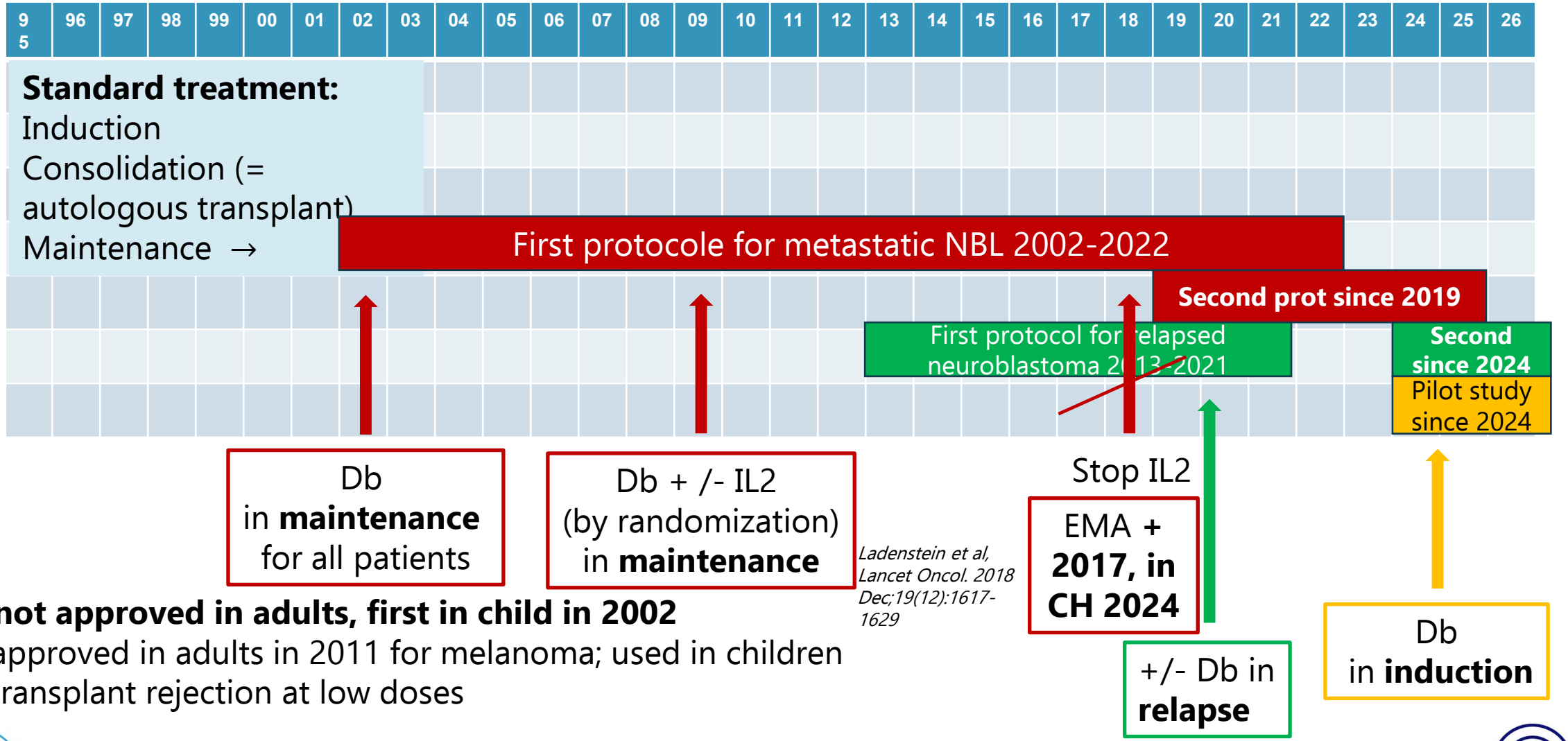
From 2001-2009: 226 eligible patients

- **Randomization** between ***standard maintenance treatment*** (retinoic acid) and ***immunotherapy*** (anti-GD2+GM-CSF+IL2) with retinoic acid
- Improvement of event-free survival (survival without relapse) by 22%
- Improvement of overall survival (including patients who have relapsed) by 10%

Courtesy from Prof. Maja Beck Popović

Dinutuximab beta (Qarziba^{R}) (anti-GD2), treatment of metastatic neuroblastoma

Courtesy from Prof. Maja Beck Popović



Db not approved in adults, first in child in 2002

IL2 approved in adults in 2011 for melanoma; used in children for transplant rejection at low doses

Table 1. Current challenges and potential solutions to promote pediatric research.

Stakeholders	Influencing factors and challenges	Potential solutions and opportunities
Pediatric patient[4,5,34]	• Rapid growth and development • Unique and changing healthcare needs • Low disease frequency and burden • Emerging diseases (e.g., COVID-19) • **Lifelong impact of early life conditions** • **Fetal origins of adult-onset diseases**	• Lifelong benefit of prevention and therapy of early life diseases • ↓ Chronic adult disease burden • ↓ Healthcare costs and utilization • ↑ Workforce productivity • Advocacy initiatives
Regulators and the public[4,23,24,33]	• Parental reluctance to enroll children in clinical trials • Recruitment • Ethical and safety concerns for clinical trials in children and pregnant women • Liability risk	• Community-based participatory research and parental engagement • Research network organizations • Centralized IRB approvals • Policies for inclusion of children in human subject research (e.g., NIH Inclusion Across the Lifespan Policy) • **Communicating science to the public**
Academic institutions and pediatric departments[11,13]	• Pediatric payer mix (↑ Medicaid recipients) • Institutional funds flow disadvantageous to pediatrics • ↑ Provider costs • ↑ Regulatory requirements • ↓ Institutional funding • ↑ Consumer expectations • Competing institutional missions (teaching, research, and patient care) • Impact of COVID-19	• Aligned strategic institutional funds flow • Institutional networks • Incorporation of pediatric research training and funding into departmental funding models • Adjusted compensation benchmarks and productivity models
Extramural federal funding[1–3,5,14]	• Limited federal pediatric research funding • Unequal distribution of federal pediatric research expenditures • ↓ Pediatric research career awards • Limited industry and foundation funding • Increased costs of pediatric clinical trials • High inflation • Impact of COVID-19	• Alignment of pediatric research funding with disease burden • NIH reporting requirements of pediatric research spending • Sustained growth of pediatric and perinatal federal research funding • Diversification of federal funding • Incentives and requirements for industry-sponsored pediatric trials • Advocacy for pediatric care and research funding
Investigator[14–22,33]	• Declining and aging pediatric scientist workforce • ↓ Physician-scientist training • ↑ Competing responsibilities (clinic, administration, education) • Individual career and lifestyle choices • ↑ Educational debt • Gender, equity and diversity challenges • Impact of COVID-19 on young and mid-level investigators	• Programs fostering inclusion of women and minorities in research • Integration of IMGs in the pediatric research workforce • Formal research training during residency and fellowship • Institutional and national research mentorship programs • Student debt forgiveness • NIH Loan Repayment Program • ↑ Early and mid-level federal pediatric research career awards • **Science communication training**
Experimental and trials design[7,10,32]	• Limited pediatric disease models available • Variation in pediatric and neonatal clinical criteria and outcome measures • Prolonged observation • Impact on neurodevelopment • Increased costs of pediatric clinical trials	• Defining pediatric disease and outcome parameters internationally • Collaborative science • National and international research networks
Pediatric drug and device developmental[8–10]	• Limited pediatric drugs and devices • Lack of FDA approval • Lack of safety and efficacy data for children	• Initiatives to improve pediatric clinical trial processes and device development ◦ SHIP-MD ◦ I-ACT for Children ◦ International Neonatal Consortium ◦ Best Pharmaceuticals for Children Act • Post-marketing surveillance and approvals
Dissemination, data sharing and reuse[6,25–29]	• Limited peer-reviewed publications of pediatric RCTs and systematic reviews • Lower quality of pediatric studies (small-scale, single-center) • Many uncompleted trials • Limited and delayed dissemination of results	• Reporting of clinical trial results in registries and data repositories • Data sharing and reuse • Enforcement of existing NIH and FDA policies ◦ NIH Policy on Data Sharing ◦ FDA Amendment Act ◦ **Communicating science**

The most important factors are highlighted as bold text.
I-ACT for Children Institute for Advanced Clinical Trials in Children, *IMG* international medical graduate, *NIH* National Institutes of Health, *RCT* randomized controlled trial, *SHIP-MD* System of Hospitals for Innovation in Pediatrics-Medical Devices.

Speer EM, Lee LK, Bourgeois FT, Gitterman D, Hay WW Jr, Davis JM, Javier JR. The state and future of pediatric research-an introductory overview : The state and future of pediatric research series. Pediatr Res. 2023 Jan 24:1–5. doi: 10.1038/s41390-022-02439-4. Epub ahead of print. PMID: 36694026; PMCID: PMC9873210.

Table 1. Key Challenges and Proposed Solutions in Pediatric Drug Development.

Challenge	Description	Proposed Solutions
Underfunding	Limited investment in pediatric research compared to adult-focused R&D.	Increase funding allocations (e.g., NICHD), adopt alternative funding models (e.g., venture philanthropy).
Regulatory Complexity	Stringent and often fragmented regulatory requirements across regions.	Harmonize global regulations (e.g., align FDA, EMA, and PMDA frameworks), streamline pediatric study plans.
Ethical Barriers	Heightened safety concerns, challenges in obtaining consent/assent, and long-term follow-up requirements.	Develop patient-centered trial designs, leverage real-world data for external controls.
Limited Advocacy and Public Awareness	Lack of organized and well-funded advocacy compared to adult conditions.	Strengthen patient advocacy groups, use digital storytelling to amplify patient and family voices.
Industry Disengagement	Closure of pediatric research programs and focus on more profitable adult markets.	Introduce stronger incentives (e.g., exclusivity extensions), promote public-private partnerships.
Data Gaps and Infrastructure	Insufficient real-world data and interoperable systems for pediatric research.	Build comprehensive registries, promote data-sharing consortia, and standardize data formats.
Logistical Challenges in Trials	Small sample sizes, heterogeneity of pediatric populations, and limited trial networks.	

Singh, K., Franson, T., McCune, S. *et al.* Breaking the silence: challenges and opportunities in pediatric drug development. *Pediatr Res* **98**, 807–812 (2025). https://doi.org/10.1038/s41390-025-03923-3

Regulatory Measures Promoting Paediatric Research

EU

- Clinical Trial Regulation (2014): protection of research participants
- Paediatric Regulation (2006): obligation to invest in paediatric investigation plan (PIP) and incentives (6 months for all indications)
- Orphan Regulation (2000): incentives (2 years for the orphan use)

USA

- Innovation in Pediatric Drugs Act (2024): helds pharmaceutical companies accountable and provides additional funding for pediatric research
- Best Pharmaceuticals for Children Act (BPCA) (2007/2002)
- Pediatric Research Equity Act (PREA) (2007/2003): Obligation to present a pediatric assessment for any “new” drug unless a waiver or deferral has been obtained and incentives

From DoH (2013)

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Strict subsidiarity

To DoH (2024)

Individual, Group, and Community Vulnerability

Responsible inclusion

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.

From DoH (2013)

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

To DoH (2024)

Free and Informed Consent

25. Free and informed consent is an essential component of respect for individual autonomy. Participation by individuals capable of giving informed consent in medical research must be voluntary. Although it may be appropriate to consult family members or community representatives, individuals capable of giving informed consent may not be enrolled in research unless they freely agree.

28. In medical research involving human participants incapable of giving free and informed consent, the physician or other qualified individual must seek informed consent from the legally authorized representative, considering preferences and values expressed by the potential participant.

    Those 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.

29. When a potential research participant who is incapable of giving free and informed consent is able to give assent to decisions about participation in research, the physician or other qualified individual must seek that assent in addition to the consent of the legally authorized representative, considering any preferences and values expressed by the potential participant. The potential participant's dissent should be respected.

30. Research involving participants who are physically or mentally incapable of giving consent (for example, unconscious patients) may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician or other qualified individual must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the research may proceed without informed consent provided that the specific reasons for involving participants with a condition that renders them unable to give informed consent have been stated in the research protocol and the research has been approved by a research ethics committee.

    Free and informed consent to remain in the research must be obtained as soon as possible from a legally authorized representative or, if they regain capacity to give consent, from the participant.

Free and informed consent

To DoH (2024)

Meaningful engagement

6. Medical research involving human participants is subject to ethical standards that promote and ensure respect for all participants and protect their health and rights.

   Since medical research takes place in the context of various structural inequities, researchers should carefully consider how the benefits, risks, and burdens are distributed.

   Meaningful engagement with potential and enrolled participants and their communities should occur before, during, and following medical research. Researchers should enable potential and enrolled participants and their communities to share their priorities and values; to participate in research design, implementation, and other relevant activities; and to engage in understanding and disseminating results.

Nothing for the patients without the patients, their parents and their communities

See also ICH-GCP(E6)(R3) (2025) and the CIOMS International Ethical Guidelines for Health-Related Research Involving Human Participants (2016)

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)

(43) The members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have agreed on a detailed set of guidelines on good clinical practice which is an internationally accepted standard for designing, conducting, recording and reporting clinical trials, consistent with principles that have their origin in the World Medical Association's Declaration of Helsinki. When designing, conducting, recording and reporting clinical trials, detailed questions may arise as to the appropriate quality standard. In such a case, the ICH guidelines on good clinical practice should be taken appropriately into account for the application of the rules set out in this Regulation, provided that there is no other specific guidance issued by the Commission and that those guidelines are compatible with this Regulation.

(83) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter and notably human dignity, the integrity of the person, the rights of the child, respect for private and family life, the protection of personal data and the freedom of art and science. This Regulation should be applied by the Member States in accordance with those rights and principles.

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:

(a) the informed consent of their legally designated representative has been obtained;

(b) the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;

(d) no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;

(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;

(f) the clinical 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;

(g) there are 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.

2. The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.

3. If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

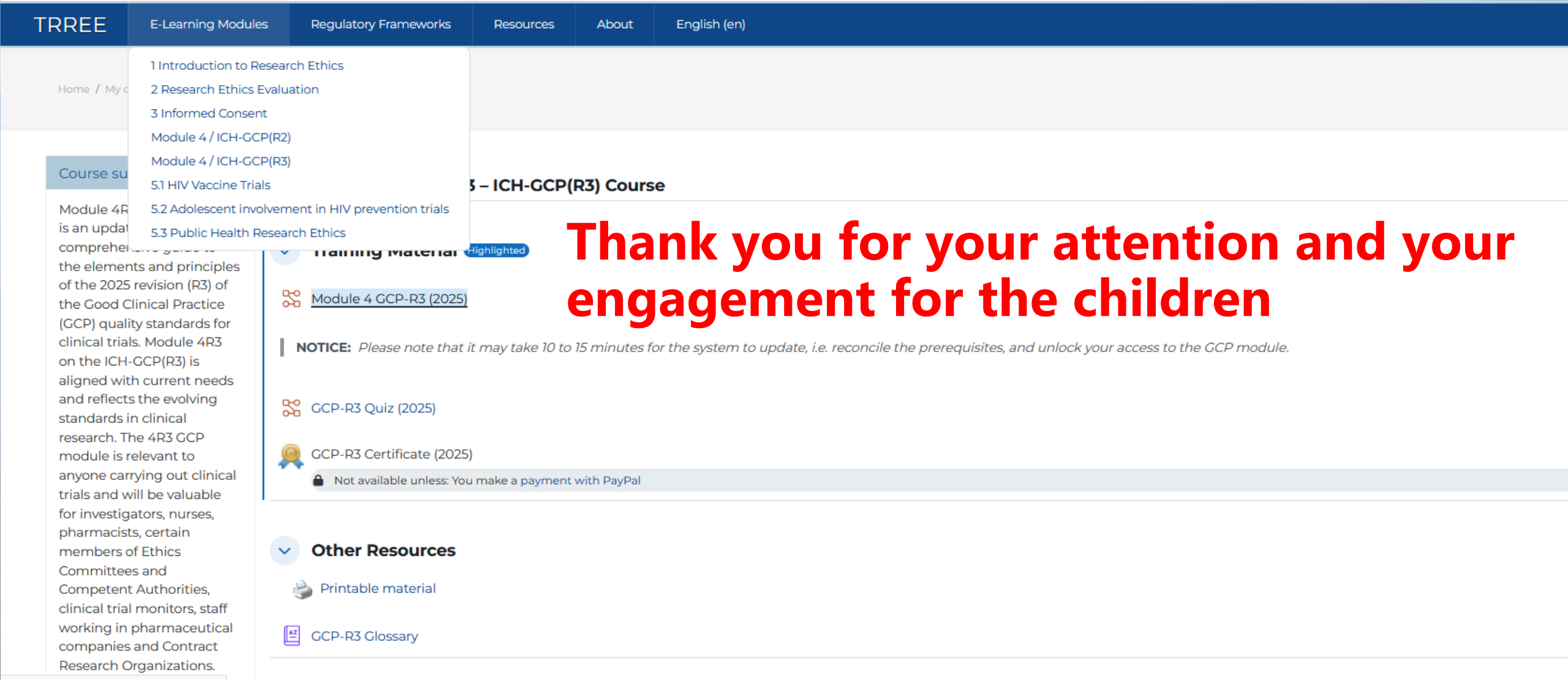
Next Step: Making the Best of the Flexibility and Critical Thinking at the Core of ICH-GCP(R3) to Develop Patient-Centered Trial Designs

- **Fit-for-purpose Technologies**

ICH-GCP(R3) encourages the utilization of fit-for-purpose technologies as a new strategic approach to integrating new technologies into clinical trials based on their alignment with specific trial objectives, patient needs and regulatory requirements, recognizing new data sources (e.g., ePRO tools and wearables), and facilitating the inclusion of wider and more diverse participant populations in clinical trials.

TRAINING AND RESOURCES IN RESEARCH ETHICS EVALUATION

https://elearning.trree.org/



Thank you for your attention and your engagement for the children