The process of drug development in pediatric oncology: a review of basic principals and a look into the future

**Clinical Trial Perspective**

This article will focus on basic concepts in the development of new agents for pediatric malignancies and future directions, while considering the limitations we have today and the lessons we have learned from adult cancers. In addition, basic ethical principles for conducting trials in children are summarized. The rising numbers of targeted agents that have become available over the last few years will significantly change the way clinical studies are planned and a shift towards the use of alternative end points, different selection criteria and innovative designs is necessary. Pediatric malignancies have specific particularities and disparities that distinguish them regarding the conduction and design of clinical trials, which may influence the use of novel compounds. Due to the rarity of these diseases, international groups have cooperated to increase accrual rates, and incentives to the pharmaceutical companies have been made available by regulatory authorities; however, despite this a lack of trial participation in developing countries still remains.

**Keywords:** biomarkers • clinical trial design • drug development • ethics • informed consent • pediatric oncology • research • targeted therapy

The conduction of clinical trials is a key component for improvements in survival in childhood cancer. Due to the uncommonness of this disease, initiative of cooperative groups and multicenter collaboration allows the accrual of a sufficient number of patients during a limited period of time. Importantly, pediatric oncologists have integrated clinical trials into a culture of standard practice. Whereas only 2% of adult cancer patients enroll in National Cancer Institute (NCI)-sponsored clinical trials, more than 50% of children with cancer do [1]. Well developed research protocol guidelines and collection of data under quality control assessment represent the main steps for conducting clinical trials with particular ethical and emotional aspects involving children. A multidisciplinary review team should participate in the designing of pediatric oncology protocols, to make sure it follows the methodological principles to assure excellence during the conduction of a study and adequate ethical implications. Prioritization of resources is a significant concern in designing pediatric oncology trials because the number of patients available for enrollment is often inadequate to test multiple hypotheses [2,3].

The field of drug development has advanced over the last few years and anticancer medicines are now being rationally designed to regulate or arrest specific pathways that are thought to be important for cancer progression. Molecularly targeted agents have a major implication on clinical trial design compared with standard chemotherapy combinations and are now becoming part of the therapeutic strategies to improve survival in childhood malignancies. Alternative trial designs and pharmacodynamic (PD)-driven biomarkers evaluate drug-target effect and can demonstrate proof-of-concept for intended target modulation. This should be facilitated by validated biomarker assays, which are critical to understand which agents are likely to
benefit in different cancer subtypes [4]. Limitations from adult cancers in trial development should be understood and lessons learned should be incorporated into trial design for childhood malignancies, with respect to the particularities of the pediatric population.

The process of developing a new drug: current standards in oncology

- **Preclinical data**
  ‘In vitro’ and ‘in vivo’ studies provide information regarding side-effects, dosing, pharmacokinetic (PK) and PD data to guide initial protocol/trial design in humans. General guidelines for the preclinical evaluation of antineoplastic medicinal products have been regulated by the European Medicines Agency (EMA) and the Committee for Proprietary Medicinal products (CPMP) [101]. Basic principles and guiding for starting dose for Phase I trial design are outside the scope of this review; however, the initial dose and schedule for adult studies are based on nonclinical data derived usually in at least two relevant animal species.

- **Phase 0 trials**
  Phase 0 trials represent a novel attempt to accelerate the testing of experimental agents. The main goal is intended to inform decision making on whether further development of a relevant compound should be attempted based on its PK/PD properties. Guidelines for the exploration of investigational new drugs (IND) by the US FDA have been made and recommendations are available on a guidance IND document [102]. The definition for the exploratory Phase 0 study is that it should involve limited human exposure and have no therapeutic or diagnostic intent. They are typically conducted prior to dose-escalation Phase I trials and can be carried out even in healthy volunteers. Human cell products, blood products, vaccines or devices are usually excluded. Overall it is not yet clear that Phase 0 trials accelerate anticancer drug development.

- **Phase I trials**
  The main goal of a Phase I trial is to describe the toxicity profile of new investigational agents and to recommend a dose and schedule for further testing of these novel compounds. In a standard dose escalation Phase I trial, cohorts of three to six patients are treated at each dose level, following an algorithm based on observed dose-limiting toxicity (DLT). The doses are then escalated until the maximum tolerated dose (MTD) is reached and usually the recommended Phase II dose is set as the level just below the MTD. DLTs should be predefined-defined in the protocol and are usually described as the drug-related toxicity grade 3 or worse according to US National Cancer Institute Common Terminology Criteria for Adverse Events [103]. Various methods attempting to decrease the number of patients needed and the time to complete the Phase I trial have been proposed. The most frequently used is the 3+3 design [5] consisting of cohorts that are treated at increasing dose levels that have been fixed in advance; however, accelerated titration designs are now becoming increasingly more common. Most protocols will have strict inclusion/exclusion criteria for organ function status, but will allow participation of patients from a mixture of solid tumors or might be restricted to those likely to express the target. Limitations can be made depending on expected side effects from the experimental agent. Measurable disease is not always necessary unless response is an important study end point.

- **Phase II & III trials**
  Phase II trials are designed to assess drug efficacy usually in a cohort of patients with a specific histological subtype or those likely to express the molecular target when investigating biological agents. Randomization is not mandatory and usual end points include response rate, which is usually assessed by radiological criteria for most solid tumors, clinical benefit rate for novel agents and progression-free survival (PFS) for longer follow-up cohorts. A two-stage design may be used for Phase II trials where the sample size in the first stage is designed to confirm a minimum response rate, and the second stage is conducted only if this level of activity is observed. Usually efficacy end points are compared with similar regimens or lines of therapy in historical controls or comparable studies. Toxicity is evaluated in larger cohorts of patients in Phase II studies and dose adjustments can be made accordingly. Promising experimental agents or combinations are then selected for Phase III studies where they are randomly compared with standard treatment or best supportive care. The gold standard of efficacy for Phase III trials is overall survival (OS), although some investigators advocate that PFS may be a surrogate for OS, at least in some malignancies. Phase IV studies are those conducted after marketing approval.

- **Standards of efficacy & drug approval**
  There are numerous known limitations and there has been large debate in the medical community as to which efficacy end points should be used for final drug approval. Over the last few years there has been increasing pressure from pharmaceutical companies and patients for early approval of investigational agents based on data from published Phase III and, occasionally, Phase II trials in specific tumor types, for end points such as response, PFS and disease-free survival (DFS). Different trials may even show conflicting results for
OS for similar treatment indications; crossover designs and subsequent treatment lines can mask potential gains in OS for many malignancies and quality of life; and cost-efficacy studies should be taken into consideration before final FDA drug approval. In addition, the overall impact on disease outcome in randomized trials should be taken into account by regulatory authorities. For example, it may be accepted that an OS gain of 2–3 weeks is statistically significant but not cost effective for certain diseases and, therefore, should not be funded by the public health system.

Drug development in the era of targeted therapy

■ Biological agents & trial design

The introduction of molecularly targeted therapies [6–8] in specific histological cancers has changed the natural course of some diseases and influenced the conventional way we rationally develop cancer drugs. Intra- or extracellular pathways that are thought to be important for cancer progression are now being modulated by agents that can block the signal that is triggering tumor progression. In traditional Phase I studies, the PD effects of the drug are generally used for decisions on dose escalation and recommended Phase II dose. Toxicity has been the primary end point for this purpose for decades; however, novel targeted compounds are characterized by the lack of significant clinical toxicity compared with conventional cytotoxics. As a result, alternative end points have emerged to guide dose selection and give supportive evidence of drug activity. These may include PK measures, level of target inhibition on normal or tumor tissue or functional imaging [9].

A significant change in the way we design and conduct clinical studies is needed in the era of biological agents and a shift towards the use of different end points, alternative selection criteria and innovative designs is necessary. When assessing efficacy in Phase II trials, response rate assessment may not always be appropriate in agents that are cystostatic. In addition, newer investigational products may have fewer side-effects compared with classical cytotoxic chemotherapy and end points such as quality of life can be decisive when evaluating treatments with comparable outcomes using different regimes or combinations.

■ Biomarker-driven drug discovery

The understanding of the molecular pathogenesis of cancer has enabled a rational strategy to overcome the unselected cytotoxic approach where the same treatment is given to tumors with distinct molecular aberrations that drive the malignant phenotype. Molecularly targeted agents act on highly specific targets that are differentially expressed or activated in cancer cells and may result in no or very little normal tissue toxicity. In addition, biological agents may have a wide therapeutic window and increasing doses based on toxicity to reach MTD may be an irrelevant end point [10,11]. The determination of the optimal biologic dose or ‘biologically active dose’ required to inhibit the pathway should be the preferred end point for targeted agents. However, it is essential to have a reliable and validated assay to evaluate for target inhibition in order to universally apply to other populations the results obtained. The use of biomarkers should preferably be applied throughout the drug-development process to screen and optimize candidate compounds; identify and validate therapeutic targets; predict response, resistance and toxicity to treatment; provide proof-of-concept; enhance the mechanistic understanding of a drug or combination; and identify optimal target populations [4].

■ Emerging biomarkers

PD biomarkers are markers of a drug’s effect on tissue and body. When involving biological agents, the effect is usually associated with the molecular target or downstream consequences of target or pathway modulation, which can include molecular, cellular, genetic or imaging parameters. Biomarkers can be linked to a stepwise decision making process for all different levels in the biological process of inhibiting a molecular target. Their classification may be diagnostic, prognostic, and predictive of response or efficacy. Moreover, biomarkers can be classified based on their mechanistic target effect, that is: target binding or inhibition, downstream pathway modulation, desired biological effects, off-target effects or cell survival and apoptosis. Incorporation of poorly validated biomarkers into clinical trials may lead to misleading results and inappropriate decision making on whether the novel compound is really effective and should be assessed in later stages of development. The perfect biomarker should ideally be reproducible, repeatable, minimally invasive, with no risk to the patient and cost effective. As a result, it is particularly difficult to discover a biomarker with all these characteristics, which, in turn, makes drug development highly dependent on systematic collaborative approaches between research centers to design and conduct early clinical trials.

In early studies with anti-EGFR therapies [12,13], the skin was selected as a potential normal tissue for EGFR inhibition in vivo because of easy access and the established role of the EGFR in renewal of the dermis [14]. Changes in phosphorylation of EGFR in sequential skin biopsies have been shown to be useful at demonstrating target (EGFR) inhibition markers post-treatment with anti-EGFR therapy [13–15]. Surrogate tissues may not reflect the intra-tumoural PD effect of the drug;
therefore tumor biopsies are ideally the preferred tissue to explore these end points as they can give direct assessments of drug effect on cancer cells. Essentially, tumor biopsies hold a resource of molecular and genetic information that can be retrieved. They can also allow morphologic examination in the assessment of biologic effects with better understanding of the consequences of drug exposure and target modulation. PD data from tumor biopsies may generate useful insights into mediators of response or resistance to treatment, or may help generate hypotheses with regard to feedback loops, off-target effects, or alternative mechanisms of resistance. A more comprehensive profiling of the effects of a drug on multiple pathways may facilitate the conception of agents being developed and the understanding of their complexity.

Functional imaging can evaluate PD end points pre- and post-therapy and is now becoming part of our armamentarium for assessment of early end points and exploratory analysis in clinical trials. The most common techniques include functional or dynamic computed tomography (CT) scanning, dynamic contrast enhanced MRI (DCE-MRI), diffusion weighted MRI and PET. Overall, there still remains little agreement on the precise way to assess, repeat and compare functional imaging across different studies. In addition, there is no uniform methodology for acquiring, analyzing and reporting results; although Leach and colleagues have made specific recommendations for MRI assessment [16]. Some investigators have suggested that PET imaging may differentiate therapy responsive and nonresponsive tumors early in the course of treatment for adult malignancies [17,18], although it is very unlikely that data on the performance of fluoro-deoxyglucose -PET (FDG-PET) for rare cancers such as those seen in the pediatric population will ever be performed due to lack of robust data [19]. Adopting the widespread use of PET without validation from clinical trials would be poorly advised and potentially expose patients to more radiation with unknown benefits [20,21].

The utility of FDG-PET in the diagnosis and ongoing surveillance of children with cancer is not clear and further research is necessary to refine its specific roles in individual tumor types.

Incorporating biomarkers into clinical trials

The uses of novel biomarkers in drug discovery have increased considerably over the last few years in Phase I trials at least as exploratory end points [22]; although, Parulekar and Eisenhauer showed that the majority still use traditional end points (toxicity and PKs) for establishment of recommended Phase II dose [9]. Non-traditional end points, such as molecular effects on surrogate tissue or functional imaging, were not routinely incorporated into the study design and rarely formed the primary bases for dose selection. A review published in 2005 by Ludwig and Weinstein showed only 24 FDA-approved cancer biomarkers, examples include HER-2 expression or gene-copy number change, and circulating tumor markers, for example CA-125 and CEA [23]. This emphasises how difficult it is to incorporate biomarkers into drug discovery as, like drugs, they require various phases until robust validation is made. Ideally, biomarkers should be developed as intermediate end points in early clinical trials and the degree of validation should not be related to the stage of clinical drug development (early vs late), but more importantly be balanced to the intended role of the biomarker. One of the suggested reasons for the lack of reliable assays is the failure to start their development adequately early to allow them to be validated and implemented in early clinical studies [24]. Early stage biomarker incorporation should be considered for hypothesis-testing and -generating studies, without impacting on the main primary trial decisions. It is crucially important to ensure uniformity of methodology and technical platforms and that an adequate degree of technical standardization is made before biomarkers can be integrated into early trial primary end points, purposely for dose decision.

Drug development in pediatric oncology: what are the differences?

Pediatric population

Cancers in adults and children often behave and respond differently to established agents. Pediatric cancers are frequently more aggressive and rapidly progressive than many of the more indolent adult cancers. This is one reason to explain why pediatric cancers are frequently more responsive to cytotoxic therapy, which targets rapidly dividing cells. Rapid response allows efficacy assessments to be carried out sooner, supporting the use of early response as a surrogate marker and thereby expediting drug development. In solid tumors, carcinomas are rare and most pediatric tumors are either sarcomas, blastomas or germ cell cancers. Unlike carcinomas, many of these tumors are sensitive to chemotheraphy or irradiation [25]. This in turn impacts the approach to traditional clinical trial design. Molecular agents are usually less effective as monotherapy and this may not be the optimal approach to develop agents in aggressive and rapidly growing cells.

Moreover, cure rates in children are acceptably higher than in adults with an average of 70% or more being alive at 5 years [25]. This may have implications for statistical power in randomized Phase III trial designs that warrant larger patient numbers for small increments in OS. Quality of life is another important aspect to consider, specifically for agents with late side-effects,
where long-term consequences of survivorship will have a major physical and emotional impact, such as infertility and cardiomyopathy, or even a second malignancy. Most of what has been learned about the late effects of cancer treatment has been the result of longitudinal or cross-sectional data collection from survivors of standard-protocol treatments. Because the majority of children with cancer live longer and are likely to be cured by modern treatments, it is absolutely essential that long-term follow-up and serial surveillance of survivors should be built into such studies. Longer follow-up is difficult and expensive to maintain because the frequency and severity of late effects tend to progress with time off treatment, making follow-up beyond the usual 5–10 years essential.

The average age a child can begin swallowing pills is approximately 7 years and for younger children, inability to swallow oral agents poses a significant treatment obstacle. If an oral agent has no liquid formulation, patients may have no other treatment options available. There is currently little financial incentive for pharmaceutical companies to invest the time, effort and capital needed to develop pediatric liquid formulations. Taste is also important, as it will increase the likelihood of refusal or vomiting, compromising effective therapy.

Moreover, toxicities observed in Phase I clinical trials are not comparable between children and adults, nor are the biologic responses evaluated during Phase II and Phase III clinical trials [26]. Efforts to conduct clinical trials in a pediatric population may not only expose these PK differences, increasing the efficacy and safety of such studies, but also contribute to the discovery of new therapeutic targets. One of the most important differences between children and adults with regard to safety is the issue of growth and development. For instance, in studies evaluating IGF inhibitors, the hypothetical concern of disruption of normal growth must weighed against the pressing issue of tumor progression [27,28]. Moreover, extrapolation of dose per square meter of adult for children is not straightforward, and should consider the ratio of water and fat, changes in organ development, and its effects on drug metabolism. It is also very difficult in practice to study PKs at an adequate level, because the number of blood samples is limited in children.

**Pediatric population: molecular level**

Unlike adult tumors, which are considered multifaceted given the vast array of factors (environmental exposures, infections, hormonal changes and oxidative damage to name a few) contributing to their inception and progression, pediatric tumors differ in the fact that environmental factors are much less important in the accumulation of genetic mutations leading to transformation of a normal cell into a neoplastic cell. Most genetic aberrations in pediatric cancers are acquired as somatic mutations due to change in fast-growing cells, which play a role in the malignant transformation. These somatic mutations also play a role in adult cancer, although they usually differ in the tissue of origin or stage of development. Ewing’s sarcoma [29], neuroblastoma [30], medulloblastoma [31], retinoblastoma [32] and acute lymphoblastic leukemia (ALL) [33], for example, are all linked to genetic mutations, which invariably lead to constitutively active mechanisms such as those involving proto-oncogenes, or to faulty cell-cycle progression checkpoints involving tumor-suppression proteins. Since the ensuing defects at the protein level are the same as the ones observed in adult tumors, and given the complexity of including children and adolescents in clinical trials, most treatments for pediatric tumors are adapted from protocols developed for and carried out in an adult population. Although this approach has been accepted by the scientific and medical community, certain considerations must be made. Most adult tumors are inherently different from pediatric tumors at the molecular and cellular level, which may or may not amount in a need for different therapeutic agents [34–36]. In addition, there are limited preclinical models available for pediatric malignancies which may further delay screening of potential agents specifically engineered and designed for the pediatric population. Having said this, it is important to recognize that childhood tumors often use the same mechanistic hallmarks of cancer seen in adults. It provides the window of opportunity to use targeted agents developed for adult diseases in children and many effective drugs used today have gone through this pathway.

Researchers focusing on the development of new targeted therapies for the treatment of pediatric cancer should keep in mind that, although the origin of several pediatric malignancies involves defined genetic alterations, the altered gene is not always the most promising or unique molecular alteration to be targeted. For example, in Ewing’s sarcoma, chromosomal translocation giving rise to the EWS-FLI1 fusion protein is the primary biological alteration and provides an obvious molecular target; however, many tumors are intrinsically resistant to IGF inhibitors. This may be a consequence of the target, which is a transcription factor and difficult to drug; or because of a wide range of other components of cell signaling, including receptor tyrosine kinases, intracellular protein kinases, cell cycle and apoptosis regulators, and histone deacetylases, which might be co-activated in Ewing’s sarcoma. Optimal strategies may involve the blockage of various simultaneous pathways to increase overall efficacy of novel approaches and decrease resistance to standard combinatorial treatment; or the development of agents that can effectively block or suppress the gene product [37,38].
Drug development in brain tumors

While leukemia is the most common childhood malignancy, brain tumors are the most common solid malignancy, representing 21% of all cancers in children [25] and this may pose significant additional challenges with developing effective drugs for pediatric tumors. There have been increasing pitfalls in developing new targeted agents for adult gliomas, as recently review by Roesler and colleagues [39]. The considerable heterogeneity and low prevalence of each molecular abnormality in this population have reduced the statistical power of clinical trials to establish which prognostic biomarkers will define the best therapeutic approach needed as opposed to seen in other tumor types [6,8,40]. Delays in the development of targeted agents for gliomas have many known barriers in comparison with other malignancies. Patients with cancers that arise in the CNS are normally excluded from traditional Phase I trials, allegedly because neurologic deficits may compromise their general wellbeing and daily functions and also prevent adequate evaluation of side-effects from treatment. Most Phase I trials do not sufficiently address PK interactions with enzyme-inducing drugs, which are frequently used in patients at risk of seizures. In addition, the capacity of the investigational agent to cross the intact blood–brain barrier is commonly not assessed in such trials and there are enormous difficulties in obtaining tissue for correlative studies for predictive and prognostic biomarker evaluation.

Moreover, optimal clinical trial design and study end points for biological agents have been intensively debated with the strict response criteria usually applied, considering that targeted agents may have a cytostatic rather than a cytotoxic effect on cancer cells [41]. Alternative Phase II trial designs with different radiographic criteria and uses of surrogate markers have been proposed, but their validity remains controversial and exploratory. In addition, the evaluation of radiological response to anti-angiogenic agents with gadolinium-contrast MRIs may give false responses, which is influenced by a rapid reduction in vascular edema, and this may not translate into improvement in PFS or OS [42]. The North American Brain Tumor Consortium (NABTC) has suggested key factors to ensure the achievement of an integrated approach to conduct clinical studies in neurooncology [43].

There are further limitations that need consideration for developing new agents in the pediatric population, including the limited numbers and the heterogeneity of tumor types [44]. One additional weakness is the fact that most patients are included on the basis of their original diagnosis without considering a second biopsy, and likelihood of treating a tumor with a different biology does exist and has been illustrated in medulloblastoma studies [45]. Furthermore, better responses are achieved in newly diagnosed rather than in relapsed patients, and this encourages up-front window studies. The histological type is of major importance for chemosensitivity and end point evaluation. Good response rates are seen in germinomas and medulloblastoma, while only rare responses are observed for high-grade and brainstem gliomas. In addition, encouraging results are being obtained with dose intensity and prolonged low-dose strategies, which warrant assessment in large cooperative groups [46]. Recommendations for the reporting of trials in pediatric oncology have been made by the SIOP Brain Tumor Subcommittee [47].

Early trials for children: general principals & innovations

Pediatric Phase I studies are almost always performed following adult Phase I trials and are initiated an average of more than 2 years after the adult Phase I trials are published. This traditional pattern of evaluation, which regulates children to second-class status, may further delay newer treatments from reaching children. Although this delays the timeline of pediatric drug development, it offers the advantage of having data available from adult patients for the design of pediatric trials and also avoids exposing children to bad drugs. As reviewed previously in this article, whereas the starting doses for adult Phase I trials are based on animal toxicology, pediatric trials historically begin at approximately 80% of the adult maximum tolerated dose, which can greatly diminish the likelihood of pediatric patients being enrolled at biologically ineffective doses. Pediatric oncologists have tried to address this issue by using newer clinical trial designs, such as administering novel agents in brief windows followed immediately by administration of combination cytotoxic chemotherapy [48].

Lee and colleagues examined 69 Phase I trials in nearly 2000 patients, during an era when dose-intensive therapy was routinely administered as initial therapy in pediatric patients with high-risk tumors [49]. They found that limiting pediatric Phase I trials to a maximum of four levels would significantly shorten the timeline for study conduct without compromising safety. Treatment-related mortality was less than 0.5%. They also showed that the likelihood of achieving an objective response was similar to Phase I trials in adults. The response rate was higher in trials that combined an investigational drug with drugs with known anticancer activity (20.1%) versus an investigational drug alone (6.8%). The overall response rate for participating in a pediatric Phase I trial was 9.6%.

Targeted agents have the potential to increase treatment efficacy, and usually have nonoverlapping toxicities with chemotherapy, making them attractive agents for addition to chemotherapy induction and consolidation.

Clinical Trial Perspective
Brunetto, Roesler, Abujamra, de Castro, Schwartsmann & Brunetto
regimens for patients with relapsed ALL [50]. Investigators have also moved toward eliminating single-agent Phase I leukemia trials altogether, choosing instead to extrapolate toxicity and dosing information from pediatric solid tumor and adult leukemia trials. Defining appropriate toxicity in studies incorporating novel agents into known cytotoxic backbone regimens used to treat ALL is challenging and requires a method to account for toxicities of the disease state and the cytotoxic chemotherapy backbone into the DLT assessment. Horton and colleagues have reviewed several potential approaches to defining DLTs, each of these having advantages and disadvantages [51]. Modifying the standard DLT definition may enable evaluation of new drugs within multi-agent clinical trials for children with ALL at doses that are safe and effective.

Furthermore, the use of population PK models has enabled the feasibility of doing such studies with a limited number of samples, and is now being explored for pediatric oncology. Along with advances in pharmacogenetics, the advances made in the conduct of PK studies in children with cancer have enabled establishment of sophisticated phenotype–genotype correlations, which may ultimately improve care. Panneta and colleagues address the need to perform PK studies throughout the drug-development process and review methods used to develop and validate limited sampling models in PK studies in children with cancer [52,53].

### Ethical & regulatory considerations for clinical trials

#### Ethical considerations for trial participation

The possibility of personal clinical benefit and the potential help to other cancer patients in the future are the main motivations for trial participation for most patients [54]. They can usually underestimate possible toxicity caused by experimental treatment and its impact on quality of life [55]. Patients may also agree to participate for many reasons as follows: to ensure adequate medical attention during the final stages of illness, holding on until there is a cure, to do it for their families and friends, and to decrease the costs of medical and supportive care [56]. Participation in later stages of development theoretically has a higher chance of benefit than early studies; although current evidence shows that trial participation for new treatments tends to be, on average, neither better nor worse than standard therapies [57–59]. Phase I and II trials of novel treatments may seem promising, even though they do not predict in a good way the outcomes of the Phase III trials that will inform practice [60]. In addition, Kumar and colleagues have shown that the same seems to apply to Phase III trials in pediatric oncology where randomized trials are as likely to be inferior as they are to be superior to standard treatments [61].

In addition, with the development of molecularly targeted agents, efficacy and selection of patients can be made upon surrogate predictive and prognostic biomarkers. As commonly seen in adult malignancies, the ideal tissue to obtain these samples is the tumor itself, particularly after a drug is administered in an attempt to measure for effect on the desired target. This again raises ethical concerns, specifically in earlier stages of drug discovery. Is it ethically appropriate to subject a child on a Phase I study to the pain and possible complications involved with a repeat tumor biopsy to assess molecular response that may not correctly reflect the activity of the drug in the malignant cell?

#### Regulation for conduction of clinical trial under GCP

Ethical considerations have been part of the design and conduct of studies with humans for several decades. GCP is an international ethical and scientific quality standard for trials involving patients. Activities covered by GCP include trial design and supervision of study activities, definition of scientific and ethical trial objectives, data collection and quality assurance, study analysis, and human subject protections. All of these activities are intended to support clinical research, with the final goals of improving the health and interests of patients and advancing medical research. The guiding principles were collaboratively developed by the USA, EU and Japan over the past 25 years through the International Conference on Harmonization (ICH), which has been established to develop and harmonize technical requirements for drug development [62]. It is vital that clinical researchers follow GCP to ensure the safety of the clinical trial subjects as well as the integrity of the data, which will be used to support changes in evidence-based care and the regulatory approval of new medicines. In addition, the investigator should submit all research to the Institutional Review Board/Research Ethics Board (IRB/REB) of record for approval before initiating any clinical research study at the local site.

In the USA and Europe, clinical trials have been a standard approach to the care of children with cancer for many years. Because childhood cancer is rare, advances in therapy depend on collaborative clinical trials conducted by cooperative groups and consortia [63]. The Children’s Oncology Group (COG) is presently an NCI-funded international multicenter clinical trials organization that brings together specialized professionals to conduct investigations in children with cancer. While clinical trials have become a standard approach to cancer treatment and have improved pediatric cancer outcomes, clinical research introduces additional risks that must be balanced with potential benefits [64]. Current efforts are directed towards being a legal organization with a consortium agreement between the centers, to further improve the...
Clinical Trial Perspective

Brunetto, Roesler, Abujamra, de Castro, Schwartsmann & Brunetto

collaboration and the capacity to collaborate with pharmaceutical companies. Innovative therapies with children with cancer (ITCC) is an academic European consortium, comprising a preclinical network of nine research laboratories specializing in pediatric tumor biology and preclinical drug evaluation, and a clinical network of pediatric oncology centers with specific expertise in early phase clinical trials and pharmacology in six European countries. In addition, a broad program to scientifically evaluate novel compounds against childhood solid tumor and leukemia models has been built and is supported by the NCI – the Pediatric Preclinical Testing Program (PPTP). The primary aim of the PPTP is to develop first-class preclinical data in order to assist pediatric oncology researchers in identifying new agents that will demonstrate significant efficacy when clinically evaluated against selected childhood malignancies.

Clinical trials & collaborations in developing countries

While in Europe and the USA the majority of children are treated in regional specialized children’s cancer centers according to well-defined protocols; by contrast, in developing countries the vast majority of children are treated outside research protocols and often at non-specialized centers. Despite the significant improvement in assisting patients over the last decade, only a few of these centers are enrolling patients in clinical trials, and even fewer are recruiting into translational studies. It is not surprising therefore that the survival rates in such settings are much lower.

To overcome the gap between what is common practice in Europe/USA and developing nations the international community must be supportive towards initiatives from emerging cooperative groups. In South America, for instance, the Grupo Latino Americano de Oncologia Paediatrica (GALOP) group in collaboration with COG is carrying out studies aiming at improving clinical trials participation in Brazil, Uruguay, Argentina and Chile. Similarly, several other groups in different continents are also developing cooperative trials under the guidance of partnership from European and American groups. These initiatives, however, to successfully reach long-term goals, do require changes in the current policies of national and international collaboration, including: the transfer of knowledge, methodologies and technologies from experienced international cooperative groups to emerging cooperative groups in developing countries; the conduct of multinational clinical trials in conjunction with pediatric cooperative groups in other countries; access of patients who currently do not participate in cooperative group trials; to establish a stable source of funding for national and international cooperative pediatric cancer clinical trials; the creation of a web-based system that can link pediatric oncology centers in Latin America and optimize data collection; and, to secure the support from the governments in covering and funding clinical trials in this population.

One of the major limitations for clinical trial participation in developing countries is the lack of trained personnel to properly collect data for these studies. There is still lack of recognition concerning the importance of clinical research assistants to join the multidisciplinary team at the majority of the centers. Data collection in many pediatric oncology units are usually carried out by very busy junior doctors as it is not considered a priority for most institutions. At present, however, there is growing understanding from principal investigators that there is a need not only to assist patients following recommendations from international studies, but also to design trials through multi-institutional collaboration. This in turn can only be accomplished when a true recognition is achieved for the value of qualified data collection from the few existing trials and the increment that it should be expected for future studies.

Informed consent/assent in children

Consent and assent forms constitute requirements for all aspects of medical care, diagnostic or therapeutic clinical trials. These forms promote and protect the dignity, privacy and confidentiality of the child and her family. Because children may represent a vulnerable population with developmental, physiological and psychological differences from adults, laws and declarations have viewed patients younger than 18 years as not having the capacity to consent due to limitations in their ability to understand certain issues in the decision process related to taking part in a clinical trial. Therefore, parents or a legal representative should act on behalf of them. Once the investigator is assured that parents or a legal representative understand the implications of participating in a study, they have the right to give informed permission, guided by GCP and local IRB/REB.

Dorn et al. showed that emotional factors were more frequently related to the understanding of research participation rather than age or cognitive development. In addition, Chappuy et al. assessed the parental understanding of the consent information. They described that although parents were more likely to better understand the aims, risks, potential benefits of the study and the right to withdraw; they were less likely to understand the procedures, the possibility of alternative treatments and the duration of participation. Many people involved in treating young people believe that the child or adolescent should play a role in the decision to enter a research study. Children are capable of assent when they become able to understand the research in question. This will require that the minor knows the procedures that will be performed...
and is aware that he may withdraw from participation at any time. Encouraging their involvement in decision-making is done out of respect for their rights as individuals and the desire to give them a sense of ownership in what happens during the trial. Even though children cannot consent, they are now routinely asked whether they agree (assent) or do not agree (dissent) to participate [60].

■ Regulatory incentives
Due to the rarity of pediatric malignancies when compared with the number of adulthood cancers, it is not surprising that pharmaceutical companies clearly favor investment in clinical trials for common diseases such as breast, colorectal, lung and prostate cancer. In 1998, the FDA finalized the Pediatric Rule, requiring pharmaceutical companies to carry out pediatric studies under certain circumstances. However, in December 2000, the Association of American Physicians and Surgeons, the Competitive Enterprise Institute and Consumer Alert filed a lawsuit against the Pediatric Rule, claiming that the FDA had no legal authority to mandate pediatric studies. In October 2002, a Federal District Court invalidated the Pediatric Rule. However, in 2003, the Congress passed the Pediatric Research Equity Act (PREA), which reiterates many of the Pediatric Rule principles and failure to conduct or complete these studies can result in economic penalties [2].

Furthermore, the FDA shifted its plan toward offering financial incentives for the conduction of clinical trials in pediatric malignancies and this resulted in the Pediatric Exclusivity Provision, which extends patent protection on novel investigational agents for an additional 6 months for pharmaceutical companies that do pediatric studies requested by the FDA. To begin with, the provision was a part of the FDA Modernization Act of 1997 and later renewed as part of the Best Pharmaceuticals for Children Act (BPCA), which also established the Pediatric Subcommittee of the Oncology Drugs Advisory Committee (ODAC). This Subcommittee is composed of experts in pediatric oncology and other fields, and patient, consumer and industry representatives. The ODAC is a forum for discussion of pediatric oncology drug development [2,62]. Hirschfeld et al. investigated more than 100 drugs that had been approved by the FDA for the treatment of malignancies. Only 15 had pediatric use information in their labeling, which was less than 50% of the drugs commonly used in the treatment of pediatric malignancies [2].

In 2007, a new legislation governing the development and approval of medicines for children was introduced in the EU. Regulation, as amended the ‘Pediatric Regulation’, presented many new tasks and responsibilities to the EMA, chief of which is the creation and operation of a Pediatric Committee to provide objective scientific opinions on any development plan for medicines for use in children [62]. An alternative strategy is to seek accelerated approval as described under a subpart of the Code of Federal Regulations. Under this provision, improvement of a surrogate marker likely to predict clinical benefit for a serious or life-threatening disease that has no satisfactory available therapy could lead to approval. There are large differences between the EMA and FDA-approach, which will not be within the scope of the review and can be addressed elsewhere [62].

Future perspective
In Europe, approximately 12,000 children are affected by cancer each year. Childhood cancer remains the major cause of death from disease after the age of 1 year, representing 3000 childhood deaths from cancer each year [25]. Because of small patient numbers, clinical researchers in pediatrics are often forced to weigh the consequences of conclusions drawn from studies with limited statistical power. Novel approaches to clinical trial design are needed, including designs that require fewer patients. Recently, research in this field has been facilitated by the creation of translational research teams. In this context, the NCI and the ITCC share common objectives to merge research on biological and preclinical evaluation of new drugs and to perform Phase I and II clinical studies in pediatric oncology. Analyzing the results from both adult trials and preclinical studies will help to prioritize potential drugs of interest for the pediatric population. Further progress depends on the development of molecularly targeted therapies based on the understanding of tumor biology [70]. On one hand, pediatric tumors might display fewer mutations and more defined biological alterations in comparison with adult tumors, suggesting that pediatric tumors may respond better to targeted therapies acting on specific genes and cell signaling pathways [70,71]. However, because pediatric solid tumors are rare, the availability of tumor and DNA samples from patients is limited, and clinical trials can only be carried out in cooperative settings involving different sites and including developing countries.

This review highlights some of the challenges in developing effective drugs for adulthood malignancies and common particularities for childhood cancers. Above all, for the process to be cost and time effective, study designs need to be able to adapt to rapidly growing changes in molecular biology, and be able to integrate some of the technological advances in engineering, computational and physics methods. This route must be facilitated by validated preclinical tumor models and biomarker assays, which will aid our ability to conduct successful hypothesis-testing clinical trials for biological agents in molecularly distinct tumor types, with better use of predictive, prognostic and PD biomarkers.
The growing understanding of the genetic landscape of tumors and the progress of molecular profiling technologies to assess protein, RNA, DNA and metabolites driving the malignant phenotype provides the potential to tailor medical care and trial design. Biological, medical and technological advances can elucidate representations of the network of interactions within a cell that regulate cellular and tumor behavior. In place of traditional methods, multidimensional data may allow a comprehensive map of how components of a biologic system integrate and may optimally predict the behavior of the cancer cell. This may have the potential to predict the natural course of diseases and its response to specific therapeutics in the near future [72,73].

### Executive summary

**Current standards in oncology for developing new agents**
- Preclinical studies should provide information regarding dose, schedule, toxicity, pharmacokinetic and pharmacodynamic data to guide initial dosing and trial design.
- Exploratory pharmacokinetic Phase 0 studies should involve very limited human exposure and have no therapeutic or diagnostic intent.
- The primary end point of a Phase I trial is to recommend a dose/schedule for further development and to describe toxic effects of new agents.
- Phase II trials are designed to assess drug efficacy, usually in a cohort of patients with a specific histological subtype or those likely to express the molecular target. Comparison can be made with historical controls.
- Phase III studies randomly compare to standard treatment or best supportive care with efficacy end points such as progression-free survival, disease-free survival and overall survival.
- Phase IV studies are those conducted after marketing approval.

**Drug development in the era of targeted therapy**
- Alternative end points have emerged to guide dose selection. Level of target inhibition on normal or tumor tissue, pharmacokinetic measures and functional imaging have become part of the tools that are being incorporated into early clinical trials as secondary end points to measure target modulation and give supportive evidence of drug activity.
- The determination of the ‘biologically active dose’ or optimal biologic dose required to inhibit the target or pathway should be the primary end point for targeted agents.
- The rational use of biomarkers should be applied throughout the drug-development process to identify and validate therapeutic targets, provide proof-of-concept, predict response and distinguish responders to a therapeutic intervention.
- Incorporation of poorly validated biomarkers may lead to misleading results and inappropriate decision making.
- The use biomarkers in early drug discovery may allow for a streamlined approach in identifying efficacious targeted therapies and possibly reducing costs.

**Drug development in pediatric oncology**
- Pediatric cancers are frequently more aggressive and rapidly progressive than many of the more indolent adult cancers and this in turn may impact the approach to traditional clinical trial design.
- It is essential that long-term follow-up and serial surveillance of survivors is built into studies as many patients are cured.
- Toxicities observed in Phase I clinical trials are not comparable between children and adults, nor is the biologic responses evaluated during Phase II and III clinical trials.
- Different pharmacokinetic profiles and differences between children and adults with regard to safety are issues for growth and development.
- Pediatric tumors arise and develop mainly as a result of one or more genetic aberrations, which invariably leads to constitutively active mechanisms such as those involving proto-oncogenes, or to faulty cell-cycle progression checkpoints involving tumor-suppression proteins.
- Limited preclinical models are available for pediatric malignancies.
- Pediatric Phase I studies are almost always performed after adult Phase I trials.
- The starting dose for adult Phase I trials are based on animal toxicology, pediatric trials historically begin at approximately 80% of the adult maximum tolerated dose.

**Ethical & regulatory considerations for clinical trials in children**
- Activities covered by good clinical practice include trial design and supervision of study activities, definition of scientific and ethical trial objectives, data collection and quality assurance, study analysis, and human subject protections.
- Particular emotional aspects involving children should be considered.
- In the USA and Europe, clinical trials have been a standard approach for the care of children with cancer for many years.
- Advances in therapy depend on collaborative clinical trials conducted by cooperative groups and consortia in Europe and the USA.
- Regulatory incentives are given to pharmaceutical companies to promote clinical trials in the pediatric population.
- In developing countries, the vast majority of children are treated outside research protocols and often at nonspecialized centers.
The process of drug development in pediatric oncology

Clinical Trial Perspective

Financial & competing interests disclosure

R Roessler is supported by the National Council for Scientific and Technological Development (CNPq) grant number 303703/2009-1. R Roessler, G Schwaertmann, AL Abujamra and AL Brunetto are supported by the National Institute for Translational Medicine (INCT-FTM), the South American Office for Anticancer Drug Development and the Children’s Cancer Institute (ICI-RS). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Clinical Trial Perspective
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The process of drug development in pediatric oncology

Clinical Trial Perspective


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