ACCELERATE Annual Conference 2021

Topic: RACE for Children Act – Early impressions and what are the best metrics to measure its success

Executive summary

During the 2021 Annual ACCELERATE conference, participants were split in small groups to work on five topics related to the development of innovative therapies for children and adolescents with cancer in order to identify issues and propose solutions. Proposals were discussed thereafter in plenary sessions to define actions. An executive summary has been prepared for each topic.

Disclaimer: The views expressed in this Executive Summary are the personal views of the participants of the Breakout Session and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations, including ACCELERATE, with which the authors are affiliated.

Chairs: Susan Weiner (Children’s Cause), Andy Kolb (Nemours Al du Pont Hospital for Children), Elly Barry (Pfizer), Cormac Owens (Children’s Health Ireland at Crumlin)

1. Rationale

The FDA Reauthorization Act of 2017, section 504, which incorporates the Research to Accelerate Cures and Equity (RACE) for Children Act, came into effect on August 18, 2020. This law aims to promote research into, and development of, new treatments for children with cancer. It gives FDA the authority to require companies to conduct the paediatric evaluation of a new drug or biological product intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be “substantially relevant to the growth or progression of a paediatric cancer.” FDA published in 2019 a list of molecular targets that, on the basis of adequate data, determined to be substantially relevant to the growth and progression of a paediatric cancer and that may trigger the paediatric investigation requirement. The new regulatory environment is intended to promote the paediatric development of novel anti-cancer drugs through their mechanism of action instead of their adult indication. It aimed to accelerate research and start paediatric investigations earlier in cancer product development. Considering the number of oncology medicinal products under development in adults and the rarity of paediatric cancers, prioritization will be crucial to meet the needs of children.

The aim of this session was to discuss what stakeholders’ first impressions and experiences were after the recent implementation of the RACE for Children Act and to begin to define metrics of its success.
2. Topics discussed

**What are the early impressions by stakeholders?**

- The FDA has received more inquiries than anticipated, with 151 iPSP reviews and 21 planned paediatric trials. Sponsors are committing to trials earlier in the development of a medicinal product that might have been expected prior to the RACE Act.
- Waivers issued for inappropriate trials may come too late for some classes of new agents.
- It is a concern that trials in rare subgroups may take too long to yield meaningful data. Therefore, there is a need for guidance on trial designs that can meet regulatory requirements while minimizing the number of patients required.
- There is also a concern that companies’ enthusiasm to conduct RACE trials may be determined by the estimates of the potential market value of an asset for adult malignancies.
- The FDA reports that companies are influenced by recommendations from ACCELERATE’s Paediatric Strategy Forums to guide prioritization for the development of drugs for children in high value targets. Enhanced preclinical testing data from, e.g., ITCC-P4 and ACT4PED (the FNIH PPP/PPTC initiative), will further help for prioritization purposes.
- Many industry partners appreciate early discussions with FDA. Cluster calls (with the EMA, FDA and other regulatory agencies) and Scientific Advice (that can reference/incorporate FDA guidance) and mechanisms for improved alignment are very welcome.
- Stakeholders are frustrated by the need to conform to conflicting regulatory requirements regardless of the shared goal to benefit children.
- Some positive indirect outcomes of the enactment of RACE include the generated attention and enthusiasm for paediatric oncology (positive publicity). Furthermore, more discussions are occurring between academia and industry on paediatric development for novel therapies, and there are more paediatric development groups with specific paediatric oncology expertise forming within companies.

**What are the metrics to inform future evaluations?**

<table>
<thead>
<tr>
<th>Short-term</th>
<th>Med-term</th>
<th>Long-term</th>
<th>Success beyond the RACE Act</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new medically and scientifically appropriate trials</td>
<td>Number of trials that detect signal of activity</td>
<td>Number of drugs approved for use in children</td>
<td>Pursuit of science-driven paediatric-centric drug development</td>
</tr>
<tr>
<td>Increase in industry-academia interactions</td>
<td>Phase 1/2 studies that lead to an indication</td>
<td>Time between adult approval and paediatric indication approval</td>
<td>Repurposing abandoned drugs for paediatric cancers</td>
</tr>
<tr>
<td>Increase in industry-funded academic trials</td>
<td>Number of definitive efficacy trials</td>
<td>Basket and Cooperative Group Master platform trial development (efficient mechanisms to test multiple targeted therapies in a single trial)</td>
<td>A strategy to develop drugs with a signal in children but abandoned in adults</td>
</tr>
<tr>
<td></td>
<td>Feasibility of iPSP/PIP trials</td>
<td>Use of Scientific Advice and Cluster Call process to navigate alignment issues</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to first-in-child study, Time to progress through phases</td>
<td>Number of paediatric patients cured</td>
<td></td>
</tr>
</tbody>
</table>

www.accelerate-platform.org | contact@accelerate-platform.org
What are the challenges and remaining issues?

- Waivers based on sound scientific/medical rationale are important and appropriate. It would be useful, if possible, for waivers granted to be more transparent/granular. If information were publicly available, time could be saved and resources refocused, although there might be conflicting confidentiality issues.

- So far, industry partners are engaging academic paediatric oncologists with adult data only and little if any paediatric pre-clinical data and with different expectations for early development. A guidance is needed to determine a sufficient level of pre-clinical evidence to advise drug development (ITCC-P4 - PPTC publication currently in press).

- Prioritisation is key, as there are too many molecules to evaluate in children. ACCELERATE Paediatric Strategy Forums (PSFs) are the gold standard for prioritization. Prioritisation could be facilitated prioritised by a list of diseases and targets with linked data packages/research, created by molecular profiling platforms with pre-clinical work carried out by the pharmaceutical industry and academia. Furthermore, updating prioritisation after a Paediatric Strategy Forum is necessary to respond to emerging science. There are some concerns that the overall acceptance of the importance of PSFs could create a bottleneck for drug development – this may need to be addressed.

- It is paramount to avoid competition when too many trials with similar patient enrolment criteria for drugs within the same class or for the same molecular targets exist. A consensus round table approach to create guidance for the “Right patients, right drugs” paradigm is needed, with engagement and endorsement by advocates, support for the pharmaceutical industry, and clear communication for academia and regulators.

- The lack of alignment of regulations poses an important and continuing challenge. Even if a positive signal is detected, no incentive or requirement exists for companies to conduct follow up paediatric trials after RACE trial requirement is met. Misalignment of PIP and iPSPs timing and requirements impede international planning of trials as does conflicting advice from FDA and EMA about trial requirements. The greater use of Cluster Calls/Common Commentaries, requested by the pharmaceutical industry, should improve alignment.

3. Next steps & Output

- The use of clear metrics to evaluate (and possibly refine) the implementation of the RACE for Children Act is key.
- One of the most important metrics is the time lapse between first patient recruited into adult trials and the first patient recruited to a paediatric trial for a given drug.
- Every effort should be made to aim for alignment between the regulatory processes in the US and EU