Despite significant advancements in cancer research and discovery, childhood cancer remains a major cause of death among children globally.

This summary of the R&D landscape for childhood cancer advocates for more investment in research and clinical trial architecture for paediatric oncology.

**KEY MESSAGES**

- **Ensure equitable conduct of paediatric clinical trials:** only 28% of clinical trials take place in countries with 90% of the childhood cancer burden.

- **R&D on childhood cancers should place greater emphasis on product development** designed for children and the unique biology of childhood cancers.

- **Innovators and generic manufacturers** should develop age-appropriate formulations to meet the needs of children with cancer globally.

- **Faster regulatory approvals and greater reliance practices** are crucial to enable greater access to health innovations for childhood cancers.

- **WHO policies or guidelines** remain critical enablers to ensure wide adoption and implementation of evidence-based treatment for children with cancer.

- **Strengthening the R&D ecosystem:** efforts must be made to make the dynamic R&D pipeline for cancer medicines deliver more affordable, targeted solutions to the most affected communities.
Introduction

Despite significant advancements in cancer research and discovery, childhood cancer remains a major cause of death among children globally. Every year, an estimated 400,000 children and adolescents aged 0–19 years develop cancer, and more than 100,000 deaths occur due to childhood cancer (1).

Although research and development (R&D) in cancer have seen many advances in the past few decades (2), few clinical trials have addressed the effect of investigational medicine on tumour biology in children, particularly those living in low- and middle-income countries (LMIC). A contributing factor is the rarity of childhood cancer and the subsequently smaller market size, resulting in lack of prioritization in medicine development. Furthermore, there is little commercial incentive to provide child-friendly formulations. The specific ethical and clinical considerations necessary in designing and implementing clinical trials with children further constrain clinical trials. The consequence is relatively little investment in and limited access to innovations for children with cancer; furthermore, the available funding is concentrated mainly in Europe and the USA (3).

This summary of the R&D landscape for childhood cancer advocates for more investment in research and clinical trial architecture for paediatric oncology. The document highlights the gaps and barriers in the R&D landscape for medicines for childhood cancer according to data from the WHO Global Observatory on Health R&D (GOHRD). The analysis of current data on R&D shows that more investment is necessary in research on medicines, diagnostics and other interventions to improve access to new interventions and, thereby, the clinical outcomes of children with cancer in the long term.

¹ Note: Our data analyses are limited to children up to 16 years.
Most R&D for childhood cancer is conducted in high-income countries (HIC)

Clinical trials are essential for the development of safe, efficacious medicines and regimens for children. Trials provide data on, for example, efficacy, adverse reactions, toxicity and the need for supportive care, in settings where other variables might also affect outcomes. The results of these trials typically lead to the licensing and marketing of new medicines, their inclusion in treatment guidelines and clinical management of various cancers in children.

As shown in Fig. 1, 78.9% of trials are conducted in HIC in Europe and North America and, in LMIC, in China. Of the nearly 400 000 cases of cancer that occur in children every year, approximately 90% are in LMIC (1), where only 28% of trials are conducted. Globally, therefore, a large proportion of children with cancer are excluded from trials. For example, most clinical trials in Africa are conducted in only four of the 54 countries on the continent (Algeria, Egypt, Kenya and South Africa). In the past 10 years, only 15 clinical trials on childhood cancer were completed in Africa, whereas there were 63 in the USA and 57 in Europe and the United Kingdom (4). Patients recruited and treated in these trials had longer overall survival than those not in trials (5,6). Dramatic improvements in survival have been attributed to patient participation in clinical trials in HIC, with an increase of about 5% in 5-year survival during a 15-year period in children, adolescents and young adults diagnosed with leukaemia in Australia, France, New Zealand, Switzerland, the United Kingdom and the USA. The improvement was due mainly to better survival rates among children enrolled in clinical trials conducted over many years. Greater improvements in survival were observed for all leukaemias combined among adolescents (15–19 years) than among young adults (20–24 years), implying that early diagnosis improves survival outcomes (7). In trials conducted in HICs, unfavourable prognoses were more common among children in minority populations, due to factors including age at diagnosis, differences in prognostic indicators, cytogenetic profiles and socioeconomic status (8).

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1 Some of the trials are multinational.
There is an overwhelming need for more clinical trials and implementation research in LMIC. Better research capacity for paediatric cancers in LMIC will help reduce gaps in clinical management, improve data systems and increase the quality of care in those countries. Equal access to innovation begins by increasing research equity – innovative products can be used reliably only when adequate research has been conducted to validate them, the specificities of different target populations (with different molecular subtypes of cancer) and system readiness (e.g. diagnostic capacity) to deliver the products are in place.

Ensure equitable conduct of paediatric clinical trials: only 28% of clinical trials take place in countries with 90% of the childhood cancer burden.
There is insufficient R&D on childhood cancers

The number of trials dedicated exclusively to children is insufficient, given the disease burden. When trials are conducted concomitantly for adults and children (Fig 2) the focus of the trials may not meet the R&D needs for children as the most common cancers in adults are those of the lung, breast, colorectum and prostate. In contrast, children are more often affected by haematological malignancies and by brain and spinal cord tumours, which are less common in adults (9). Cancers in children are often biologically different from those with the same name in adults (10), indicating that child-specific research is necessary. For example, identification of new cancer targets in children requires a thorough understanding of the developmental microenvironment, which is essential to identify developmental pathways that may be valuable targets for therapy. The past decade has seen an acceleration of approvals for new medicines in childhood cancer; however, many of these products are being approved based on real-world data and not clinical trials (11).

Fig. 2. Numbers of trials by age of participants

R&D on childhood cancers should place greater emphasis on product development designed for children and the unique biology of childhood cancers.

Treatments for children may have a broader spectrum of side-effects than in adults because of their age and the extent of treatment, increasing the potential concomitant impact of side-effects due to frequent use of multi-modal therapy. Radiation therapy, for example, increases the risk of severe long-term sequelae affecting neurological, endocrine and cognitive functions (12). R&D on childhood cancer does not reflect the incidence of and mortality from childhood cancer.

1 For example, paediatric tumours (mostly glial and neuronal) are more sensitive to adjuvant irradiation and chemotherapy than adult tumours.
There are few age-appropriate formulations for childhood cancer

Age-appropriate formulations for childhood cancers are lacking. Often, adult medicines are manipulated to obtain appropriate doses for children, such as by dividing a tablet or preparing a suspension by crushing a tablet (i.e. compounding). Such manipulations can affect the bioavailability of the product and increase the chances of inaccurate measurement, errors in manipulation and the risk of adverse effects.

Fig. 3 shows the available paediatric-friendly oral formulations (tablets, capsules, crushable or commercial liquids, compound liquids). Only 34% (58/170) of the oral medicines studied were available in paediatric-friendly formulations.

**Fig. 3. Medicines administered orally, by their availability in paediatric-friendly formulations**

Solid oral dosage forms, that cannot be dispersed in water or sprinkled on food, are poorly accepted by children under 6 years, resulting in poor compliance and difficult administration. The WHO-hosted Global Accelerator for Paediatric formulations (GAP-f), with the WHO team for the Essential Medicines List, assessed the age-appropriateness of formulations listed in the WHO Model List of Essential Medicines for Children. They identified medicines that are not available in age-appropriate formulations for paediatric cancers and promoted their development to address the unmet needs of the paediatric population.

Ten of 46 essential medicines (oral and intravenous) in the “Immunomodulators and antineoplastics” section of the eighth WHO Model List of Essential Medicines for Children (2021) are not available in age-appropriate formulations (13). Even for essential medicine groups such as antineoplastics, age-appropriate formulations for children are not available.

Innovators and generic manufacturers should develop age-appropriate formulations to meet the needs of children with cancer globally.
Approval of medicines for children with cancer can be lengthy

As shown in Fig. 4, only two to five medicines have been approved solely for paediatric use (0–1% of all approvals).

**Fig. 4.** Numbers of medicines according to status of approval by the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA)

Furthermore, there is an average of 4–8.5 years difference in the time between approval of cancer medicines for children and those for adults (Fig. 5). Approval of some medicines for children has taken more than 22 years after approval for adults. It has been suggested that studies for development of paediatric medicines should start early in the life cycle, i.e. before or at the time of initial regulatory approval for adults, to reduce the lag between marketing authorization for adults and the type 2 variation for paediatric use. Examples of incentives to reward early development of paediatric medicines in the product lifecycle for medicine development can be found in the field of rare diseases (14,15) and could be considered for childhood cancers.

**Faster regulatory approvals and greater reliance practices** are crucial to enable greater access to health innovations for childhood cancers.
Use of unlicensed and off-label medicines for treating cancer in children is widespread. Most medicines that are used in children have not been approved by regulators for paediatric use, mainly because there are insufficient high-quality data or incentives for regulatory submission (16). Unauthorized purchase of sub-standard and falsified medicines increases the burden on the national regulatory authorities in some countries, who expend resources on checking the quality of medicines (17). Moreover, children receiving cancer medicines are at significant risk when the medicines have not been studied properly or approved for or delivered specifically for paediatric populations.

The regulatory landscape must be improved globally for faster approval.
Historically, legislative obligations to study medicines in children have been driven by adult indications. Thus, if similar cancers did not occur in children, there was no obligation to study use of a medicine in children. To address this issue, the USA passed the Research to Accelerate Cures and Equity (RACE) for Children Act in 2017 to accelerate development of targeted therapies for children. The Act authorizes the US FDA to direct companies that are developing cancer medicines for adults to study their use in children if the molecular targets of the new products are substantially relevant to children’s cancers. A non-binding list of 200 molecular targets relevant to paediatric cancers was published. A later analysis showed that clinical trials registered on clinicaltrials.gov between 2010 and 2021 for target-directed agents for paediatric enrolment had identified at least one investigational agent in the pipeline for 155 (78%) of the 200 molecular targets included (15), providing an opportunity to increase the number of new treatments for paediatric cancers studied. Similarly, a reform of the European Union pharmaceutical legislation proposes that paediatric studies be based on mechanism of action to better guide medicine development (18).

Sample recommendations and guidance for best practice to improve the regulatory landscape for drugs for cancer in children

- Use of paediatric extrapolation, when possible, is described in the draft International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidance E11A (19) to optimize the use of existing data on efficacy and safety in adults or other age groups to inform the development of medicines for the paediatric population and promote international harmonization to reduce exposure to unnecessary trials, reduce substantial differences between regions and facilitate more timely access to medicines.

- An innovative approach suggested in the ACCELERATE programme (20) for timely investigation of new anti-cancer medicines, called “Fit for Filing”, proposes inclusion of datasets from academic trials in any format in a package for regulatory submissions and marketing authorization. Their working group identifies the circumstances in which use of real-world evidence is appropriate, the elements necessary to ensure data quality and how data registries could generate real-world evidence for regulatory use. This could result in faster approval of childhood cancer medicines.

- International collaboration among regulators is essential in paediatric cancer (14) to ensure the best use of regulatory resources and alignment of requirements as far as possible through the paediatric cluster or the WHO paediatric regulatory network (21). Close collaboration between the EMA and the US FDA ensures agreement on the issues commonly requested in paediatric plans through the “common commentary”. Such mechanisms could help sponsors to understand the issues identified by regulatory agencies with regard to paediatric medicine development and could facilitate optimal global coordination in development of paediatric oncology medicines.
Once products are approved by stringent regulatory authorities or have been prequalified by WHO, “reliance mechanisms” can be used to improve access to the medicines. WHO launched a collaborative registration procedure for accelerated registration in 2013 by providing assessment and inspection reports to facilitate countries’ decisions. Reliance mechanisms as the collaborative procedure for accelerated registration can speed up authorization of paediatric medicines and approval in LMIC, thus reducing the time to national registration. Products will then enter the market and be made available to patients more quickly.

**WHO policies or guidelines** remain critical enablers to ensure wide adoption and implementation of evidence-based treatment for children with cancer.
Differences in funding and access to funding between countries should reduce

Advanced newer agents (forms of therapy, such as immunotherapy, cellular therapy and molecular targeted therapy, are increasingly used in the treatment of cancer. Cellular therapies such as chimeric antigen receptor T cells (CAR T) are currently prohibitively expensive, but this is a rapidly growing treatment strategy that will be available in the future as the field matures.

Currently, 291 of 440 newer medicines and targets, i.e. 66% of all investigational medicines, consist of immunotherapy, of which are 48 CAR-T therapies. While the percentage of new therapeutics that are immunotherapies is increasing, enabling measures are necessary for their effective use in all settings.

Fig. 6 shows the sponsors of studies on the use of CAR-T cells. In Europe, an average of 72% of studies are funded by industry, especially in France (88%), Germany (75%) and Italy (58%). In China and the USA, more than half of such studies are funded by academic institutions. Venture capital and government funding are also available in these countries (22).

**Fig. 6. Clinical studies of use of CAR T cells in children by country and type of funding**

Source: https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/pediatric-cancer-car-t-pipeline-overview
Health systems must be ready for children with cancer to benefit from new agents such as CAR T cells. Evaluation of health system readiness includes studying and contextualizing health-care delivery models and improving diagnostic capability and infrastructure. Particular investment must be made in molecular pathology and biomarker testing laboratories, genomic databases, developing standards of practice for all workers involved in patient management, documentation and verification for administration, ensuring quality of care throughout the cancer care continuum, specialized training and registration for physicians who can assess patients for therapy, including the management of adverse effects, stock, data systems and data management for obligatory data reporting on outcomes particularly for severe adverse events (22).

**Strengthening the R&D ecosystem:** efforts must be made to make the dynamic R&D pipeline for cancer medicines to deliver more affordable, targeted solutions to the most affected communities.
Conclusions

R&D in childhood cancer must be adapted to meet the needs of children globally. Research on childhood cancer in LMIC is limited, resulting in poor generalizability of findings and lack of capacity to use novel therapies. Collectively, these factors contribute to slower improvement of cancer survival in children, particularly in LMIC.

More investment must be made to support clinical research to address child-specific oncology questions on products that may have no commercial value. Clinical trials and implementation research in lower-income countries are essential to improve access to and the applicability of results globally.

Funding and contributions must be more transparent. Currently, data on commercial research funding, which applies to 50% of all medicine trials and medicine development research in oncology, are neither disaggregated (especially by cross-cutting themes such as biomarkers, diagnostics and screening, cancer biology and medicine research) nor publicly available. This limits further analysis of funding and our understanding of investments based on need and priority. The case for transparency in funding should be backed by alignment of research strategies in all regions and improvements to reduce research waste (3).

Development of age-appropriate formulations should be undertaken at the same time that regulatory approval is sought for adult therapies. To support this, alignment among global regulatory agencies is necessary to promote paediatric medicine development and encourage new medicine discoveries. Regulatory approval timelines, processes and submission requirements must be transparent. Closer alignment of the global regulatory environment through better cooperation among regulatory agencies is especially critical, given the demand for international collaboration in clinical trials necessitated by small study populations for rare diseases, such as in paediatric oncology.

While the clinical and research community is gaining an understanding of the optimal use and management of powerful new therapies, parallel investments are necessary in infrastructure and training of human resources to ensure better patient outcomes. Without targeted support and substantial improvement of the clinical trial ecosystem, communities living in settings with weak health systems are at risk of being left behind with even greater delays in access to cancer innovation.

Enabling measures for evidence-based clinical management must be in place to ensure effective newer therapies in all WHO regions and to ensure that the continuum of research and access to care is maintained to serve the paediatric population.

By meeting global needs for childhood cancer interventions, prioritizing access in the R&D phase, preparing health systems to adopt innovations and providing innovative solutions to improve local R&D and manufacture, the global community will reduce barriers to access and improve the health of children with cancer globally.
References


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