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A Framework to Develop Adapted Treatment Regimens to Manage Pediatric Cancer in Low- and Middle-income Countries: The Pediatric Oncology in Developing Countries (PODC) Committee of the International Pediatric Oncology Society (SIOP)

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Abstract

Many children with cancer in low- and middle-income countries are treated in hospitals lacking key infrastructure, including diagnostic capabilities, imaging modalities, treatment components, supportive care, and personnel. Childhood cancer treatment regimens adapted to local conditions provide an opportunity to cure as many children as possible with the available resources, while working to improve services and supportive care. This paper from the Adapted Treatment Regimens Working Group of the Pediatric Oncology in Developing Countries committee of the International Society of Pediatric Oncology outlines the design, development, implementation, and evaluation of adapted regimens and specifies levels of services needed to deliver them.

Introduction

Need for adapted regimens for use in low- and middle-income countries (LMIC)

Many pediatric cancer units (PCUs) in low- and middle-income countries (LMIC) treat children with cancer, but lack the infrastructure available to PCUs in high-income countries (HIC). Treatment using standardized regimens or protocols has led to unprecedented improvements in survival of children with cancer, but most published regimens are based on therapies developed and delivered in HIC. Treatment outcomes with these regimens differ in PCUs that treat different patient populations and lack a full complement of diagnostic facilities, imaging modalities, treatment components, and supportive care.[1] Accordingly, treatment risks and benefits may differ substantially between LMIC and HIC.

For example, the Total XI protocol for childhood acute lymphoblastic leukemia (ALL) achieved a 72% event-free survival (EFS) in the United States, but when implemented in Recife, Brazil, the EFS was 32%.[2,3] The same regimen was used in El Salvador with adaptations designed to reduce toxicity, including a 3-drug induction without anthracyclines.[4] This approach increased 4-year EFS from less than 10% to 48%. However, despite these adaptations, the rate of toxic death was 12.4% during remission induction therapy and another 4.6% in remission. This emphasizes the need to not only adapt treatment for LMIC, but also to carefully evaluate the results of adapted regimens to identify opportunities for further improvement.[5]

The first adapted regimens developed were called "graduated intensity regimens," a term replaced by "adapted treatment regimens" because the necessary adaptations often do not involve changes in chemotherapy intensity, but also incorporate use of distinct methods of staging, risk stratification, local control, and supportive care.[6] For example, the retinoblastoma guidelines applied this adaptation process to outline treatment based on availability of specific ophthalmologic interventions.[7] Similarly, additional chemotherapy was used for Wilms tumor and Hodgkin lymphoma when radiation therapy is unavailable.[8,9] Adaptations may include major changes in therapy, such as addition of chemotherapy and omission of radiation therapy in Wilms tumor, but could also include relatively minor alterations, such as

omission of 2 doses of doxorubicin from acute lymphoblastic leukemia remission induction therapy or use of prophylactic antibiotics when the risk/benefit ratio differs in LMIC and HIC.

It might be tempting to defer childhood cancer treatment in settings with suboptimal infrastructure, but this would be unwise, since most children have no option for transfer to a more advanced PCU, and many are curable even in settings with limited resources. For example, Burkitt lymphoma in African PCUs has been successfully treated with reduced-intensity regimens, despite very limited supportive care and related infrastructure.[10-12] Indeed, treatment with a high-intensity regimen when supportive care is inadequate can lead to paradoxically lower EFS by increasing toxic death more than it decreases relapse.[13-16] Cure rates can rise quickly with focus on preventing treatment abandonment, reducing toxic death, and adapting the diagnostic strategy, risk stratification algorithm, and treatment regimen to the local situation.[4] In Recife, Brazil, the cure rates for childhood ALL increased from 32% to over 65% using adapted regimens accompanied by rigorous programs to prevent treatment abandonment and reduce toxic death.[3,17] Curing the curable is ethically mandatory and highly cost-effective even in LMIC.[18-20]

Obstacles to adapting treatment regimens

Obstacles to adapting treatment regimens to local conditions have included an unwillingness to deviate from published regimens used in HIC due to provider preferences, cultural or historical reasons, misperception that 'more is better,' lack of published evidence about adapted regimens, insufficient local data on which to base rational adaptations (due to lack of hospital-based registries and routine outcome evaluation of locally treated patients), perceived ethical concerns about using a less intense regimen, and lack of time and expertise by LMIC physicians to adapt each regimen to local conditions. In some cases, physicians practicing in LMIC care for 10 times more patients than their counterparts in HIC. This makes it very challenging for them to engage in activities other than direct patient care, even if those activities might ultimately improve survival in their PCU. Furthermore, conditions in PCUs vary greatly, even within the same country. While there is general agreement that patients should be treated at the PCU that

offers the highest chance of cure, many LMIC have heterogeneous levels of care at various centers combined with complex health systems that may mandate treatment at a specific PCU based on insurance coverage and other factors unrelated to expertise.

Development and implementation of adapted treatment regimens

Several strategies have been employed to overcome the aforementioned obstacles (Table 1). Many clinicians have devised strategies to try to cure as many patients as possible despite the lack of key infrastructure at their center. For example, treatment of Hodgkin lymphoma and Wilms tumor without radiation therapy was first considered in PCUs without access to radiation therapy, and use of reduced doses of high-dose methotrexate in ALL and non-Hodgkin lymphoma regimens has been studied extensively in LMIC.[9,21-24] In fact, these and other innovative strategies now used in HIC to minimize toxicity and optimize long-term outcomes were pioneered in LMIC to address conditions that made the HIC regimen impractical in the local setting, including retinoblastoma staging, treatment of osteosarcoma without high-dose methotrexate, and others.[25,26]

To develop and disseminate adapted treatment strategies, the Pediatric Oncology in Developing Countries (PODC) Committee of the International Society of Pediatric Oncology (SIOP) established the Adapted Treatment Regimens Working Group, charged with providing such regimens for use in LMIC.[30] The volunteer leaders serve for 3-year terms and volunteer members carry out the projects. Meetings are conducted online via www.Cure4Kids.org and members listed on the SIOP web site (www.siop-online.org). To date, working group members have published adapted regimens for 7 cancers along with 2 supportive care manuscripts.[5-7,27-34] The published adapted regimens were developed with broad input from clinicians in multiple disciplines, and experts from LMIC and HIC, and have been improved during extensive review by peers from the global oncology community. Where possible, recommendations have been evidence-based, but when published evidence to guide regimen selection was not available, as is often the case in the most resource-limited settings, expert opinion was used. Four of these guidelines (Wilms tumor, Kaposi sarcoma, Burkitt lymphoma, and supportive care[35-37]) were designed for settings in

low-income countries where only the minimal requirements for treatment with curative intent are available (defined as setting 1, see Table 2). However, for some cancers, definition of an overall level of care was insufficient to select the best treatment regimen, because they depend on access to a particular component of care, such as neurosurgery for brain cancers or radiation therapy for unresectable sarcomas. Therefore, a framework based on specific service lines was required to guide clinicians to the best treatment, and to highlight the need for certain service lines to treat specific cancers. This paper provides such a framework and suggests components for each adapted regimen to make it maximally useful and applicable.

Choosing the optimal therapy depends on the setting

The "optimal" therapy in LMIC is not necessarily that used in HIC, but that which provides each child with the highest probability of cure in the given setting at the time of diagnosis. Of necessity, in LMIC the optimal therapy will change over time, with improvements in diagnostic accuracy, surgical expertise, improved access to supportive care and treatments such as radiation therapy or new drugs, implementation of treatment abandonment prevention programs, and as improved regimens are identified by research in HIC and LMIC. If the relapse rate with a given therapy is excessive, then the treatment may need intensification; however, if toxic death rates are too high, de-intensification may save more lives, pending improvements in supportive care. Therefore, constant evaluation of the regimens is imperative.

Selection of the optimal regimen for patients treated in a specific setting does not preclude making every effort to improve the environment of care. Explicit identification of the care that can be safely delivered may help prioritize quality improvement efforts. In general, priorities to improve survival rates include investments in core services for appropriate diagnosis and management: pathology and diagnostic imaging; nursing and access to essential medicines; prevention of toxic death by hand hygiene programs and rapid access to effective antibiotics; prevention of abandonment by provision of subsidized transportation, local housing, and food baskets; and family education and support programs. However,

after these essentials are in place, whether efforts should be put toward early diagnosis of retinoblastoma, local control for sarcoma patients, development of neurosurgical expertise for brain tumors, improved diagnosis and risk stratification systems, or other important aspects of pediatric cancer care depends on many factors. Of course, the initial focus should always be on curing the most curable patients. While the choice of focus and resource allocation will differ in different centers, prioritization can be evidence-based once incidence and outcome data are available for the various cancer types treated with adapted regimens and explicit evaluation criteria are formulated for each. For example, a PCU in which 20% of children with ALL die of toxicity during the first 3 months of therapy would appropriately select the Level 1 regimen for ALL, but as supportive care improves and toxic death decreases to 3%, excess relapse with a low-intensity treatment regimen may merit stepping up to the Level 2 regimen (Table 2).[5] However, if toxic death occurs in 5 of the next 25 patients treated with the Level 2 regimen, the stopping rule would be triggered and clinicians would know to step down to the Level 1 regimen and redouble efforts to improve supportive care. Decisions about the optimal regimen for a PCU would ideally fit within the context of regional and international disease-specific networks, such as the Global Neuroblastoma Network where peers and colleagues provide advice about treatment regimens and specific patients and implemented in the context of regional collaboration networks such as those listed in Table 1.[33]

Adapted treatment regimens, research, and individualized care

Adapted regimens for each pediatric cancer unit

Adapted regimens apply to groups of patients, and are based on the axiom that standardized care and following a specific regimen improves results for pediatric cancer patients, who require complex, prolonged treatments, often involving many disciplines. Minimizing variation in the regimen used for patients with the same disease allows oncologists, pediatricians, nurses, pharmacists, and other caregivers

to develop expertise and a deep understanding of the regimen's, expected toxicities while improving communication among team members.

Adapted regimens and research

Adapted regimens are not research protocols *per se*; rather, they represent efforts to improve care in each PCU for each disease. Adapted regimens are best applied in conjunction with a data management program and frequent, rigorous outcome evaluation to determine whether the regimen is achieving the expected results. In some cases, such quality improvement programs produce generalizable knowledge and are appropriate subjects for research to improve care and save lives even beyond the local setting.

One might argue that application of an adapted regimen that has not been validated by results from clinical trials represents a departure from standard care and therefore would constitute research. However, use of a regimen developed and studied only in HIC *without* adaptation for LMIC also represents a departure from standard care, since the context of treatment is different and limitations in supportive care and specific treatment modalities in LMIC can render a HIC regimen irrelevant or dangerous. In all cases, when treatment is provided with the goal to optimize the cure rate of an individual, consent for treatment should be obtained from the patient and family. By contrast, when information about outcomes is collected to produce generalizable knowledge with the intent to publish results, research committee approval should be obtained in advance, and the patient and family should provide consent for both treatment and participation in research.

This framework document facilitates the adaptation process, standardizes terminology and levels of care, and assures that all necessary elements are included in each published adapted regimen. We hope that this will be followed by a proliferation of regimens adapted to various situations and prospectively validated in research studies. In this regard, the Wilms tumor regimen for Level 1 settings is being studied by a group of 8 centers in sub-Saharan Africa, which will show how the adapted regimen and its implementation can be further improved.[32]

Standardized definitions of levels of care by service line

Levels of care available at a PCU are defined by service lines for infrastructure and personnel (Table 2) needed to manage each pediatric cancer. Heterogeneity of services is common in LMIC, and service line levels are distinct from the regimen level selected for a particular cancer or patient: a PCU may have Level 0 radiation therapy (none) but may offer Level 3 chemotherapy and supportive care. For the ALL regimen, such a PCU should choose the Level 3 treatment, but for Hodgkin lymphoma or Wilms tumor an adapted chemotherapy-only regimen is warranted.[38,39] The selection of the initial treatment regimen for each disease should be based on levels of service relevant to the disease and available to the patient, not on the overall level of the PCU. Service levels for this framework paper were developed by a consensus of working group members in consultation with domain experts from HIC and LMIC (e.g. radiologists for radiology section, surgeons for surgery section). These represent a starting point for definition of service levels, which require significantly more nuanced and disease-specific definition and validation. For example, management of Hodgkin lymphoma generally does not require MRI, so one could consider availability of Level 3 diagnostic imaging services for Hodgkin lymphoma even if the center lacks access to MRI. However, for sarcomas, a hospital lacking MRI would be considered Level 2. Ultimately, we envision using this framework to help writing groups created service levels that are disease-specific and to some extent protocol-specific.

Service levels outlined here are not primarily meant to be used to evaluate PCUs; rather, to help clinicians best choose the starting level for each disease (from which they will "step up" or "step down" as indicated by the stopping rules in each adapted regimen based on toxic death and relapse rates). Nuanced definition of service lines and application to adapted regimens for specific cancers will be carried out by global strategy groups like the World Health Organization, commissioned strategy groups like the Lancet Commissions, SIOP PODC Working Groups, regional networks, and others.

Assessment of levels of care by service line and the importance of effective access

This paper does not purport to offer a detailed guide to assessment and classification of PCUs; however, assessment of the level of each service line relevant for each cancer is a necessary first step to select the appropriate treatment regimens that will optimize outcomes. It must be emphasized that the level of each service line should reflect the level of service to which most patients have "effective access." The existence of services is irrelevant if the patient cannot access them due to overcrowding or inability to pay. A hospital with a Level 3 intensive care unit that is always full and therefore does not accept oncology patients is considered to have Level 0 intensive care, and the regimens adapted accordingly. Using an intense regimen that requires intensive care is a mistake at this hospital, since effective access influences toxic death rates. When determining the levels of service lines available, clinicians are encouraged to think in narrow terms: what services are effectively available to most patients most of the time?

Supportive care is important in the management of all pediatric cancers, but the level needed for acute myeloid leukemia (Level 3 for services including blood bank, intensive care, infection prevention and control) is higher than that needed for low-stage Wilms tumor (Level 0 or 1). Nutritional support is particularly important in LMIC, where malnutrition at diagnosis or during treatment is prevalent, and can increase the complication rate even for therapies that had minimal toxicity in HIC.[40-43] The PODC Adapted Treatment Regimens Working Group Guidance for supportive care in LMIC has published guidance for LMIC, and many HIC guidelines are relevant for LMIC.[28,44] All PCUs should have a multidisciplinary team, regardless of resource constraints. A team of doctors from multiple specialties, nurses, social workers, pharmacists, and data managers can accomplish most when working together. This core team can later mobilize other key professionals and community advocates needed for cancer care.

Adapted regimen manuscript preparation, review, and publication

Available infrastructure and personnel services at each "Level" should follow the standard descriptions provided herein and need not be repeated in future publications of SIOP PODC adapted

treatment regimens. However, the disease- and regimen-specific requirements along with additional disease-specific services should be included in the adapted regimens for each disease (e.g. neurosurgery for brain cancer, ophthalmology for retinoblastoma, N-MYC testing for neuroblastoma). Authors should define the minimum requirements for each service line to deliver each proposed adapted regimen, including chemotherapy regimens, dosing levels and intervals, and radiation therapy suggested by level of care. Development of SIOP PODC adapted regimens occurs in collaboration with the Adapted Treatment Regimens Working Group, whose membership is open. A flow chart describes the process of development (Figure 1) and Figures 2 and 3 provide examples.

Review by Working Group members and approval by group leaders is mandatory for all adapted regimens prior to submission to the SIOP Publications Committee to assure that all criteria are met and that the final product is clear and practical. Once approved, the manuscript may be submitted for additional peer review and publication. All manuscripts describing SIOP PODC adapted regimens should conform to the requirements enumerated in Table 3. Adapted regimens are designed with curative intent, even if conditions at the PCU suggest a regimen with a cure rate known to be less than that achievable in HIC. Use of the adapted regimen is ethically supported by the fact that alternative regimens, or lack thereof, would result in even lower cure rates. However, if a patient has access to a PCU with a higher cure rate for their disease, referral to that center is ethically mandatory. Furthermore, if patients have access to a locally adapted clinical trial this would be preferred over an adapted treatment regimen, which purports to describe the best standard therapy available for a given patient in a specific setting. However, awaiting the development and funding for such a clinical trial before implementing the best standard local care possible is not acceptable. Clinicians must attempt to choose the best treatment for each new patient each day, and adapted regimens are designed to facilitate this choice while awaiting better evidence (and better services within the PCU) to cure even more patients in the future.

Adapted regimen dissemination, field testing, and updates

The dissemination strategy has several components, including publication, presentation at SIOP Annual Meetings, regular open meetings of the SIOP PODC Adapted Treatment Regimen Working Group, education sessions via www.Cure4Kids.org, and creation of a repository of adapted regimens available via the SIOP web page and Cure4Kids. Extension of the concepts by Childhood Cancer International, consortia like GFAOP and AHOPCA, and groups like the Lancet Oncology Commission will provide further visibility. Getting the first set of adapted treatment regimens into the public sphere was the first priority of the SIOP PODC Adapted Treatment Regimen Working Group, because as Loblaw et al. point out: "…it is often the areas of greatest uncertainty in which the evidentiary base is incomplete, and thus, guidelines are needed most."[45]

The initial group of adapted regimens were developed using a series of consensus meetings held via regular online meetings by disease-specific working groups with feedback from the larger Working Group that includes all members of the disease-specific working groups. After the first step (creation of the adapted regimen), the critical next steps include 1) prospective validation in a variety of centers that use the adapted regimen, 2) evaluation of practical implementation barriers, and 3) documentation of patient outcomes. This process is ongoing for acute lymphoblastic leukemia and Wilms tumor, and will be followed by revision of the adapted treatment regimen to address implementation barriers and modify the regimen as necessary based on results plus any new published relevant literature from HIC or LMIC. The Working Group should review each adapted treatment regimen annually and update it every 3 years.

Selection of the optimal regimens for the Pediatric Cancer Unit

The "optimal" treatment regimen depends on rates of treatment failure, toxic death, abandonment, second cancer, and the salvage rate for those who relapse. Ideally, treatment regimens best suited to each site would be established in collaboration with local clinicians, national, and international disease experts. The adapted regimen anticipated to cure the highest number of patients given the current status of the PCU should be used. It may be more intense, less intense, or simply different (such as using additional chemotherapy when radiation therapy is not available) than regimens used in HIC.

Hodgkin lymphoma illustrates the nuances of "optimal" regimen selection. In HIC, the benefits of radiation therapy were documented in the short term (5-10 years) for various subgroups of patients. In the CCG5942 trial, patients with complete remission after chemotherapy were randomized to no further therapy or involved-field radiation therapy.[46] At 10 years, EFS of children who received radiation therapy was 8% higher than with chemotherapy alone, but overall survival was similar.[47] However, as late effects of radiation therapy occur longer than 10 years after treatment, in the long-term, omission of radiation therapy actually predicted better outcomes (in HIC). Indeed, a recently published decision analysis of patients treated in HIC found that average conditional life expectancy was higher without radiation therapy (57.2 years versus 56.4 years).[48] However, this model does not apply in LMIC, where the rates of successful salvage therapy for those who relapse may be much lower than in HIC.[49] In settings where salvage therapy is suboptimal, and few survivors are seen following relapse, a more intense front-line regimen may be preferred, and the benefits of radiation therapy may be greater than they were in HIC.

Thorough evaluation of the level of each service line, combined with prospective analysis of outcomes for patients treated previously to document rates of abandonment, toxic death, relapse, and successful salvage allows selection of an appropriate approach for each cancer that will cure the greatest number of patients at each PCU. Service lines provide a framework for initial selection of the adapted regimen likely to have the highest cure rate in the specific setting, but the regimen may need adjustment based on outcome evaluation in case the initial selection was not optimal. Furthermore, regimens should be periodically evaluated and adjusted based on changing conditions: if the PCU improves access to intensive care for cancer patients, adds a guest house for patients who live far away, increases the number of nurses, or improves the speed with which antibiotics can be administered to patients with febrile neutropenia, then the best adapted regimen for some diseases may change.

Individualized treatment for specific patients

Individualized management of specific patients, whether on an adapted regimen or not, is inevitable in oncology. Such individualized management depends on the experience of the treating clinician, ideally

complemented by local multidisciplinary tumor boards and consultation with national or international disease experts. Although beyond the scope of this paper, the guiding principle for individualized management is to maximize the probability of cure for each individual patient. Conditions for a specific patient may warrant adjusting the regimen at the beginning for that individual to maximize her/his probability of cure. For example, in a pediatric cancer unit that uses a Level 1 regimen for childhood ALL, a patient with high risk of relapse due to adverse presenting leukemia features, who tolerated initial therapy in good condition, and who lives 100 meters from the PCU may be safely treated on a Level 2 or 3 regimen. Such exceptions to the standard protocol used at the PCU should each be carefully justified and documented, and the regimens designed so that the treatment intensity can be increased without completely changing the backbone. Toxicities or other events that occur during therapy may warrant adjusting the regimen for an individual to maximize her/his probability of cure. Many PODC members participate in regular online meetings via www.Cure4Kids.org to discuss the management of individual patients and practical aspects of applying protocol-based care in diverse settings. Most such meetings are open, and there are several hundred per month in many regions, different languages, and for different diseases.[50] No adapted regimen can substitute for the experience of the clinician and ready access to advice from expert colleagues.

Conclusion

Implementation of standardized care adapted to local conditions has the potential to improve outcomes and establish a global community using similar regimens in similar situations, thereby facilitating future treatment advances. Coupled with a data management program and continuous quality improvement, adapted regimens can produce the highest probability of cure for children with cancer in all settings.

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Table 1. Examples of strategies to development and implement adapted treatment regimens for children with cancer in low- and middle-income countries

Strategy	Examples	Mission	Methods
SIOP PODC Working Groups	SIOP PODC Adapted Treatment Regimens Working Group	Develop, adapt, implement, and improve treatment regimens for children with cancer in LMIC	1. Regular online meetings (www.Cure4Kids.org) to develop adapted treatment regimens 2. Implementation of adapted treatment regimens in LMIC with dissemination of results via SIOP presentations and peer-reviewed publications 3. Improvement of regimens based on their utility and effectiveness
Regional networks of peer pediatric oncology units	AHOPCA GFAOP	Improve care and outcomes for children with cancer and blood disorders in Central America (AHOPCA) and French-speaking African countries (GFAOP)	1. Email contact to discuss patients, protocols, and supportive care issues 2. Regular online meetings (www.Cure4Kids.org) to discuss patients, protocols, and supportive care issues 3. Shared treatment regimens adapted to conditions of the PCUs in the regional network[12,51-56] 4. Shared strategies to reduce treatment abandonment and toxic death 5. Annual or bi-annual meetings to review all treatment regimens and discuss ways to further improve them 6. Facilitated outcome evaluation, statistical analysis, and publication of results
National networks of pediatric oncology units	SOBOPE[57] GATLA[58,59] TPOG[60] InPOG[61] IPHOG[62] PINDA[63]	Improve care and outcomes for children with cancer by implementing national protocols	1. Shared protocols adapted to national conditions 2. Shared strategies to address medication shortages and other national issues 3. Annual meetings to review protocols and discuss ways to improve them 4. Facilitated outcome evaluation, statistical analysis, and publication of results 5. Educational exchange among participating PCUs
Global disease-specific networks	Global Neuroblastoma Network	Improve care and outcomes for children with neuroblastoma in LMIC and HIC	1. Case discussion via online meetings (www.Cure4Kids.org) 2. Development of adapted treatment regimens 3. Facilitation of protocol design for PCUs in LMIC

SIOP, International Society of Pediatric Oncology; PODC, Pediatric Oncology in Developing Countries committee of SIOP; LMIC, low- and middle-income countries; HIC, high-income countries; AHOPCA, Asociación Hemato-Oncología Pediátrica de Centroamérica; GFAOP, Groupe Franco-Africain d'Oncologie Pédiatrique; SOBOPE, Sociedade Brasileira de Oncologia Pediátrica; GATLA, Grupo Argentino de Tratamiento de la Leucemia Aguda; TPOG, Turkish Pediatric Oncology Group; InPOG, Indian Pediatric Oncology Group; INPHOG, Indian Pediatric Hematology-Oncology Group; PINDA, Programa Infantil Nacional de Drogas Antineoplásicas; PCU, pediatric cancer unit

Table 2. Characteristics of infrastructure and levels of each service line relevant for selection of SIOP PODC adapted treatment regimens*

Service line	Level 0	Level 1	Level 2	Level 3	Level 4
General description					
Pediatric cancer unit general description*	Pilot project	Some basic oncology services	Established pediatric oncology program with most basic services and a few state-of-the-art services	Pediatric oncology program with all essential services and most state-of-the-art services	Pediatric oncology center of excellence; state-of-the-art services and some highly-specialized services (e.g. proton beam radiation therapy, MIBG therapy, phase I studies)
Typical settings	Centers in LIC in disadvantaged areas	Centers with relatively greater resources in LIC, disadvantaged areas in lower MIC	Centers with relatively greater resources in lower MIC, disadvantaged centers in upper MIC	Many centers in upper MIC, most centers in HIC	Selected super-specialty centers that offer very advanced and high-quality tertiary and quaternary care
Medical facilities					
Inpatient ward	No pediatric oncology inpatient unit	Area of the hospital where children with cancer are admitted when possible; frequent overflow to other wards; no fixed staff	Pediatric oncology inpatient ward available to most patients; limited fixed staff (e.g. oncology nurse permanently assigned)	Pediatric oncology inpatient ward separate from inpatient units for other patients; sufficient beds such that oncology patients rarely require admission to other wards	Subspecialized pediatric oncology wards (e.g. transplant, neurooncology, acute myeloid leukemia)
Inpatient ward effective access	Very limited access (e.g. due to lack of beds or high cost relative to typical family's salary)	Accessible to some patients sometimes	Accessible to most patients most of the time	Accessible to all patients almost always	
Isolation rooms for infected patients	None	Isolation rooms exist but rarely available	Isolation rooms usually available when needed	Isolation rooms almost always available when needed	
Outpatient facilities	None	Outpatient area for chemotherapy and some emergency care; services for surgery/diagnostic	Outpatient area for chemotherapy and some emergency care available most	Full-service outpatient care available 24 hours/day for chemotherapy and emergencies; pediatric-specific	Outpatient satellite facilities available to provide care close to home

		imaging may be primarily for adults but can partially accommodate pediatric patient needs	of the time; services that can mostly accommodate pediatric patient needs for surgery and diagnostic imaging	surgery and diagnostic imaging suites and services	
Outpatient facilities effective access	Very limited access (e.g. due to lack of space or high cost relative to typical family's salary)	Accessible to some patients sometimes	Accessible to most patients most of the time	Accessible to all patients almost always	
Radiation therapy					
Radiation therapy facilities	None	Cobalt machine	Linear accelerator or cobalt machine (cobalt machine is preferable in areas with poor electricity supply)	Linear accelerator with fully integrated planning system	Proton beam facility; advanced photon radiotherapy
Radiation therapy planning tools	None	2D planning	Some 3D planning available to some patients	3D planning, full conformal therapy available; intensity-modulated and volumetric modulated arc therapy (VMAT) available to some patients	All specialized techniques available, including proton beam, radiosurgery, and VMAT
Radiation therapists	None	Radiation oncologists with adult expertise	Radiation oncologists with some pediatric experience	Radiation oncologists with pediatric expertise	Pediatric radiation oncologists with highly specialized disease-specific expertise
Anesthesia for radiation therapy	None	Sedation only	Sedation/anesthesia from general anesthesiologists available for some pediatric patients	Sedation/anesthesia from pediatric anesthesiologists available for most pediatric patients	Experienced pediatric anesthesiologists routinely available for all pediatric patients requiring radiation therapy
Radiation therapy personnel (medical physicists, radiation therapy technicians)	None	Few personnel, no pediatric expertise	Adequate personnel with some pediatric expertise	Adequate personnel with experience using advanced techniques and with pediatric expertise	Subspecialty expertise in specific pediatric cancer types (e.g. brain cancers)
Radiation therapy effective access	None	Radiation therapy available to some patients some of the time; frequent delays	Conformal radiation therapy available to most patients most of the time; occasional delays	Modern radiation therapy options reliably available to all patients in a timely way	Full range of radiation therapy options available to all patients
Access to medications					

Antineoplastic drug availability	Very limited access to a small selection of oncology drugs	Access to a limited selection of oncology drugs; frequent shortages	Access to most essential oncology drugs; occasional shortages	Access to almost all commercially available drugs; rare shortages	Access to all approved drugs, plus phase I and phase II studies
Antineoplastic drug quality	Low or unknown quality	Variable or unknown quality	Occasional access to high-quality branded medicines; generic medicines of mostly good quality	Consistent access to high-quality branded and generic medicines	
Antineoplastic drug effective access	Dependent entirely on NGO support or out-of-pocket payment	Limited supply of basic drugs accessible from the health system; dependent on NGO support or out-of-pocket payment for some drugs much of the time or most drugs some of the time	Basic drugs provided by the health system, more expensive drugs may depend on private insurance or NGO support	Most oncology drugs provided by the health system or private insurance available to most patients	Full access to all drugs by all patients
Antimicrobial drug availability	Limited selection, delayed access	Limited selection available to most patients, some delays	Wide selection available to most patients with minimal delays, some antifungals available	Wide selection of antibiotics, antifungal agents, and antiviral agents available to all patients with rare delays	Access to compassionate use (single-patient exceptions for unapproved medicines) and protocols for new antimicrobials
Antimicrobial drug effective access	Dependent entirely on NGO support or out-of-pocket payment	Limited supply of basic drugs from the health system; dependent on NGO support for some drugs much of the time or most drugs some of the time	Basic drugs provided by the health system, more expensive drugs may depend on private insurance or NGO support	Most antimicrobial drugs provided by the health system or private insurance available to most patients	Full access to all drugs by all patients
Analgesic drug availability	Limited selection of analgesics, delayed access	Limited selection of opioid and non-opioid analgesics available to most patients, some delays	Moderate selection of opioid and non-opioid analgesics available to most patients with minimal delays	Wide selection of analgesic agents, access to multiple pain management modalities (e.g. nerve block); pain management specialists available when needed	Wide range of enteral and parenteral opioid and non-opioid analgesics; full spectrum of pain management modalities; pain management specialists embedded in the multidisciplinary team
Analgesic effective access	Dependent entirely on NGO support or out-of-pocket payment; significant regulatory or	Limited supply of basic drugs from the health system; dependent on NGO support or out-of-pocket payment for much of the time; some regulatory and cultural barriers	Basic drugs provided by the health system, more expensive drugs may depend on private insurance or NGO support; few regulatory or cultural barriers	Most drugs provided by the health system or private insurance available to most patients; no regulatory or cultural barriers	Full access by all patients with no delays

	cultural barriers				
Supportive care drug availability (e.g. anti-emetics, constipation management, growth factors)	Limited selection, delayed access	Limited selection available to most patients, some delays	Wide selection available to most patients with minimal delays	Wide selection of anti-emetics, growth factors, and other supportive care medicines available to all patients with rare delays	Access to compassionate use protocols for new and experimental supportive care medicines
Supportive care drug effective access	Dependent entirely on NGO support or out-of-pocket payment	Limited supply of basic drugs from the health system; dependent on NGO support or out-of-pocket payment for some drugs much of the time or most drugs some of the time	Basic drugs provided by the health system, more expensive drugs may depend on private insurance or NGO support	Most oncology drugs provided by the health system or private insurance available to most patients	Full access to all drugs by all patients
Supportive care					
Blood product availability	Whole blood	Some blood products available sometimes for some patients; no irradiation/filtration possible	Red blood cells, platelets, cryoprecipitate, and fresh frozen plasma often available; irradiated/filtered blood products sometimes available	Ready availability of all blood products, including pheresed platelet units; routine access to irradiated/filtered blood products	
Blood product effective access	Accessible to a few patients; long and frequent delays	Accessible sometimes for some patients; frequent delays	Usually accessible to most patients within a reasonable time period	Accessible to all patients within 2 hours	
Intensive care availability	None	Intensive care unit present; limited equipment; personnel with limited pediatric experience	Mechanical ventilators, inotropes, central venous access, dialysis; personnel with some pediatric expertise	Pediatric intensive care unit with all necessary equipment and personnel with pediatric intensive care expertise	Advanced cardiopulmonary support available (extracorporeal membrane oxygenation)
Intensive care effective access	Not accessible to most patients	Accessible to some oncology patients occasionally; frequently delayed access	Accessible to some oncology patients when space available; occasionally delayed access	Readily accessible to all patients	
Infection prevention and control	None	Hand hygiene stations usually available; prophylactic antibiotics for *Pneumocystis jiroveci* usually available	Hand hygiene widely practiced; prophylactic antibiotics for *Pneumocystis jiroveci* always available	Universal hand hygiene, adequate positive and negative pressure isolation rooms	

Nutritional support availability and effective access[6]	None	Limited nutritional support available to some patients; staff with limited training or experience in management of nutritional issues	Enteral feeding always available and parenteral feeding available sometimes; some staff with nutrition training or experience	Enteral and parenteral feeding (including individualized preparations) always available; trained pediatric nutritionists available to all patients	Full access to a wide array of specialized nutritional support modalities by trained pediatric oncology subspecialist staff
Venous access	Peripheral IV access	Mainly Peripheral IV access; PICC available to some patients	Central venous access and a care plan for patients with a central line available to selected patients	Central venous access and a care plan for patients with a central line available to all patients	
Safe chemotherapy preparation infrastructure	None	No special chemotherapy preparation area; no access to personal protective equipment	Ventilated chemotherapy preparation area (e.g. to outside); access to personal protective equipment usually available	Chemotherapy preparation hood available; access to personal protective equipment always available	
Pain and symptom management team	No specific program	Pain and symptom management by oncology personnel without special expertise in this area	Some specialized pain and symptom management personnel; some pediatric experience	Specialized pain and symptom management personnel; pediatric expertise	Service with a full range of pharmacologic and non-pharmacologic tools for pain and symptom management tailored for children
Diagnosis and staging					
General laboratory availability	Must send out even basic labs	Blood chemistry profile and hemogram	Blood chemistry profile and hemogram, plus some specialized testing (e.g. ferritin, urine catecholamines); rapid turnaround time possible for critical labs	Blood chemistry profile and hemogram, wide range of specialized testing (e.g. methotrexate levels, fractionated plasma/urine metanephrines); rapid turnaround time routine for critical labs	Reference laboratory including specialized testing for pharmacokinetics, phase 1 studies, etc.
General laboratory effective access	Rarely accessible, depends on NGO support	Accessible to some patients sometimes; may depend on financial situation or NGO support	Accessible to most patients; partial dependence on financial situation or NGO support	Accessible to all patients with rare exceptions; 24-hour service 7 days per week and holidays	
Pathology availability	None	Microscope, H&E staining, CSF cytology	Limited immunohisto-chemistry panel (disease-specific), cytospin for CSF samples	Complete immunohisto-chemistry panel; molecular pathology and cytogenetics for most diseases; pediatric expertise necessary for specific diagnosis and staging; access to consultation with disease-specific expert pathologists at other centers	Research diagnostics, whole genome sequencing, molecular pathology for all diseases

Pathology effective access	Rarely accessible; depends on NGO support; long delays	Accessible to some patients sometimes; may depend on financial situation or NGO support; frequent delays in access to results	Accessible to most patients; partial dependence on financial situation or NGO support; occasional delays in access to results	Accessible to all patients with rare exceptions; rare delays in access to results	
Pathology personnel	No pathologist	Pathologist available for some cases	Pathologist available for all cases	Pediatric pathologist available for all cases	Pathologist with highly specialized disease-specific expertise
Hematopathology availability	None	Microscope, H&E staining, CSF cytology	Limited immunohisto-chemistry panel (disease-specific), flow cytometry and cytogenetics available most of the time	Flow cytometry of high quality; minimal residual disease testing; molecular pathology and cytogenetics; pediatric expertise; access to consultation with disease-specific expert pathologists at other centers	Research diagnostics, whole genome sequencing, molecular pathology for all diseases
Hematopathology effective access	Rarely accessible, depends on NGO support	Accessible to some patients sometimes; may depend on financial situation or NGO support	Accessible to most patients; partial dependence on financial situation or NGO support	Accessible to all patients with rare exceptions	
Hematopathology personnel	No hemato-pathologist	Hematopathologist available for some cases; hematologist with some hematopathology expertise	Hematopathologist available for most cases; oncologist with extensive pediatric hematopathology expertise	Hematopathologist with pediatric expertise available for all cases	Hematopathologist with highly specialized disease-specific expertise
Diagnostic imaging availability	None	Radiographs, ultrasound	CT scan, bone scintigraphy, gallium scintigraphy; occasional availability of anesthesia when needed	Magnetic resonance imaging PET-CT available to most patients; routine availability of anesthesia when needed	Specialized imaging; advanced nuclear medicine applications (e.g. metaiodobenzylguanidine [MIBG] scanning)
Diagnostic imaging effective access	Rarely accessible, depends on NGO support	Accessible to some patients sometimes; may depend on financial situation or NGO support	Accessible to most patients; partial dependence on financial situation or NGO support	Accessible to all patients with rare exceptions	
Diagnostic imaging personnel	No radiologist	Radiologist available to interpret most imaging, occasional delays	Radiologist available to interpret all imaging in real time; some interventional radiology	Pediatric radiologist available to interpret all imaging in real time; advanced interventional radiology	Pediatric radiologist with highly specialized disease-specific expertise
Personnel not included with specific service lines above					
Multidisciplinary team	Absent	Ad hoc meetings for special cases	Routinely scheduled meetings with reasonable attendance	Real-time discussion of all complex cases to guide important care decisions	Incorporation of molecular and genetic expertise in meetings; cancer-specific multi-disciplinary

					meetings like a CNS tumor or a sarcoma meeting.
Oncology team leader	Primary care physicians care for cancer and many other diseases	Primary care provider with interest in oncology	Primary care provider with pediatric oncology experience or some training, medical oncologist without pediatric expertise	Pediatric oncologist or medical oncologist with significant pediatric experience or training	Pediatric oncologist with highly disease-specific expertise
Oncology team training and experience	A few staff members with basic training	A few oncology personnel with some oncology training; trainees responsible for many aspects of patient care	Generally adequate numbers of oncology personnel; consistent supervision of any trainees involved in patient care	Full complement of pediatric oncologists; specialized oncology nurses; pharmacists with oncology training	Full complement of oncology personnel, including specialized physician extenders (e.g. nurse practitioners, hospitalists)
Oncology physician effective access	Rarely accessible; for private patients only	Occasionally accessible; most oncology work done by non-oncologists	Usually accessible, some oncology work done by non-oncologists or medical oncologists with some pediatric expertise	All patients cared for by pediatric oncologists	
Nurse training and expertise	No nurses with oncology training and no experience with oncology patients	Nurses with no specialized oncology training; some experience with cancer patients	Nurses with some dedicated oncology training and experience (e.g. the ability to handle chemotherapy); oncology nurses not permanently assigned to the oncology unit; nurse educator available sometimes	Nurses with oncology training and experience who are permanently assigned to the pediatric cancer unit; nurse educators available	Highly specialized pediatric cancer nurses with disease-specific expertise
Nursing effective access	Extremely low nurse-to-patient ratio for oncology patients (1:25 or lower)	Very low nurse-to-patient ratio for oncology patients (1:15 or lower)	Low nurse-to-patient ratio for oncology patients (1:7 or lower)	Adequate nurse-to-patient ratio for oncology patients (1:6 or higher)	
Surgery	No surgeon	General surgeon; limited pediatric experience	Pediatric surgeon with limited oncology experience, oncology surgeon with limited pediatric experience	Pediatric oncology surgeon	Pediatric cancer surgeons with highly specialized disease-specific expertise
Surgical subspecialties relevant for oncology	None	Adult subspecialty surgeon (neurosurgeon, orthopedic surgeon, ophthalmologist, other)	Some pediatric subspecialty surgeons (neurosurgeon, orthopedic surgeon, ophthalmologist, other)	Full range of pediatric subspecialty surgeons (neurosurgeon, orthopedic surgeon, ophthalmologist, other)	Pediatric subspecialty surgeons with highly specialized disease-specific expertise

Anesthesiologists	None	Anesthesiologist available sometimes	Anesthesiologists available for major procedures	Pediatric anesthesiologists available for all procedures; cancer surgery experience	Pediatric anesthesiologist with highly specialized disease-specific expertise
Pharmacists	None	Pharmacist in the hospital to dispense medications, but not available to prepare chemotherapy	Pharmacist available to prepare most chemotherapy and provide support to doctors and nurses	Dedicated oncology pharmacist with expertise preparing chemotherapy and monitoring drug safety	Highly specialized pediatric oncology pharmacists with expertise with specific patient groups (e.g. transplant) and medicine classes
Infectious disease specialists	None	General pediatricians manage infectious disease problems	Pediatricians with special interest in infectious disease available for some patients	Pediatric infectious disease subspecialist available for most patients	Pediatric infectious disease subspecialist embedded in the multidisciplinary oncology team
Pediatric subspecialty support (e.g. nephrology, neurology, endocrinology)	None	General pediatricians manage subspecialty problems	Pediatricians with a special interest in subspecialty care	Pediatric subspecialists in most specialties	Pediatric subspecialists in all specialties
Professions allied to medicine (e.g. physical therapist, occupational therapist, speech therapist, psychologist)	None	Some availability of some professionals	Some availability of most professionals for most patients	Full range of allied healthcare professions available	Professionals with specialized, pediatric, disease-specific expertise
Social workers	None	Small number of social workers available to some patients	Social workers available to most patients	Adequate number and training of social workers available to all patients	Professionals with specialized pediatric, disease-specific expertise
Logistical and social support					
Abandonment prevention program	None	Limited support for some patients' non-medical expenses. Limited support for some medical expenses. Limited access to psychologists, social workers, and parent support groups.	Guest house, subsidized food and subsidized transportation for some patients some of the time. Substantial support for most medical expenses for most patients. Some access to psychologists, social workers, and parent support groups.	Guest house, subsidized food and subsidized transportation provided to all patients with documented need. Full support for almost all medical expenses for almost all patients. Reliable access to psychologists, social workers, and parent support groups for all patients.	Full support for housing, food, transportation, and daily non-medical necessities. Vocational training and support for school for patients and families. Full support for all medical expenses for all patients. Universal access to psychologists, social workers, and parent support groups for all patients.

Guest house (patient/family lodging)	None	Available to a few patients; delayed access; over-crowded	Available to many patients; occasional overcrowding	Adequate number of rooms, rapid and easy access to the hospital or outpatient care	
Appointment scheduling and call-back system	None	Appointment records kept, no systematic way to identify patients who miss an appointment	System to identify patients who miss appointments; ad hoc tracking and call-back	Electronic appointment system with automated warnings for missed appointments; tracking system to contact patients who miss appointments	Electronic appointment and tracking systems fully integrated into a state-of-the art electronic health record
Transportation support	None	Some transportation subsidy for some patients	Transportation subsidy for most patients who need it	Full transportation subsidy and tracking to proactively identify patient needs	
Patient and family education	None	Some education for some patients and families	System for patient and family education for most patients	Routine and continuous patient and family education for all patients	
Patient and family support groups	None	Ad hoc support by some families of others; not supported by the oncology service	Support groups that meet regularly; support from the oncology service	Routine and integrated patient and family support groups fully supported and moderated by trained pediatric oncology personnel (e.g. psychologist, social worker)	
Health system					
Satellite centers for shared care	None	Informal relationship with local primary care colleagues. Communication delayed or sporadic.	Network of primary care colleagues willing to facilitate some aspects of treatment and follow-up. Communication as needed for specific patients	Network of primary, secondary, and tertiary care centers with established communication methods and written procedures for the care that should be provided at each center.	Advanced, integrated referral and communication pathways and fully shared medical records
Data management program	None	Record of patients treated is kept ad hoc by various staff members	Data manager collects basic information about most patients. Electronic database with occasional back-ups.	Data manager collects basic information about all patients and detailed information for those treated with specific regimens. Regular evaluation of outcomes, including toxic death, abandonment, and event-free survival. Electronic database with daily back-up procedure, access controls, and security procedures.	Data manager career ladders fully implemented and local team capable of advanced data analysis to guide care. Database fully integrated with the electronic health record.

Research focused on quality improvement and enhancing clinical care	None	Limited single-center research including retrospective analyses with limited outcome data	Single-center retrospective studies with good follow-up and outcome data, prospective studies	Multi-center retrospective or prospective observational studies or those with single arm interventions; benchmarking against other hospitals to identify areas for improvement	Part of prospective multi-center Phase III randomized controlled trials; Phase I/II trials; contributing to generalized knowledge locally, regionally, nationally, and internationally

* These categories are provided to facilitate initial selection of the appropriate SIOP PODC adapted treatment regimen for each type of cancer, not primarily as an evaluation tool for PCUs. PCU, pediatric cancer unit; PICC, peripherally inserted central line, PODC, Pediatric Oncology in Developed Countries; CSF, Cerebrospinal fluid; CT, computed tomography; H&E, Hemotoxylin and Eosin; NGO, non-governmental organization; LIC, low-income country; MIC, middle-income country; HIC, high-income country; MIBG, metaiodobenzylguanidine

Table 3. Requirements for SIOP PODC adapted regimen publications

Component	**Requirement**
Service lines and levels	Use the service lines and levels outlined in this guidance paper (Table 2).
	The writing committee for each adapted regimen is expected to elaborate where necessary.
Diagnosis and risk stratification	Specify the approach to the disease-specific elements needed for adapted diagnosis, staging, and risk stratification
	Include a flow chart with a clear algorithm to guide application of the adapted diagnosis, staging, and risk stratification to arrive at the correct adapted treatment regimen (see the example in Figure 3).
Treatment regimens	Identify the levels of each service line needed for each level of the adapted regimen (see the example in Figure 2).
	Specify adapted treatment regimens and response evaluation in a table with details sufficient to treat the patient (number of cycles, criteria to start each cycle, required and recommended monitoring, dose modification recommendations for toxicities, timing of local control when relevant, timing of response evaluation, response criteria).
	Include alternatives with similar efficacy where they exist (e.g. ABVD vs. OEPA/COPDac for Hodgkin lymphoma).
	Outline key management differences for initial regimen selection and any alteration in timing of surgery or chemotherapy as mandated by local surgical or patient factors (e.g. upfront surgery vs. chemotherapy for retinoblastoma or Wilms tumor).
	Provide detailed recommendations and rationale to guide potential decision-making for chemotherapy substitution or regimen readjustments when individual chemotherapeutic agents are missing.
	Provide treatment roadmaps that include all elements of treatment for all phases of the regimen (drugs, doses, route of administration, fluid in which to mix the chemotherapy, schedule, recommended evaluations, timing of local control).
	Explicitly recommend strategies to treat patients when key elements are missing (e.g. lack of radiation therapy, laser therapy for local control of retinoblastoma, or access to stem cell transplantation).
	Make the adapted regimens as evidence-based as possible and provide supporting references.

Evidenced-based recommendations	Note the level of evidence available for specific recommendations, and outline to the extent possible the practice settings where evidence has been primarily generated.
Supportive care	Provide supportive care recommendations that address common toxicities of the proposed regimens and any unique complications of the cancer.
	No need to provide general recommendations, which are available from various sources.[23]
Diagnostic evaluation and monitoring	Consider any data that may support less intense diagnostic evaluation or monitoring.
	Consider evidence that justifies allocation of resources for specific testing.
Selection of the most appropriate initial regimen for a particular pediatric cancer unit	Provide guidance to help clinicians identify the optimal regimen for their patients given the available resources.
	Include stopping rules for toxic death when one should "step down" to a less intense regiment.
	Provide criteria to "step up" to the next regimen and specific guidance about when and how to step up or step down to a different regimen to cure the highest number of children possible.
Review process	Follow the approval process that includes review by the SIOP PODC Adapted Treatment Regimens Working Group leaders and by the SIOP Publications Committee prior to submission for publication (See Figure 1)

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