ACCELERATE Annual Conference 2022

**Topic:** When is a Randomized Clinical Trial not required for registration?

**Executive summary**

*During the 2022 Annual ACCELERATE conference, participants were split in small groups to work on four topics related to the development of innovative therapies for children and adolescents with cancer in order to identify issues and propose solutions. An executive summary has been prepared for each topic.*

*Proposals were discussed in the Plenary Session of the Annual Conference to define actions. The ACCELERATE 2022 work plan describes the objectives of ACCELERATE on this 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:** Elizabeth Fox (St. Jude Children's Research Hospital), Dominik Karres (European Medicines Agency), Alberto Pappo (Paediatric ODAC / St. Jude Children's Research Hospital), Andy Pearson (ACCELERATE Paediatric Strategy Forum Oversight Committee Chair).

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1. **Rationale**

Randomised clinical trials are acknowledged globally to be the gold standard to generate evidence on efficacy of new therapies or therapeutic approaches. However, recently certain innovative drugs have been approved without a randomised clinical trial under specific circumstances. This has been predominantly when there was an exceptionally rare population with outstanding activity of the new agent. Some examples include:

- **Tisagenlecleucel**, a CAR-T cell therapy that received FDA (2017) and EMA (2018) approval for children with refractory/relapsed B-cell acute lymphoblastic leukaemia, following the results of a single-arm trial (n=63) with CR of 83%.
- **Larotrectinib**, an NTRK inhibitor, that was approved by FDA (2018) and EMA (2019) for refractory NTRK-positive solid tumours. Approval was achieved with data from three single-arm trials in adults and children (n=12) with an ORR of 75%.
- **Selumetinib**, a MEK inhibitor that received approval for inoperable plexiform neurofibromas (in patients with neurofibromatosis type I) with data from a single-arm trial (n=50) with ORR of 66%, at FDA (2020) and EMA (2021).

In parallel, there are ongoing initiatives to define how to introduce big data and real-world data in the regulatory decision-making processes.
The main two questions to be addressed are:

1. How can we optimize the current drug development plans for licensing for a paediatric cancer indication when randomized trials are not feasible?
2. How can academia, industry, regulators, payers, and patient advocates work together on this topic?

2. Topics discussed

a) Framework

The unifying goal is to rapidly develop, evaluate, and achieve regulatory and payer approval (authorization) for effective therapies to ensure broad and equitable access to the most effective therapies for children and adolescents with cancer.

The evidence needs to satisfy patients, families, and advocates, academic investigators, industry partners and sponsors, regulatory agencies, and payers.

Currently, randomized clinical trials (RCTs) are the gold standard for efficacy testing, but there may be room to improve comparator data without randomization.

b) When is an RCT not feasible?

Feasibility is defined differently among stakeholders demonstrating the need for early multi-stakeholder discussion. From a regulatory perspective, feasibility is context-specific (individual trials and populations).

Some of the products that have so far been approved in children/adolescents without paediatric-specific RCT are histology-agnostic trials that simultaneously enrolled children and adults. The approval in children was based on well controlled trials in adults coupled with pharmacokinetic, safety and tolerability in children for cancer that are same in adults and children (including those that are very rare in children). Approval followed single arm trials with large effect size in overall response rate (primary endpoint) and demonstration of duration of response (secondary endpoint).

During the discussion, there seemed to be a consensus that robust evidence can be gathered from alternative trial designs when:

- The size of the population is small (rare diseases, small well-defined subsets)
- Major treatment effect is postulated based on pre-clinical and early clinical data
- Lack of equipoise between the arms
- Major differences in toxicity expected based on prior clinical experience

b) Improving comparator data without randomization
### Innovative trial designs

- Platform trials with common control groups
- Use of extrapolation
- Bayesian method to incorporate adult and other data
- Reduction of the evidentiary threshold (relaxing Type I error) may reduce sample size but may not be *feasible* in rare cancers in children.
- Randomized Phase 2 Trials, using novel endpoints, could be key to address some of the difficulties.

### Increase the strength and depth of external controls / real world data

- Well defined populations
- Ability to match for patient characteristics and response assessment
- Scope and availability of patient level data
- Acknowledge the complexity and effort to obtain high-quality real-world data
- Assessment of robust registry data efforts ongoing or planned

### 3. Next steps & Output

A high priority is to increase the capacity of high-quality real-world data that can be utilized as robust comparator. Early input from all stakeholders (including Health Technology Assessment bodies) is crucial.

ACCELERATE could serve as catalyst to define criteria for collection and validation of high-quality real-world data by convening stakeholders and this could lead to real-world data registries.