# ACCELERATE – Five years accelerating cancer drug development for children and adolescents

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Review

# ACCELERATE – Five years accelerating cancer drug development for children and adolescents

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**Abstract** Rapid evaluation and subsequent regulatory approval of new drugs are critical to improving survival and reducing long-term side-effects for children and adolescents with cancer. The international multi-stakeholder organisation ACCELERATE was created to advance the timely investigation of new anti-cancer drugs. ACCELERATE has enhanced communication and understanding between academia, industry, patient advocates and regulators. It has promoted a mechanism-of-action driven drug development approach and developed Paediatric Strategy Forums. These initiatives have facilitated prioritisation of medicinal products and a focused and sequential strategy for drug development where there are multiple potential agents. ACCELERATE has championed the early assessment of promising drugs in adolescents through their inclusion in adult early phase trials. ACCELERATE has strongly supported alignment between the European Medicines Agency and the US Food and Drug Administration and identification of unmet medical needs through multi-stakeholder collaboration. Early engagement between all stakeholders in the development of new drugs is critical. Innovative clinical trial designs are required, necessitating early discussion with sponsors and regulators. Amplifying the patient advocate voice through inclusion across the drug development continuum will lead to better, patient-centric trials. By these means, children and adolescents with cancer can maximally and rapidly benefit from innovative products to improve outcomes and reduce burdensome sequelae.


## 1. Introduction

Despite substantial advances made through international, collaborative multidisciplinary clinical trials, recently the improvement in the survival rates for childhood malignancies has plateaued [1]. Furthermore, severe acute toxicities of many paediatric oncology regimens and the long-term side-effects of therapy are increasingly apparent and are substantial [2,3]. Thus, there remains an unmet need for drugs with novel mechanisms of action that not only improve survival but also reduce the acute and long-term burden of therapy.

Many steps are needed to introduce a new drug into standard of care for paediatric cancer [4]. The first is the scientific discovery of the genomic, proteomic, metabolic or immunological drivers responsible for tumour formation and progression may be leveraged to develop new drugs. These may have been already developed for adult malignancies; however, a specific drug discovery process addressing unique targets that drive paediatric cancers may be required. After relevant preclinical evaluation, drugs then require evaluation in early phase clinical trials in a paediatric population ideally as rapidly as possible, with a regulatory plan comprising a Paediatric Investigation Plan (PIP) in the European Union and initial Paediatric Study Plans (iPSPs) in the United States. If early phase results support further evaluation, late-stage studies, as outlined in the agreed PIP, may be performed, aiming at regulatory approval (marketing authorisation). Importantly, agreement for national adoption and reimbursement is the next step to allow access for all children and adolescents who are potentially expected to benefit from the medicinal product (Fig. 1). This process has failed children with cancer; while there have been great advances in scientific discovery, roadblocks to clinical translation for children persist and include limited early access to investigational drugs, leading to subsequent lack of assessment and approval and insufficient access to agents that have achieved marketing authorisation.

Evaluating new anti-cancer drugs in children and adolescents is critical ethically, and enrolment in early phase clinical trials is an option to be proposed to the patient and his or her parents or carers. Therapeutic intent is central and protocols should be designed with the aim of minimising aspects related to distress for patients. The way forward is that early drug development in children should be efficient based on scientific information whilst abiding by ethical constraints.

Although the European Medicines Agency (EMA) has approved over 169 anti-cancer medicines for use in adults between 1995 and 2021, only 16 new products received marketing authorisations in children (GV unpublished analysis). This is the result of anti-cancer drug development almost exclusively focused on adult conditions with larger patient populations. The small paediatric population renders drug development more challenging. Therefore, paediatric product development has often been waived or delayed, resulting in poor access for children to innovative drugs.

In 2015, 'Creating a unique multi stakeholder paediatric oncology platform to improve drug development for children and adolescents with cancer' was published [5]. The manuscript highlighted that seven years after the launch of the European Paediatric Medicines Regulation [6] (which had brought expansions of

expertise in paediatric drug development, increases in paediatric clinical trials, paediatric formulation development and a rise in marketing authorisations in Europe for children), limited progress had been made in paediatric oncology drug development. The dearth of early phase studies of new drugs was a major unmet need. Against this landscape, ACCELERATE was created as a multi-stakeholder platform with equal involvement of clinicians/researchers, regulators from the EMA, patient advocates and industry representatives. Two important changes to the orthodox approach were needed to accelerate the development of new medicines for the maximum benefit of children with cancer. The first was that the development of anti-cancer medicines for children should be driven by an agent's mechanism of action (MOA) rather than by its adult condition. The second was that new drugs with high potential for benefit must be quickly assessed and evaluated in children and adolescents early in their development. It was foreseen that implementing these changes was critical in helping overcome the current deficits where 54% of oncology medicines receive regulatory waivers for paediatric assessment in Europe despite having mechanisms of action potentially relevant to paediatric tumours [7]. Such changes would also reduce the unacceptable delay (median 6.5 years) from the initiation of first-in-human trials of FDA approved drugs to the start of first-in-child trials [8]. In light of the need for rapid introduction of new medicines for children with cancer into frontline care, collaboration between stakeholders was highlighted as a key priority.

In 2020, the international landscape significantly changed with the implementation of the Food and Drug Administration (FDA) Reauthorisation Act of 2017, section 504, which incorporates the Research to Accelerate Cures and Equity (RACE) for Children Act [9]. The RACE Act requires companies to evaluate pharmacokinetics, safety and preliminary efficacy of their anti-cancer medicines in children if their target [10] is relevant to the growth and progression of paediatric malignancies. The European Commission is currently launching the revision of the European Union (EU) Paediatric and Orphan Regulations as part of the new EU Pharmaceutical Strategy [11]. Health Canada and Therapeutic Goods Administration (Australia) are starting to work in their jurisdictions where neither mandates nor incentives for paediatric medicine development exist. These changes will facilitate science-driven (instead of adult indication driven) paediatric oncology drug development that will better meet the needs of patients.

Six years after the initial publication first framing ACCELERATE, this article highlights the achievements of ACCELERATE, a truly multi-stakeholder initiative, the changes in the landscape of paediatric oncology drug development and the challenges remaining.

## 2. Landscape in 2014

In 2014, although the overall survival for childhood cancer had improved in high-income countries, 20% of children still died and certain subgroups continued to have dismal outcomes. In addition, the burden of therapy had increased in long-term survivors leading to chronic and disabling morbidities [12]. Although molecularly targeted therapeutics were available for adults, very few had been advanced in children or integrated into frontline paediatric therapy (Table 1).

For parents and the rest of the childhood cancer community, there was enormous frustration at the lack

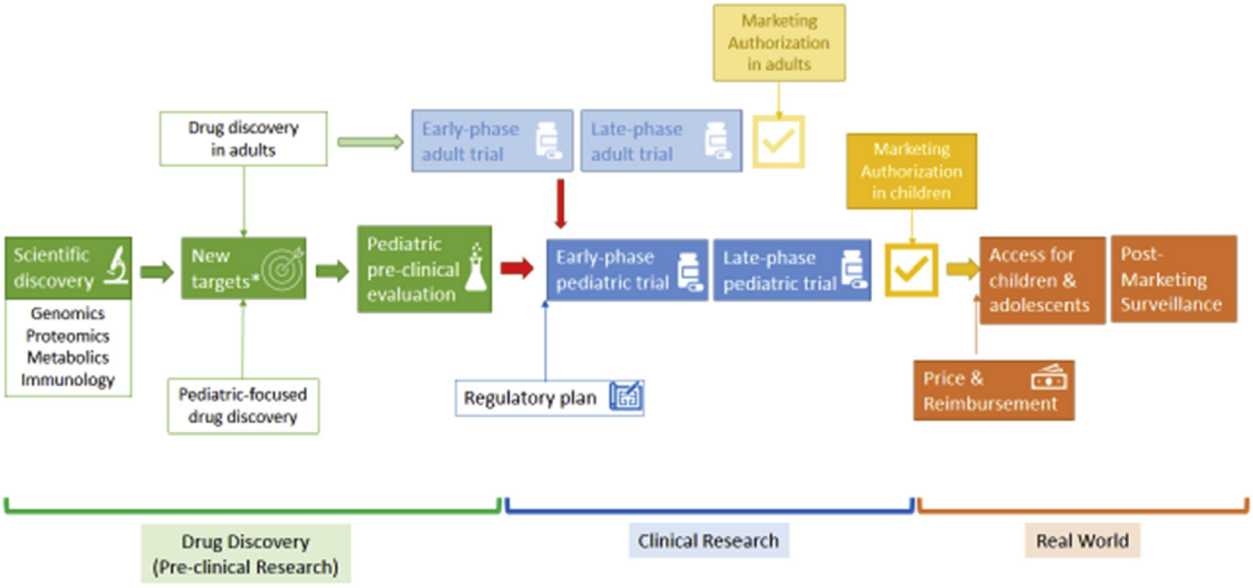


Fig. 1. Pathway for drug development for children's malignancy.

Table 1
Challenges in Paediatric Oncology Drug Development 2015 and situation in 2021.

| Topic | 2015 | 2021 |
|---|---|---|
| Drug development | Driven by the adult condition (not by science, mechanism of action or unmet need) | Change to a mechanism of action approach<br>RACE Act in US [9], change of Class Waiver List in Europe [19] |
| Multi-stakeholder collaboration | Lack of true understanding and communication between the stakeholders (Industry, Academia, Regulators, Patient Advocates) | Increase in multi-stakeholder interaction, especially within ACCELERATE Paediatric Strategy Forums |
| Molecularly targeted therapies | Very few assessed in paediatrics and integrated into front-line therapy - BCR-ABL | Increasing inclusion in front-line therapy - ALK [56,57], BRAF [58], TRK inhibitors [59] |
| Immunotherapy | New and effective therapies approved for adult cancers, none for children | Blinatumomab, dinutuximab, dinutuximab beta, CAR T-Cells approved for paediatric malignancies |
| Early-phase trials | In Europe early phase trials delivered by ITCC increased: from one in 2007 to 12 in 2013 | In Europe, 26 open studies in ITCC<br>One multi-arm (now 15 arms) combination phase I/II platform trial (ESMART) [60] |
| Number of PIPs | The expected increase after change in EU regulation not materialised<br>17 PIPs in 2007–2013 | 124 PIPS in oncology after 2013<br>141 PIPS in oncology 2007–2021 |
| Approved anti-cancer agents with at least one paediatric indication | 9 | 19 |
| PIP strategy | Multiple PIPs in very rare paediatric populations | Focused and sequential strategy for development of novel agents has been developed [31] |
| Access of AYAs to adult trials | PIPs for conditions in adolescents were not possible to complete (rarity in the population)<br>Adolescents were denied access to adult clinical trials investigating innovative drugs when suffering from the same malignancy, such as metastatic melanoma | Increasing the inclusion of adolescents in adult trials and age inclusive marketing authorisation using of extrapolation [61–63] |
| Methodology innovation | Lack of innovative trial designs | Increasing the use of platform trial designs – ESMART [60], Pedal/EUPAL [64], GloBNHL, Paediatric MATCH [65] |
| Incentives | No incentives to develop drugs against specific paediatric targets | No incentives to develop drugs against specific paediatric targets |

of new drugs for children and the absence of a strategic approach. Specifically, the dearth of available options at time of relapse, the very slow pace of progress and the perceived absence of urgency, especially in advancing new drugs to frontline therapy, were major concerns. There was an apparent lack of coordination and inequality between Europe and the US in innovative trials, options for therapy and reduced access to novel drugs in Europe. Parents were understandably dissatisfied, which led to some parents in Europe taking their children to the US for treatment. Like-minded parents in different countries were starting to gain knowledge and communicate with each other about the 'big picture' challenges, realising that families could drive change through patient advocacy groups lobbying policy makers.

In 2007, the European Paediatric Regulation provided the regulatory framework and tools for drug development for children and adolescents, including those with cancer. It aimed to increase the availability of authorised medicines for children by generating safety and efficacy data via high-quality ethical paediatric research [6]. The Paediatric Regulation stipulated that pharmaceutical companies should have a PIP or waiver approved by the Paediatric Committee (PDCO) of the EMA before seeking marketing authorisation for new medicine. PIPs include a comprehensive study plan aiming to generate age-appropriate safety and tolerability, pharmacokinetic and efficacy data for medicines to obtain approval for specific indications in children. However, waivers for PIPs could be granted on three grounds: i) if the product is likely to be not effective or unsafe in children; ii) if the condition or disease does not occur in children or iii) if the product does not represent a significant benefit over existing treatments. Completed PIPs, regardless of the results of the trials, are rewarded with a six-month extension of the medicine's Supplementary Protection Certificate (SPC), if study results are reflected in the Summary of Product Characteristics (SmPC). In the case of an orphan designated medicine, an additional two-year extension of the 10-year market exclusivity is awarded. However, to reap these economic

benefits an approval in an adult indication is ultimately required.

In 2011, the Commission reported improvement in development of paediatric medicines generally but not for anti-cancer medicines where the expectation for PIPs had not been met [13]. The number of submitted and agreed PIPs in oncology increased overall, but this had not translated into equal high numbers of successfully completed PIPs. This outcome highlights the challenges in paediatric oncology drug development, which were perceived as being dependent upon and linked to the adult condition, which commonly do not overlap between populations. In this view, not unexpectedly, there had not been an increase in the number of successful early phase trials that translated into drugs moving into frontline.

From 2007 to 2012, 45 PIPs were approved for central nervous system tumours, leukaemia, lymphoma, solid tumours and supportive care, but these approvals did not include any paediatric malignancies that occur nearly exclusively in children, such as neuroblastoma [14]. This outcome is the result, as previously stated, of drug development being driven by the adult condition. Although the number of drugs in early phase clinical trials delivered by the Innovative Therapies for Children with Cancer Consortium (ITCC) [15] had increased from one in 2007 to 12 in 2013 (half being conducted to comply with regulatory requirement of PIPs), many children still lacked access to novel therapies at the time of relapse. Furthermore, there was still a lack of early access to new drugs for both preclinical and clinical trials. As pharmaceutical companies started investing more resources into the development and delivery of PIPs, one challenge highlighted was the conflict of multiple approved PIPs in very rare paediatric populations [13]. Clinical trials associated with many of these same-in-condition or same-in-class PIPs were highly unlikely to be completed in view of the relative rarity of the specified paediatric tumour type. Additionally, many trials associated with PIPs for conditions in adolescents were not completed, again because of the rarity in the population, e.g. malignant melanoma. In such cases it would have been more efficient to include adolescents into the adult trials that led to an indication. Companies also found that the lack of alignment and differing timelines between US and European regulatory requirements presented significant challenges, resulting in the delay of regulatory submissions and opening of early clinical trials.

Very importantly, there was a lack of true understanding and communication between the stakeholders: academia, industry, patient advocates and regulators – who often worked in isolation. This failure was in part due to a paucity of opportunities for exchange of ideas, resulting in a number of misconceptions, misinterpretations and substantial delays to the detriment of young patients. There were missed opportunities to explore new drugs of potential relevance for paediatric malignancies. Furthermore, a dearth of innovative trial designs and no new incentives to develop drugs against specific paediatric targets led to needs remaining unmet. Together, these factors impeded progress to improve survival and reduce side-effects.

## 3. ACCELERATE platform development

In 2011, a programme of bi-annual paediatric oncology multi-stakeholder workshops was organised by the Cancer Drug Development Forum with the European ITCC consortium and the European Society for Paediatric Oncology (SIOP Europe), within the framework of an EU-funded project, the European Network for Cancer Research in Children and Adolescents (ENCCA). At the second workshop, the need for a multi-stakeholder platform was recognised to facilitate the timely and appropriate development of innovative drugs for children and adolescents with cancer. Thus, in 2016, the multi-stakeholder organisation 'ACCELERATE' was established as a transparent forum to discuss and address overarching issues in this critical space. The central premise of the platform was the involvement of the four stakeholder groups as equal partners and to facilitate the interaction between academia, industry, patient advocates and regulators; the phrase 'no blame, no shame' was adopted as a key principle. ACCELERATE's mission is patient-centred and problem-solving and aims to accelerate science-driven development of paediatric oncology drugs, facilitate international cooperation and collaboration between all stakeholders and improve early access to new anti-cancer drugs in development for children and adolescents. Very rapidly, the U.S. FDA joined the platform, and patient advocates and academics from around the world also became leading members of ACCELERATE.

Three main pillars of ACCELERATE activities are the Annual Conference to share information and identify timely issues and topics; working groups to analyse and deliver solutions to the identified issues and Paediatric Strategy Forums, which facilitate prioritisation of drug pipelines (Fig. 2). There have been seven Working Groups (Table 3). The first three have completed their tasks and the others are ongoing. Some indicators of the output of ACCELERATE are depicted in Table 4.

In June 2018, ACCELERATE was reorganised to strengthen the international cooperation and improve the global development of new paediatric oncology drugs and was incorporated as a not-for-profit organisation led by SIOPE and ITCC. A Steering Committee was established with a chair, senior clinical advisor and five colleges with four representatives in each: academia,

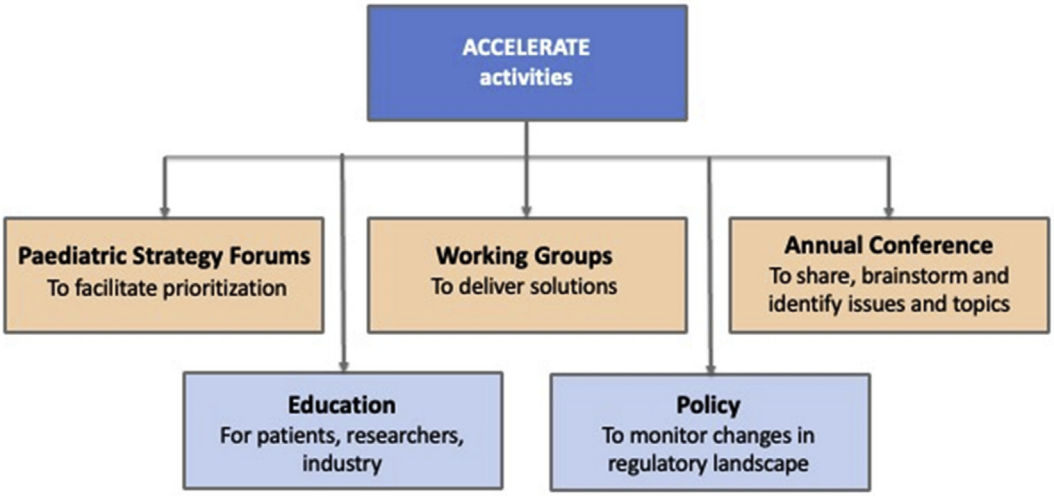


Fig. 2. Activities of ACCELERATE.

patient advocacy, industry, regulatory agencies and personal appointments by virtue of their specific skills. In 2021, 326 participants at the virtual annual conference came from 26 countries, including several European countries, Australia, Canada, Israel, Japan, Mexico and the United States.

ACCELERATE is funded by public grants and grants from non-profit organisations (e.g. Andrew McDonough B + Foundation, Alex's Lemonade Stand Foundation). Importantly, in order to ensure stakeholders' equitable participation, ACCELERATE does not receive any funding from the pharmaceutical industry to support its work. Industry representatives pay for their individual participation at meetings.

In addition to Europe and North America, ACCELERATE works with clinicians, regulators, industry and advocates in Australia, New Zealand, Canada and Japan to ensure it represents the key challenges in these jurisdictions.

## 4. Progress

### 4.1. Mechanism of action drug development

The first Working Group created by ACCELERATE was 'MOA driven drug development'. Against the backdrop of the European Paediatric Regulation [6], there was increasing sentiment that the drug development for children and adolescents with cancer should follow a MOA-based approach rather than being driven by the adult condition. In the EU, medicines which were potentially beneficial for children were being unjustifiably waived from a medical and scientific standpoint. For example, crizotinib was authorised for the treatment of anaplastic lymphoma kinase (ALK) positive lung cancer and was given a class waiver because lung cancer does not occur in children. However, ALK is also a driver of paediatric malignancies, and crizotinib showed

Table 2
Initiatives related to a mechanism of action-based approach of drug development in Europe and their current status.

| Initiative | Current status |
|---|---|
| Aggregated database of paediatric biological tumour drug targets | Application for funding of database of targets in progress |
| Joint academic–pharmaceutical industry preclinical platform to analyse the activity of new drugs | ITCC-P4 [21] funded as a project of Innovative Medicines Initiative – a public private partnership platform developing new pre-clinical models to generate information required for deciding whether or not a drug should be developed in the paediatric population and is operational.<br>A consensus has been published on the minimum pre-clinical testing requirements (excluding safety) for the development of innovative therapies for children and adolescents with cancer by the ITCC-P4 and Paediatric Preclinical Testing Consortium (PPTC) [21–23] |
| Paediatric Strategy Forums | Eight Paediatric Strategy Forums have been held [24–29,77] |
| Molecular profiling of paediatric tumours at diagnosis and relapse | Molecular proofing programmes are now operational and are available in Europe [67–72] USA [65,66,73,74] Australia [75] and Canada [76] |
| Suppression of article 11b of the European Paediatric Regulation, which allows product-specific waivers on the grounds that the associated condition does not occur in children [19]. | Revision of the Class Waiver List [19] |

Table 3
Working groups of ACCELERATE.

| Working Group | Objective | Output | Status |
|---|---|---|---|
| Mechanism of action driven drug development'[a] | To promote and develop a high-quality mechanism of action informed paediatric drug development approach including specific measures for adolescents, supported by all stakeholders | Proposed mechanism of action based approach to paediatric oncology drug development [19] with 5 initiatives: | |
| | | • Aggregated database of paediatric biological tumour drug targets | Ongoing - Application for funding of database of targets in progress |
| | | • Joint academic–pharmaceutical industry preclinical platform to analyse the activity of new drugs ITCC-P4 [21] | Achieved |
| | | • Paediatric Strategy Forums [24–29,77] | Achieved 8 Paediatric Strategy Forums delivered |
| | | • Molecular profiling of paediatric tumours at diagnosis and relapse 66-77 | Achieved molecular profiling programmes in Europe, USA, Australia and Canada |
| | | • Suppression of article 11b of the European Paediatric Regulation | Ongoing |
| New models for paediatric oncology drug development[a] | To develop a business model for the development of drugs primarily developed for children | Model developed – adopted by company | Achieved |
| New incentives for specific paediatric drug development and drug repositioning[a] | To propose more effective incentives for paediatric-specific oncology drug development | Final conclusions deferred until 2021 at time European Commission launched the revision of the European Union Paediatric and Orphan Regulations | Ongoing |
| Fostering age inclusive research (FAIR Trials) | To increase the access of adolescents to innovative treatments | • Consensus article endorsed by regulatory bodies (EMA, FDA and European Forum for Good Clinical Practice [EFGCP]) and industry [34]. | Achieved |
| | | • Ongoing actions to raise awareness to the professionals involved in trial design and approval and the general public | Ongoing |
| Fit for Filing | To develop the best principles on how to design and deliver an academic clinical trial with a dataset that can be included in a package for marketing authorisation | • Consensus of a model for investigator-initiated clinical trials of new drugs to meet the regulatory requirements through the 'Fit for Filing' | Achieved |
| | | • Educational strategy to promote this approach | Planned |
| Long-term follow up | To develop international, open, harmonised, and sustainable data registry to collect long-term side effects of new anti-cancer therapies in children | • Agreed concept proposal and proposed structure and governance of registry [40] | Achieved |
| | | • Implementation of project with the aim to create the registry has commenced | Ongoing |
| International cooperation | • Identify the obstacles to intercontinental cooperation and collaboration | • Review of intercontinental clinical trials completed [43] | Achieved |
| | • Develop principles and best practices for global clinical to enable paediatric oncology | • Data survey of intercontinental trials to identify obstacles | Ongoing |
| | | | Planned |

(continued on next page)

Table 3 (*continued*)

| Working Group | Objective | Output | Status |
|---|---|---|---|
| | focused cooperative groups to collaborate to accelerate drug development<br>• Provide synergy, but not overlap, with other working groups | • Multi-stakeholder discussion and consensus to identify solutions | |
| Real World Evidence/Data | • Indicate the circumstances when the use of RWE is relevant<br>• Identify challenges and obstacles of the use of RWE<br>• Propose solutions to these challenges | Ongoing | Ongoing |

[a] Completed.

tumour responses in paediatric phase I and II trials [16,17].

To assess the probable effect of changing the current approach, the MOA of 89 drugs granted a class waiver by the EMA between June 2012 and June 2015 were assessed to determine if they might be active against potential paediatric therapeutic targets. Forty-eight (54%) had a MOA warranting paediatric development. Two (2%) drugs were considered not to be relevant and 16 (18%) required further data to be informative [7]. The Working Group proposed a MOA-based approach with five initiatives, which all have been implemented to some degree (Table 2) [18].

The revision of the 2015 class waiver list by the EMA came into effect in 2018 [19]. Eight class waivers which had been given because the diseases did not occur in children were revoked, including two for cancer, and 15 revised. This resulted in pharmaceutical companies needing to submit a PIP or a product-specific request for a waiver, giving the PDCO the opportunity to review more applications and to provide feedback on the development of more medicines. However, if a company decides to request a waiver because the condition does not exist in children even though the drug's MOA is relevant for paediatric malignancies, the PDCO cannot mandate the company to assess the drug in children. The revised class waiver list would not prevent a repetition of the crizotinib experience, and the development of many oncology drugs for children is still dependent on the willingness of pharmaceutical companies to voluntarily provide PIPs, as has occurred with the BRAF inhibitor dabrafenib [20].

A consensus on the minimum pre-clinical testing requirements (excluding safety) for the development of investigational therapies for children and adolescents with cancer by the ITCC-P4 and Paediatric Preclinical Testing Consortium (PPTC) [21–23] could facilitate drug development.

### *4.2. Paediatric Strategy Forums*

Paediatric Strategy Forums were created as a direct consequence of the need to prioritise medicines in the landscape of a MOA-driven drug development [24–30]. A larger number of available medicinal products, as well as second- or greater-in-class drugs, relative to the limited size of the relevant population of children, mandate prioritisation for which medicinal products should be developed first. The goal of Paediatric Strategy Forums is to share information between all stakeholders in a pre-competitive setting to inform paediatric drug development strategies and subsequent integration of the clinical perspective into the development efforts. This aim is achieved by facilitating dialogue and enabling constructive interactions between all stakeholders. In this way, novel drugs with a similar MOA can then be 'compared' in a non-competitive space, such that resources are not wasted, and paediatric patients are not enrolled on sub-optimal clinical studies unlikely to benefit them.

The Paediatric Strategy Forums provide unprecedented opportunities for meaningful interaction between all stakeholders on topics that might cause a feasibility problem from an industry or academic standpoint, in paediatric and adolescent cancer drug development. They facilitate the development and discuss best choices of innovative medicines for the treatment of children with cancer to ultimately accelerate the introduction of these medicines into the standard-of-care for children. Key aspects of the Forums include discussions that while including all stakeholders, involve no regulatory decisions during the meeting. Forums either focus on disease (e.g. acute myeloid leukaemia [27]) or a target (e.g. epigenetic modifiers [28]). The current landscape of the topic and therapeutic needs are first presented, followed by presentation of non-clinical and clinical information on medicinal products being developed by

Table 4
-Indicators of the output of ACCELERATE.

| Year | Number of ACCELERATE publications | Total impact factor of ACCELERATE publications | Attendees at ACCELERATE Meetings | Number of Paediatric Strategy Forums | Number of educational events |
|---|---|---|---|---|---|
| 2015 | 1 | 9.16 | 104 | | |
| 2016 | 1 | 9.16 | 127 | | |
| 2017 | 1 | 9.16 | 135 | 2 | |
| 2018 | 2 | 68.36 | 132 | 1 | |
| 2019 | 1 | 9.16 | 167 | 1 | |
| 2020 | 4 | 38.768 | 197 | 1 | |
| 2021 | 5 | 33.4 | 326 | 3 | 2 |

pharmaceutical companies. A strategic scientific based discussion, patient advocate comments and conclusions end the meeting. The output for each Forum is a summary for EMA, FDA and ACCELERATE websites (agreed by all participants) and a published open-access manuscript.

The first Forum focused on ALK inhibition in paediatric malignancies and was held at the EMA in January 2017 [24]. A total of seven Forums (Table 5) have been held to date. They are continually being developed and adapted to the changing landscape of key issues in paediatric cancer drug development. The Forums have resulted in conclusions both specific to the topic of the Forum and more generally about criteria relevant to prioritisation and helped to frame future discussions between industry and regulators. Frequently after a Paediatric Strategy Forum, product, rather than class prioritisation is required, via a Prioritisation meeting that is held without the active participation of regulators, e.g. with bromodomain and extra-terminal inhibitors following the Forum on epigenetic modifiers [31].

Patient advocates have strongly supported the Forums due to their ability to focus on specific issues and openly discuss problems and seek solutions, with all stakeholders involved.

Overall, Paediatric Strategy Forum participants have concluded the very strong need for global collaboration in both preclinical and clinical investigations and early academia-multi-company engagement with very early involvement of regulators. The Forums have highlighted that the optimal development pathway is through international cooperative academic groups working in partnership with advocates and biotechnology and pharmaceutical companies, before PIP and iPSP submission, but cognisant of timelines. The importance of industry-supported, academic-sponsored international platform trials and agreement for sequenced development efforts has been reinforced. Both the EMA [30,32] and the FDA [33] have highlighted the value of Paediatric Strategy Forums.

### 4.3. Adolescents in adult trials

The FAIR (Fostering Age Inclusive Research) Working Group, co-led by a clinical academic and a patient advocate, aims to improve the access of adolescents and young adults (AYA) to clinical trials [34]. In some cancer types with identical drug targets in the paediatric and adult populations, adult phase II trials have demonstrated efficacy but paediatric and adolescent clinical development commenced much later or not at all. This has resulted in significantly delayed the introduction of beneficial drugs to adolescents (e.g. brentuximab vedotin in Hodgkin's disease [35,36]). In diseases too rare in adolescents to allow completion of paediatric trials within a reasonable timeframe, even with worldwide accrual over several years, a very low (but not non-existent) incidence of a condition in adolescents has triggered the regulatory requirement for an adolescent study, while waivers have been granted, based on the absence of the condition, for studies in children <12 years. This has resulted in 'infeasible' adolescent-specific phase I trials, using a drug already demonstrated to be effective in adults with the same disease (e.g. vemurafenib in malignant melanoma [37]). The working group proposed adult phase I/II trials should include adolescents 12 years of age and older. The recommendation is not only ethical, but generally feasible and safe, either where the MOA of the drug being studied is potentially relevant to adolescents or when the disease is rarely present in the adolescent population. This approach was supported by similar dosing and pharmacokinetic parameters in adolescents and adults and no extra toxicity observed in adolescents [38]. Very importantly, inclusion of adolescents in adult clinical trials should neither delay the activation, completion nor reporting and publication of the trial and authorisation process. The Working Group also proposed to include both children and adults in the phase II and III trials for diseases similar across adult and paediatric population, e.g. bone sarcoma and Hodgkin disease. Adult phase I-III trials of diseases rarely present in adolescents, e.g. carcinoma and

Table 5
Paediatric strategy forums.

| Topic | Date | Venue | Products discussed | Output |
|---|---|---|---|---|
| ALK Inhibitors | 30–31 Jan 2017 | EMA London | 6 | • Conclusions published on website [24] |
| Mature B cell Malignancies | 13–14 Nov 2017 | EMA London | 20 | • Conclusion - antibody drug conjugates, CAR T-cells and T-cell Engagers have the highest priority for investigation<br>• Manuscript [25]<br>• International platform trial -GloBNHL |
| Checkpoint Inhibitors in combination | 5–6 Sept 2018 | EMA London | 20 | • Conclusion- no scientific rationale for children to be enrolled in new monotherapy trials of additional checkpoint inhibitors with the same mechanism of action of agents already studied unless additional scientific knowledge<br>• Manuscript [26] |
| Acute myeloid leukaemia | 11–12 Apr 2019 | Rotterdam | 26 | • Manuscript [27]<br>• International platform trial – Pedal-EUPAL [64]<br>• Two prioritisation meetings – CD123 & FLT3 |
| Epigenetic modifiers | 23–24 Jan 2020 | Philadelphia | 16 | • Manuscript [28]<br>• Prioritisation meeting - BET inhibitors [31] |
| Second on ALK Inhibitors | 14–15 Jan 2021 | Virtual | 5 | • Manuscript [30]<br>• Prioritisation meeting |
| CAR-T Cells | 25–27 May 2021 | Virtual | 13 | • Manuscript [77] |
| Multi-targeted kinase inhibitors in Bone Sarcomas | 30 Nov-1 Dec 2021 | Virtual | 7 | • Manuscript in preparation |

melanoma, should include adolescents from 12 years to facilitate access to novel treatment. ACCELERATE published a position article [34], which was endorsed by regulatory bodies (EMA/PDCO [39], FDA [40]) as well as industry (Biotechnology Innovation Organisation [BIO], European Confederation of Pharmaceutical Entrepreneurs [EUCOPE], European Federation of Pharmaceutical Institute and Associations [EFPIA], EuropaBio and Pharmaceutical Research and Manufacturers of America [PhRMA] [40]). Significantly this was preceded by an FDA position article followed by a published guidance recommending the inclusion of adolescents (ages 12–17 years) in disease and target appropriate adult oncology trials [41,42]. This approach has been successful in age inclusive marketing authorisation (supported by extrapolation), with gemtuzumab (with an acute myeloid leukaemia front line indication in adolescents together with adults) and selpercatinib (for RET positive medullary thyroid cancer in adolescents and adults).

FAIR's ongoing goals are to (i) raise awareness among professionals involved in trial design, authorisation, marketing authorisation and the general public; (ii) gain endorsement of the approach; (iii) identify successful trials by creating a 'FAIR for AYA' endorsement to give credit to pharmaceutical companies that lower the inclusion age of certain trials to allow recruitment of adolescents and actively avoid unnecessary barriers based on age; (iv) develop tools for stakeholders to help facilitate the understanding of the problem and the initiation of appropriate trials.

## 5. Ongoing ACCELERATE initiatives

### 5.1. Fit for Filing

The Fit for Filing Working Group aims to develop the best principles for how to design and deliver an academic clinical trial with a dataset that meets the expectations for inclusion in a regulatory package. There is multi-stakeholder involvement with co-leaders from representatives of industry and academia. The ultimate aim is to improve the implementation of investigator-initiated-trials in intent to file, i.e. facilitating the use of the data for regulatory purposes when relevant. In the past, academic sponsored trials have been frequently found not to be 'fit for purpose' when they have been subsequently included in regulatory submissions to support application for marketing authorisation.

The Working Group has identified key general principles: (i) early planning is essential with early communication amongst academic research consortia, pharmaceutical industry and regulators; (ii) prospective collaboration and agreements; (iii) alignment of data collected to meet study objectives and regulatory commitments; (iv) recognition of shared responsibilities. The group is currently finalising a consensus manuscript

describing their recommendations and then will launch an educational strategy to inform investigators and academic sponsors on the needs for these fit for filing trials.

### 5.2. Strengthening global collaboration

This Working Group is based on the premise that intercontinental collaboration is essential in paediatric oncology to facilitate new drug development and build robust practice-changing trials with sufficient sample size to make meaningful conclusions. The objectives of the group are to (i) identify key obstacles to intercontinental cooperation and collaboration; (ii) develop principles and best practices for global clinical research, starting with the US, EU, United Kingdom and Canada, but of course applicable beyond, to enable paediatric oncology focused cooperative groups and centres to collaborate to accelerate drug development; (iii) provide synergy, but not overlap, with other working groups (e.g. Fit-for-Filing) and on-going initiatives led by the ITCC and its academic sponsors committee.

The Working Group has undertaken three work packages: (i) a systematic review of intercontinental clinical trials to describe the landscape [43]; (ii) a data survey of intercontinental trials to identify obstacles; (iii) multi-stakeholder discussion and consensus to identify solutions. It has been demonstrated that only 5.4% of paediatric cancer trials have been conducted intercontinentally over the last decade; two-thirds were industry-sponsored. The number of intercontinental trials was stable over time, with a worrisome decreasing trend for academic trials, despite the acknowledged unmet need for international collaboration for rare paediatric tumour subtypes. Industry sponsored proportionally more phase-1 trials than academia, and there were relatively few academic sponsored Europe-US phase 1 trials. The minority of clinical studies (25%) were late phase trials and most sponsored by academia were Children's Oncology Group (COG) trials (US-Oceania collaboration). The majority of industry early phase (90%) and phase 2 (95%) trials involved North-America and Europe, with less involvement of Oceania or Asia. The Group is now identifying the obstacles to collaboration.

### 5.3. Long-term follow-up

There are an increasing number of childhood cancer survivors who have been treated with new molecularly-targeted or immunotherapy agents. The current focus in clinical trials has been on the collection of acute and semi-acute toxicities, but equally important, families and clinicians need to be informed of the long-term effects of treatment to guide their decision making. In addition, there is an increasing requirement by the regulatory agencies to have a better understanding of the longer-term effects of new therapies. The current long-term follow-up programmes are focused within individual academic centres, national programmes or drug-specific by an individual company. They all have limited inter-programme data sharing. The type and depth of data collected are heterogeneous between programmes while companies, at considerable expense, only collect information on the small number of paediatric patients treated with their specific drug, limiting the evaluation and significance of uncommon toxicities. During Paediatric Strategy Forums, there were concerns that relatively infrequent late adverse effects may not be detected early enough as these late effects were being documented in silos [26]. Therefore, ACCELERATE proposed that there should be an international and inter-company registry of early and late adverse effects of new anti-cancer products. To this end, ACCELERATE convened a Working Group to develop an international data repository to collect information on long-term health in children who have received innovative medicinal products [44].

The goal is an international, open, harmonised and sustainable data registry to collect long-term side-effects of new anti-cancer therapies in children to: (i) provide knowledge of the long-term safety and follow-up care of new modalities to support the best use of these therapies and (ii) support fulfilling regulatory requirements of the marketing authorisation holders. The registry will focus on licensed drugs with or without market authorisation for use in children with cancer. Compound use can be in completed clinical trials, commercial, off-label use and/or compassionate use. The registry will rely on healthcare providers submitting data to the registry, so-called 'secondary data use', of already existing and collected data and will not require the generation of new data. A core dataset to be entered for all drugs has been developed. The registry will be developed with regulatory input (e.g. through Qualification Procedure from the EMA and FDA) how to fulfil post-marketing regulatory requirements. This ongoing project will create an asset that will follow children and adolescents exposed to innovative medicines long-term.

### 5.4. Real world evidence (RWE)

RWE from Real World Data generated in clinical practice, in healthcare settings and clinical trials [45] is an increasingly important topic. There are many potential uses of RWE in paediatric/AYA oncology, including providing historical control data as external controls to compare innovative therapies;

facilitating regulatory applications (iPSP and PIPs); determining the feasibility and design of trials or providing post marketing data. An important component of RWE is capturing data on new drugs when prescribed outside clinical trials either on compassionate use or off label indication [46–49]. There is a strong consensus that the involvement of children and adolescents in clinical trials is the clear priority and all efforts should be made to facilitate access to trials. However, currently there are children who receive innovative medicines outside clinical trials and the related data are not captured [48,49]. Furthermore, these data should be made available for prescribers and families and useable for regulatory purposes. When data are collected and analysed from patients who have received an innovative drug, a negative signal in a given indication could support no further use or formal evaluation of the drug; in contrast, a positive signal would strongly support a formal evaluation in a clinical trial and further development.

An ACCELERATE multi-stakeholder position article will describe the challenges and obstacles of the use of RWE, when RWE is not an appropriate replacement for trials and indicating the circumstances when the use of RWE may be appropriate. Concrete examples of existing data registries, which could generate RWE for regulatory decision-making and key elements of data quality needed for RWE, are being considered, e.g. the proposed long-term follow-up registry.

**Text Box 1. Future directions.**

1. Increase the number of potentially beneficial innovative drugs being evaluated in children in a timely fashion to address unmet needs of patients by:
   - Proposing revisions to the EU Paediatric and Orphan Regulations, with clear metrics to evaluate (and possibly refine) the implementation to be driven by mechanism of action and science
   - Facilitating 'first-in-child and first-in-human trials' development by lobbying for incentives
   - Define unmet needs for children and adolescents with cancer through multi-stakeholder collaboration
   - Facilitating development of medicines in children that are terminated in adults by lobbying for incentives and consensus statements
   - Facilitating innovation once PIPs or iPSPs has been completed by lobbying for incentives
   - Monitoring the implementation of the Race for Children Act
   - Encouraging alignment between the regulatory processes in Europe, US and other jurisdictions
   - Aligning regulatory and other drug development processes globally
2. Improve the selection and prioritisation of innovative drugs being evaluated for children and adolescents cancer by
   - Continuing the development of Paediatric Strategy Forums
   - Development of 'living prioritisation'
3. ACCELERATE evaluation and introduction of innovative drugs into front-line therapy by:
   - Designing a model for investigator-initiated clinical trials of new drugs to meet the regulatory requirements through the 'Fit for Filing' Working Group consensus statement and an educational strategy
   - Identifying principles and best practices for global clinical research to enable paediatric oncology cooperative groups to develop inter-continental trials
   - Overcoming challenges and obstacles of the use of RWE and indicating the circumstances when it is relevant
   - Monitoring an intended reduction in the time lapse between the first patient recruited into adult trials and the first patient recruited to a paediatric trial for a given drug
   - Providing guidance on innovative efficient trial designs that can meet regulatory requirements while minimising the number of patients required
   - Facilitating development of industry supported, academic sponsored international platform trials
4. Improve access for children and adolescents to innovative new drugs by:
   - Facilitating the access by adolescents to innovative treatments through fostering age inclusive research; continuing to raise awareness by professionals involved in trial design and by the general public
   - Increasing access of children and adolescents with treatment resistant cancers to innovative drugs (including clinical trials and by coordinating collection and evaluation of compassionate and off-label use of new drugs)
5. Increasing early global HTA and payers' involvement, engaging all stakeholders, aligning processes and specific pathways to assess new therapies
6. Document the long-term adverse effects of innovative anti-cancer drugs through a harmonised and sustainable data registry to collect long-term side-effects of new therapies
7. Strengthen and reinforce true multi-stakeholder collaboration and further define the role of patient advocates in drug development
8. Through a well-defined educational approach, ensure these strategies and lessons learnt are understood and appreciated by all paediatric oncologists involved in clinical trial design

## 6. ACCELERATE 2021–2025

### 6.1. Prioritising unmet paediatric needs

The evaluation of the Orphan and Paediatric Regulations by the European Commission has shown that new paediatric products are not being developed in the therapeutic areas where needs are greatest. In a future revision of the Paediatric Regulation, consideration will be given to designing specific rewards/incentives to direct development in specific areas of pressing need for children. It will be important therefore to identify areas or products, which would be eligible in such a system. Defining unmet needs for children and adolescents with cancer is highly complex, as unmet needs are constantly evolving. Unless the survival rate is 100% in any disease type and there are no long-term side effects that seriously affect the quality of life of survivors, there remains an unmet need for the treatment of the disease. Identifying unmet needs should be achieved through multi-stakeholder collaboration since working in isolation is ineffective and might not even be possible to be defined by one stakeholder group alone. An important question to address is whether the focus should be on prioritisation of products rather than on defining unmet needs. Optimally, a unified and interrelated process where unmet needs are identified, the underlying scientific rationale is reviewed, and then medicinal products are prioritised, will be implemented as in the Paediatric Strategy Forums. The future directions of ACCELERATE are highlighted in Text Box 1.

### 6.2. Increasing 'potentially beneficial' innovative drugs

The RACE for Children Act [9]' which came into full effect on 18th August 2020, is a landmark legislation in the transition to a MOA-based regulatory approach. The Act amends the Paediatric Research Equity Act (PREA) for targeted oncology drug products developed for adult cancers. It extends the principle of MOA further than the revised class waiver list of the European Paediatric Regulation [19] and complements it, as well as the proposed EU Pharmaceutical Strategy [11] and ongoing evaluation of the EU Paediatric and Orphan Regulations. Considering the number of oncology medicinal products under development in adults and the rarity of paediatric cancers, prioritisation will be crucial to meet the needs of children. There are already benefits following the implementation of the RACE Act, such as more voluntary PIPs in paediatric only conditions and more are anticipated (Text Box 2). Despite this substantial progress, there are still challenges to resolve and ACCELERATE will monitor the impact of the RACE Act, as well as the revised EU Paediatric Regulation, when it comes into force.

### 6.3. Rescuing drugs terminated in adults

The clinical development of anti-cancer drugs in adults can be terminated for various reasons but may be related to lack of efficacy in an adult indication(s), financial or strategic reasons, unexpected significant toxicity or production issues. Some of these drugs may target relevant alterations in paediatric malignancies, and therefore, the development should proceed in children if toxicities are not problematic. However, major hurdles exist for the paediatric development of drugs in which adult cancer development has been discontinued.

**Text Box 2. Current and anticipated benefits following the implementation of the RACE Act [78]**

**Current**

- FDA has received more inquiries than anticipated, with 151 iPSPs reviews and 21 planned paediatric trials reviews (February 2021)
- Sponsors are committing to trials earlier in the development of a medicinal product that might have been expected prior to the RACE Act
- More discussions are occurring between academia and industry on paediatric development for novel therapies
- More paediatric development groups with specific paediatric oncology expertise forming within companies

**Anticipated**

*Short-term*

- Increase in number of new scientifically appropriate trials
- Increase industry–academia interactions
- Increase industry-supported academic trials
- Even greater use of Cluster Call process to navigate regulatory alignment

*Medium-term*

- Increase the number of phase 1/2 trials that detect signals of activity that lead to an increase in paediatric indications
- Improve feasibility of trials arising from iPSPs/PIPs.
- Decrease time between first-in-adult the first-in-child trials

*Long-term*

- Increase the number of drugs approved for use in children
- Decrease time between adult approval and paediatric indication approval
- More inter-cooperative group master platform trials

To facilitate paediatric development of these terminated assets, clinical academics, patient advocates and industry believed that different avenues should be explored including incentives early in the development process, patent-life extension and paediatric price structures or transferable incentives, as well as divestment incentives incorporated into the EU Regulation review. This could also further incentivise first in human, first in child developments. Encouraging and reducing the risks to companies of the early generation of paediatric data would be beneficial. The support of a class of products in a multi-stakeholder Forum e.g. a Paediatric Strategy Forum, it would be very valuable.

### 6.4. First-in-human/first-in-child development

Significant global regulations have been put in place over the last 20 years which led to an increased number of medicines being authorised for children, showing a clear advantage for those regions where such legislation is in place. However an analysis of the outcome of the paediatric legislations has also failed to boost innovation for rare diseases that are unique to children or for which adult development cannot address the needs of children, such as paediatric malignancies. Children and adolescents with cancer, therefore, have not derived the expected benefit from these important initiatives [50]. Cancer drug development programmes remain inextricably linked to the market potential for adult cancer indications, with independent paediatric cancer drug development remaining commercially unviable. In the opinion of clinical academics, patient advocates and industry, incentives which are uncoupled from adult cancer indications and that proportionately reward the investment in paediatric-specific drug development are needed to motivate paediatric cancer drug development. Current incentives work poorly and mainly benefit large pharmaceutical companies. However, smaller biotechnology companies, which are major drivers of early innovation, cannot afford to wait for late rewards. Incentives could be introduced at an earlier stage than at the end of the SPC and be staged and milestone-driven. Academic-advocacy-industry partnerships are to be encouraged.

### 6.5. Innovation after an approved indication

For many medicinal products, there is a need for continued development after the first approved indication. This poses significant problems, especially for high-cost therapies, such as CAR T-cells, adoptive cell therapies, and anti-GD2 directed therapy. Innovation to optimise the utility of new drugs and maximise their overall benefit for children may need to continue after the first approved indication. Currently, however, there are neither regulatory requirements nor any incentives, for a company to continue to support such innovation in the same patient population once an approved indication is obtained or indeed once a PIP or iPSP has been completed.

### 6.6. Paediatric Strategy Forums

Prioritisation is key, as there are too many molecules to evaluate in children [30]. It is paramount to focus competition when too many trials with similar patient enrolment criteria for drugs within the same class or for the same molecular targets exist. It is important to note that FDA [32] and EMA [30,31] report that companies take into account the scientific recommendations from ACCELERATE's Paediatric Strategy Forums to guide prioritisation for the development of drugs for children in high value targets. There is a need for clear, multi-stakeholder endorsed criteria for second or third generation products to be developed. Furthermore, updating prioritisation after a Paediatric Strategy Forum is necessary to respond to emerging science, and therefore, there is a need for 'living prioritisation'.

### 6.7. Coordination of regulatory interactions

Substantial progress has occurred in communication and potential alignment of EMA and FDA in terms of paediatric cancer drug development plans. ACCELERATE strongly supports the EMA and FDA in their call encouraging the pharmaceutical industry to simultaneously submit iPSPs and PIPs and suggest discussion at Cluster Calls and Common Commentaries for optimal regulatory coordination of global development plans [51–53]. Differences in PIP and iPSPs timing and requirements should not impede international planning of trials [54]. Simultaneous submission will hasten drug development by introducing clarity early in global development plans. Scientific Advice could be considered in addition at any stage, e.g. when new trial methodologies or technologies are involved.

Health technology agencies' and payers' early involvement and engagement with all stakeholders in development discussions is the only way forward in which access for children and adolescents to innovative beneficial drugs can be achieved. Evaluation processes and specific pathways to assess new technologies in paediatric cancers need to be aligned. Early Health technology agency interactions are essential to obtain endorsement incentivising reasonable drug pricing. The proposed EU Regulation on Health Technology Assessment [55] is an important milestone in that regard.

## 7. Conclusion

The establishment of ACCELERATE as a multi-stakeholder, international, patient-centred and problem-solving initiative has been a transformative step towards addressing key issues in innovation of drug

development for children and adolescents with cancer. It has driven greater communication and understanding between the four stakeholder groups, and this has, without question, reaped many benefits for children with cancer. The early interaction between academia, pharmaceutical companies, regulators and patient advocates in drug development of a new product is absolutely critical. Furthermore, there has been increasing alignment between regulators in Europe and the US and encouragement of simultaneous submissions. In parallel, there is growing dialogue between pharmaceutical companies, academia and regulators, where the critical role of patient representatives is increasingly appreciated. A science-driven, paediatric-centric, MOA approach to paediatric oncology drug development is becoming established with the implementation of the RACE Act being a substantial global catalyst. Consequently, the need for prioritisation is central and this is being facilitated by Paediatric Strategy Forums. Some of the challenges of access to medicinal products and drug development generally for adolescents are being addressed by their inclusion in adult early phase studies.

Through a well-defined educational approach, it is critical that these strategies and lessons learnt are understood and appreciated by all paediatric oncologists involved in the clinical trial design.

Involving patient advocates early in clinical trial design as part of international collaboration efforts, including them in strategic discussions, such as in Paediatric Strategy Forums and Working Groups, is important in ensuring the patient voice is heard and specific needs are taken account of all phases of paediatric oncology drug development.

Although ACCELERATE is currently focussing on activities in Europe, UK, USA, Australia New Zealand, Canada and Japan, it is envisioned that progressively these initiatives will extend and become increasingly global. The ultimate outcome of developing new drugs for standard of care will benefit children not only in high income countries but also in low and middle income countries.

There is a moral obligation of all stakeholders to identify priority developments of novel agents to address the needs of children and adolescents with cancer, accelerate the introduction of innovative drugs into the standard-of-care and realise the overall goal of better therapeutic options for patients. Developing new drugs for children with cancer is a global endeavour. It is only through enhanced dialogue, collaboration, understanding and transparency among all stakeholders that this can be accomplished. Strong foundations and principles have been established and ACCELERATE's 5-year strategy will benefit all stakeholders and most importantly will focus the development efforts and contribute to further improve treatment opportunities and therewith the lives of children and adolescents with cancer.

## Previous members of the Steering Committee

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## Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of, the agencies or organisations with which the authors are affiliated.

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## Glossary

Relevant legislation (considering only the European Union and USA)

| Abbreviation | Terminology | Explanation |
|---|---|---|
| **EMA EC 1901/2006** | Paediatric Regulation | Establishes the Paediatric Committee (PDCO), a scientific advisory organ that requires a paediatric investigational plan to be available for new medicines at the time of completion of adult pharmacokinetic studies. It aims to ensure that medicines for use in children are of high quality ethically researched and authorised appropriately and improve the availability of information on the use of medicines for children |
| **PREA** | Paediatric Research equity Act | PREA **requires** a sponsor planning to submit investigational new drug application (IND) to submit an initial Paediatric Study Plan (iPSP) early in the development process. |
| **BPCA** | Best Pharmaceuticals for Children Act | Aims to stimulate the labelling of medicines for paediatric use by requesting for certain clinical trials to be run in children. These studies are specified in a written request and can be conducted by the sponsor on a **voluntary** basis |
| **Written request** | Written request issuance | The FDA may issue a written request, generally upon request of the manufacturer or at its own initiative, if a meaningful health benefit for a drug can be assumed. The written request seeks information on a drug that should allow its safe and effective paediatric use. A sponsor is not required to fulfil a written request but can benefit from an additional six months of market exclusivity if the requested information relating to the use of the active moiety in the paediatric population is submitted according to the timeline and all stated requirements of the written request. |

Study design and regulatory approval

| Abbreviation | Terminology | Explanation | Who does what? |
|---|---|---|---|
| **IND** | Investigational new drug application | The process of submitting documentation on a new investigational drug to the FDA in the USA. This submission is required before the medicinal product can be administered to humans in the context of a clinical trial. | Asset holder together with the sponsor submits to FDA, FDA negotiates contents |
| **iPSP** | Initial paediatric study plan | The initial Paediatric Study plan is negotiated between the sponsor and the FDA as part of the IND and serves to identify needed paediatric studies early in development and begin planning for these studies. The iPSP should contain a paediatric development plan, including required paediatric studies under PREA and may also include additional studies to be performed under BPCA. For initial applications of targeted drugs with new active ingredients, it includes details of the molecularly targeted paediatric evaluation (Phase I or Phase I/II study) and/or request deferral waiver, when applicable | Sponsor submits to FDA |
| **PPSR** | Proposed paediatric study request | The planned clinical trial(s) to investigate the therapeutic potential of a new agent in the paediatric population, most often for an indication separate from that for which the drug is being developed. . Includes definitive efficacy and safety study and/or investigation in all paediatric indications for which there is potential for clinical benefit. | Sponsor submits to FDA |

(*continued*)

| Study design and regulatory approval | | | |
|---|---|---|---|
| Abbreviation | Terminology | Explanation | Who does what? |
| **PIP** | Paediatric Investigational Plan | A PIP is a **required** development plan for any new indications, route of administration or pharmaceutical form for patent protected authorised products aimed at ensuring that the necessary quality, non-clinical and clinical data are obtained through studies in children, to support the authorisation of a medicine for children in an area of unmet medical need. A PIP has to be submitted usually after completion of adult Phase I studies. And has to be agreed by the EMAs Paediatric Committee (PDCO) before submission of (adult) MAA, unless a full waiver has been agreed. | Asset holder submits to EMA |
| **MAA** | Marketing authorisation application | A centralised application made to a European regulatory authority for approval to market a medicine within the European Union [79]. | Asset holder submits, EMA evaluates |
| **NDA/BLA** | New drug application/biologics licensing application | A formal request made by a Sponsor to market a new drug in the United States. The goals of the NDA are to provide enough evidence to support the safety and effectiveness of the drug and show that the benefits of its use outweigh the risks. The NDA package provides very detailed information about the drug. This includes primary data, reports and summaries of the results of the nonclinical and clinical studies, PK/PD analyses, characterisation of the drug's ingredients and impurities (including any potential toxicities), and a description of all manufacturing processes and quality control parameters. This is the FDA equivalent to the MAA. | Asset holder submits, FDA evaluates |

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