SIOP's PARC Program: Advancing research capacity for paediatric cancer clinical trials in low-resourced countries

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Sustained advances in paediatric oncology have been achieved through better organization of multidisciplinary care and embedding a research culture as part of first line therapy. High survival rates are achievable with treatment regimens using mostly generic medicines and optimized risk stratification. However, research in paediatric oncology in low-resourced countries has lagged behind that of high-income countries. To change this, and to stimulate production of evidence most relevant to local needs, the SIOP PARC Program will invest in capacity development of large-scale (international and national) cooperative groups working on paediatric oncology in low- and middle-income countries. The goal of the PARC Program is to increase the capacity for research-informed treatment of children and adolescents with cancer and to improve the quality of care and cure. Three PARC-funded capacity development projects – in Africa, Asia and Latin America – will begin in 2022.

Overall survival of children with cancer in low- and middle-income countries (LMICs) is lower than in most high-income countries (HICs). The reasons for this vary, depending on the different resource levels and organization of care and commonly include late diagnosis, inadequate diagnostic capabilities, poor access to adequate treatment, deficient supportive care and financial and other family pressures that lead to treatment abandonment. Also, patients may have clinical co-morbidities, such as malnutrition or chronic infections, that influence their tolerance of treatment *(1)*. Despite these challenges, specific initiatives within LMICs, often supported by HIC partner institutions or clinical research groups, have demonstrated successful mitigation strategies to improve survival rates of children presenting with potentially curable cancers types *(2-5)*. The treatment strategies for most paediatric tumours applied in LMICs are based on "standards of care" derived from the results of clinical trials conducted in HICs, usually with some adaptations to make them feasible in the different settings *(6,7)*.

Even though more than 90% of the world's children live in LMICs *(8,9)*, less than 10% of the research on childhood cancer is conducted there. Similar to HICs, it is highly likely that childhood cancer patients in LMICs would benefit by adopting the historical HIC "culture" of offering recruitment into a clinical trial or study as best practice in order to continually improve and further optimize first line therapeutic strategies. The relative influence of specific issues such as treatment tolerance, advanced disease, poor performance status, among others, is different in LMICs, so research strategies developed in LMICs should consider tailoring treatment to their particular situation. Hence, in contribution to the World Health Organization's Global Initiative for Childhood Cancer (GICC), SIOP aims to embed the same research culture and capacity into LMICs *(10)*.

Direct application of treatments developed in HICs may lead to poor results in some situations. A typical example is Burkitt lymphoma (one of the index cancers proposed by the WHO Global Initiative for Childhood Cancer (GICC) where increasing survival results obtained in HICs by administering higher doses of chemotherapy resulted in unacceptable fatal toxicity in low-income countries (LICs) and middle income countries (MICs) *(11)*. Therefore, the potential increased

anti-lymphoma efficacy of higher doses of chemotherapy was counterbalanced by increased fatal toxicity *(12)*. In addition, in LICs and MICs, there is usually a higher proportion of patients presenting with very advanced disease (this is a subgroup where severe toxicity is more likely), causing a higher impact on survival. This is both because of increased toxicity and also because of higher relapse rates, explaining the poorer overall survival. So, for this and many other paediatric tumours, it is necessary to propose context-adapted treatment protocols. However, only through the evaluation of results, is it possible to take informed actions to improve outcomes.

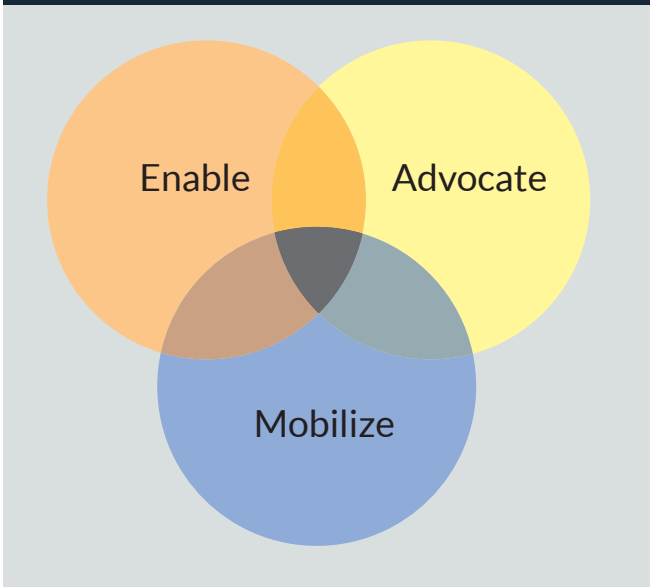
The potential importance of biological differences between global populations is also research-worthy, e.g., translational research studies on tumour genomics and genetic susceptibility to treatment toxicities *(13)*.

A pragmatic approach has been implemented by many paediatric cancer research cooperative groups in LICs and MICs. Pragmatic clinical trials are defined as research that focuses on optimization of choosing between "standard" care options that generally use generic chemotherapy drugs, surgical approaches and radiotherapy where available and deemed essential.

"Pragmatic trials evaluate effectiveness, the effect of treatment in routine (real-world) clinical practice. Some examples include treatment versus active surveillance in patient management, combinations of treatment interventions, determination of optimal dose and dose schedule, de-escalation of treatment intervention, comparative effectiveness of different treatment interventions. Health-care professionals and academia will generate clinical evidence, by evaluating effectiveness in randomized or cluster-randomized academic investigator-initiated pragmatic clinical trials, how to best perform and deploy evidence-based treatment interventions that improve outcomes in real life for routine health care, including quality of life, for cancer patients who often present with co-morbidities"*(14)*. Such studies "take into account socio-economic and biological stratification, such as biology of the disease, gender, cancer stage and age. The chosen treatment intervention(s) [is] adapted to the particular needs of the target population and to the specificities of the provision of care at local, regional or national level, duly reflecting the diversity across participating countries. Furthermore, affordability and accessibility should be taken into account" *(14)*.

Implementing pragmatic clinical trials either by adapting HICs results or by proposing original strategies have led to bi-directional learning about essential therapeutic elements. A typical example is Hodgkin's lymphoma (HL). In the 1980s, centres in South America treated HL with polychemotherapy and radiotherapy use was tailored depending on the response to chemotherapy *(15)*. This treatment was radically different

Figure 1: PARC program's 3 objectives



in some countries in Europe and the United States where radiotherapy was easily available and used for all patients; in some studies, splenectomy was routinely done *(16)*. Forty years later, the current treatment of HL in HICs is now more similar to the strategy proposed in South America, with the limited use of radiotherapy, and splenectomy for staging was abandoned. Other examples include tumours with high survival results obtained in HICs but with intense and toxic treatment which is difficult to de-escalate.

At the global level, a "standard of care" is essentially a "risk-adapted" choice of treatment options: the intensity of the chosen first-line therapy is adapted to the anticipated risk of relapse of the individual child's cancer. In LICs and MICs, patient presentation with more advanced disease is common, and this already puts doctors in LICs and MICs at a disadvantage to be able to offer effective treatment. Hence, research to improve early diagnosis is needed as much as research to improve treatment.

Less intense studies in LICs and MICs may provide important data which may be later adopted in HICs. Also, including LMICs into plans for drug development of academic institutions and pharma may propose alternative dosages or schedules which may be of relevance to LMICs and occasionally applicable worldwide at the same time as access to new treatments is offered worldwide. Hence, bi-directional learning and relevant research in LICs and MICs may, on occasion, influence the global treatment of children with cancer.

In other words, to practise evidence-based medicine in LICs and MICs, there is a need to first generate the necessary evidence relevant to these contexts. In paediatric oncology, implementing high quality pragmatic research programmes has been proven to be feasible and effective *(17)*. Directly translating the evidence generated at HIC settings or adapting

Table 1: **Excerpt of Data from the Baseline Assessment**

Cooperative group	Continent	Countries	Number of members	Publications	Protocols opened
CanCare Africa	Africa	8	11	Yes	2
GFAOP	Africa	15	>300	Yes	3
POEM	Asia	28	>500	Yes	4
AHOPCA	Central America	8	>200	Yes	13
CLEHOP	Central and South America	6	Not known	Yes	2
GALOP	South America	4	54	Yes	6

that evidence to LICs and MICs without evaluating the results may not always address the specific issues affecting survival rates in LICs and MICs. As in HICs, the best way of making progress for generating practice-changing data in paediatric oncology is by investing in multi-national cooperative groups who have the capability to implement clinical trials and studies with a sufficient number of patients. However, cooperative groups in LMICs face different challenges such as insufficient funding, which leads to fragile organizational structures, lack of dedicated personnel, insufficient resources for data management, etc. The lack of dedicated research personnel, i.e. study coordinators, clinical research assistants or data managers, makes it difficult for research cooperative groups in LMIC to perform clinical research, especially where the health-care team is already thinly stretched. Very few hospitals support the salaries of research personnel or provide protected time for research to their health-care personnel.

Nevertheless, existing cooperative groups have established themselves, creating relevant networks performing a series of pragmatic clinical trials, usually with limited funds raised by their principal investigators and a big effort of participating health-care personnel donating their time and efforts. Although there have been several very valuable initiatives globally, these efforts are not scalable without further organizational and infrastructure support.

PARC Program

In line with its new Strategy 2021–2025, the SIOP Program for Advancing the Research Capacity for Paediatric Cancer Clinical Trials in Low-Income Countries and Middle-Income Countries (PARC Program) seeks to 1) enable SIOP members and partners to expand research capacity in order to generate local evidence for cure and care; 2) advocate for increased use of research to provide evidence that optimizes the outcomes for children with cancer; and 3) mobilize resources for clinical research capacity development in LICs and MICs. The PARC Program will support the aims of the WHO GICC, to double the survival rate of children and adolescents with cancer in LMICs by 2030.

The PARC Program focuses on the most cost-effective way of supporting pragmatic clinical research in LICs and MICs, i.e., on supporting the capacity development of already existing cooperative groups so that they can increase their internal capacity to conduct pragmatic research. The PARC Program is divided into two phases, as follows: Phase 1 (May 2022–May 2025), focusing geographically on Africa, Asia and Latin America, and Phase 2 (June 2025–June 2027) which is likely to consider supporting national research groups and/or specific research proposals from cooperative groups, based on available support at the time.

The Program is led by the PARC Committee, chaired by SIOP President Guillermo Chantada. Following a call for applications, which was very well received, SIOP assembled a Committee of 12 global leaders in paediatric oncology, two ex officio officers and two ad hoc advisers. In the Committee, there is good geographic and gender balance: 36% come from HICs and 64% come from MICs and LICs; 57% are male and 43% are female.

In April–May, 2022, in preparation for Round 1 of grant-making, the PARC Program carried out a baseline assessment of the existing international cooperative groups operating in Africa, Asia and Latin America. The assessment showed the following major international cooperative groups on the three continents (Table 1).

In addition, national groups such as the Pakistan Society of Paediatric Oncology (PSPO), the Indian Paediatric Haematology-Oncology Group (InPHOG) and the Thai Paediatric Oncology Group (ThaiPOG) have comparable impact to an international group because of the size of the populations they each serve.

The assessment also showed that very few international cooperative groups are constituted as legal entities and all groups are generally operating with limited or no funding. While most groups reported that they have some administrative support, all groups reported insufficient or non-existing clinical trial management personnel, with most of this work being done currently by overstretched clinical principal

investigators. Most groups also reported a lack of an electronic data capture and management systems, which hinders their research work and capacity.

Round 1 of PARC Program investments

In Round 1, the PARC Program received seven proposals total from Africa (2), Asia (4) and Latin America (1). For this Round, it is important to emphasize that SIOP does not provide direct support for individual clinical studies; rather, the support is directed to capacity development for pragmatic clinical research. Once contracting is completed, grantees are expected to begin work in September/October 2022 for two years. Specifically, SIOP seeks to support workforce training (doctors, nurses, clinical research assistants, data managers, etc.) as well as the development of infrastructure and collaborative networks. Support includes training in good clinical practice, research design, skills in project management, etc. The long-term aim is to improve the cure rate of children and adolescents with cancer by 2030, in contribution to the WHO GICC's goals.

The winning proposals are the following:

- **AFRICA** With support from the PARC Program, the Collaborative African Network for Childhood Cancer Care and Research Cooperative Group (CANCARE Africa) *(18)*, a multidisciplinary regional network in sub-Saharan Africa with 12 hospitals in eight sub-Saharan countries, will help to improve its research capacity in several ways. The PARC grant will sustain, formalize and expand research infrastructure, including high-quality local and central project and data management, thus increasing research capacity and facilitating growth. Secondly, it will facilitate the completion, analysis and dissemination of two on-going multi-centre prospective clinical studies, Wilms Africa and SUCCOUR Phase II. This support will enable sustained research productivity. This research will provide a critical foundation for future implementation sciences-informed intervention initiatives aiming to improve care and survival of children with cancer. Lastly, the PARC grant will enable the development and submission of competitive research proposals providing funding on a larger scale to ensure future growth, essential research knowledge and, most importantly, to improve and increase research and leadership capacity in sub-Saharan Africa. Furthermore, CANCARE Africa will host a meeting in Malawi at the end of April 2023 with all its collaborators. During this meeting, it will discuss and prioritize future research initiatives based on the amount of available funding at that time.

  They aim for these initiatives to include Wilms Africa Phase III (planned to be a randomized controlled trial), "SUCCOUR Phase III" (the implementation of a local care pathway for the management of fever and neutropenia to reduce infection related mortality) and "Zero Abandonment from Start to Finish" (the implementation of a "comprehensive care package including family support to reduce treatment abandonment" – following a successful pilot in Malawi of a similar intervention which reduced treatment abandonment from 19% to 7%, $p<0.001$ – publication in press).

- **ASIA** The Indian Paediatric Haematology Oncology Group (INPHOG) *(19)* has a five year plan, starting in 2022, to enroll 7,500 children with cancer per year by the year 2027, bringing a 4-fold increase i.e., 20% of the total treated childhood cancer patients in India from the current 5%. Their goal necessitates frontline prospective treatment protocols and clinical trials for each of the major childhood cancers. To achieve this, with support from the PARC Program, INPHOG will provide support and build research capacity in 100+ INPHOG member centres that are treating children with cancer across India. The aim is to partner with these centres to conduct multicentre childhood cancer clinical trials with the mission of improving outcomes of childhood cancer in India through collaborative research. To date, the Indian paediatric oncology community has conducted 24 collaborative studies since 2015. In order to provide impetus to the five year goal, INPHOG will focus on building manpower and capacity in 50 member centres and initiating six prospective studies in the next two years (October 2022 – September 2024). This would also result in doubling the number of all children with cancer who are currently enrolled onto multicentre collaborative INPHOG studies (observational and interventional) which would represent approximately 10% of all children with cancer who are diagnosed and treated every year in India.

- **LATIN AMERICA** The Latin American Group of Paediatric Oncology (GALOP) *(20)*, created in 2008 under the auspices of the Children Oncology Group (COG), is a multinational cooperative group for clinical trials in childhood tumours in Latin America. With support from the PARC Program, GALOP aims to register as a formal institution, operating in full adherence to the local laws and international research regulations, as well as to further develop its capacity to build sustainable structures that enable to continue performing high-quality pragmatic clinical research through three distinct courses of action. Specifically, GALOP will finalize its registration as a civil society organization (CSO), in accordance with applicable laws in Uruguay and the region. GALOP is registered in Uruguay but still needs to undergo a few additional local formalities to fully operate as a CSO, particularly in the matters of billing, receipts and tax

status. At the same time, recent regional health research regulations demand a higher level of compliance and a more formal procedure for data and specimen sharing for future studies. It is crucial for GALOP to advance in formal agreements with the participating institutions which will also allow more institutions to join GALOP. To achieve this goal, GALOP will engage legal consultants, in accordance with each country's health research, patient safety and data protection body of laws and regulations.

Furthermore, the second area of support from the PARC Program is directly related to research capacity building: particularly human resources, the training of key personnel, as well as a platform for data capture that will allow GALOP to create good quality secure data and to improve the quality of data collection.

The third course of action will focus on the expansion of GALOP to more centers and more protocols. In addition to the already active protocols on retinoblastoma, osteosarcoma, Ewing sarcoma, germ cell tumours and medulloblastoma, GALOP has chosen two tumours (renal tumours and Langerhans cell histiocytosis) where there is already a GALOP group of interested members, with local expertise in which a pragmatic protocol may be developed as a demonstration project for GALOP expansion. Wilms tumour was chosen by WHO GICC as an example of multidisciplinary treatment whose improvement can be reflected in other solid tumour approaches and contribute to expanding the capacity of countries to deliver best practices in childhood cancer care *(5)*.

Latin America has a long tradition of research in histiocytosis with participation in international initiatives and local translational research projects *(21,22,23)*. During 2021, GALOP prompted and facilitated a Latin American collaboration between regional cooperative groups, along with AHOPCA, CLEHOP, and Mexican institutions, to generate a diagnostic and treatment proposal for this rare disease, within the framework of connection, debate, and cooperation. As a result of the PARC Program, GALOP will propose an adapted original protocol of continental outreach as well as an online platform for discussing difficult cases.

Conclusion

Historically, there has been little investment in building the capacity of international cooperative groups or large national groups with a patient load similar to that of international cooperative groups. The SIOP PARC Program fills this gap. By investing in the capacity development of such groups, our goal is to increase the capacity for research-informed treatment of children and adolescents with cancer and to improve the quality of care and cure. The PARC Program begins with modest investments in Round 1 of grants to three groups, thanks to the support from Amazon and Sanofi Espoir Foundation; however, we plan to build on early lessons learned from the PARC Program and release more opportunities for clinical research capacity development and support for specific research projects in the future. ■

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Tzvetomira Laub, BA, MA, is SIOP's Executive Director for Programmes and Strategy, leads on implementation of SIOP's Strategy 2021–2025 in collaboration with the SIOP Board of Directors and manages the Society's programmes. She is a seasoned programmes leader who has worked on health, education, and child protection in both development and humanitarian contexts. Prior to SIOP, Tessie worked for the International Rescue Committee in Ethiopia, Bulgaria and the United States, responding to refugee crises and supporting humanitarian response to situations of internal displacement globally. Previously, she worked as a Senoir Coordinator at the Inter-Agency Network for Education in Emergencies and as a Programme Specialist at the Watchlist of Children and Armed Conflict, both in New York City, USA. She holds a BA degree in International Relations from Mount Holyoke College and a MA in Politics from Brandeis University.

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Another of his roles is Principal Researcher at CONICET (National Council for Research and Technology) in Argentina and he is also.co-Chair of GALOP (Grupo de America Latina de Oncología Pediátrica) and past President of SLAOP (Latin American Society of Pediatric Oncology) 2019–2021. His main research interests are retinoblastoma, non-Hodgkin's lymphoma and neuroblastoma.

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