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Pediatric Oncology Clinical Trials and Collaborative Research in Africa: Current Landscape and Future Perspectives

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abstract

PURPOSE Adequate clinical services have yet to be established in the majority of African countries, where childhood cancer survival rates vary from 8.1% to 30.3%. The aim of this review is to describe the landscape of pediatric oncology trials in Africa, identify challenges, and offer future opportunities for research collaborations.

METHODS The study includes data from the International Pediatric Oncology Society (SIOP) global mapping survey, meta-research identifying trials in Africa in ClinicalTrials.gov, and a literature overview of publications on the subject of pediatric oncology clinical research supported by expert opinions on the current situation and challenges.

RESULTS The SIOP global mapping survey received responses from 47 of 54 African countries, of which 23 have active clinical research programs. A preliminary search of ClinicalTrials.gov showed that only 105 (12.1%) of 868 African oncology studies included children and adolescents. Of these, 53 (50.5%) were interventional trials according to the registry's classification. The small number of African trials for children and adolescents included palliative care and leukemia trials. In African oncology journals and international pediatric oncology journals, < 1% of the pediatric oncology publications come from Africa. Services and research were strengthened by international collaboration. National studies focused on clinical needs, local challenges, or interventional priorities. Both the literature review and the expert opinions highlight the need to expand clinical research in Africa, despite ongoing regional instability and lack of resources.

CONCLUSION While a low number of pediatric clinical treatment trials are open to African children and adolescents, clinical research of high quality is being done in Africa. Several initiatives are stimulating the development of the research capacity across the continent, which should increase the publication output.

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INTRODUCTION

By mid-2019, the population of African children age < 15 years was > 535.1 million, 41% of the total population.[1] Although infectious diseases, malnutrition, and neonatal deaths are the main causes of childhood mortality on the continent, noncommunicable diseases such as childhood cancer are becoming increasingly important, with 100,000 new diagnoses per year.[2] These figures originate in a context were only 57% of childhood cancer cases are diagnosed.[3] The overall survival for childhood malignancies is poor: North Africa reports survival rates of 30.3% for all malignancies, and Southern Africa, West Africa, and East Africa report 21.7%, 8.5%, and 8.1%, respectively.[4]

The main barriers to adequate childhood cancer care in Africa include low socioeconomic status, underdiagnosis, under-reporting, understaffing, inadequate clinical care, and a paucity of high-quality research.[5] Clinical trials facilitate the creation of evidence to guide clinical interventions and improve overall care on many levels: They represent a critical link between scientific innovation and improvements in health care delivery.[5] Prospective clinical trials may improve diagnostic accuracy, decrease treatment failure, and improve efficacy of specific interventions. Furthermore, they may assist in building capacity and consistency of clinical care in a multidisciplinary setting, improve facilities, and fund treatment and support costs for patients.[6]

The ability to participate in clinical trials is intertwined with the capacity of local pediatric oncology units (POUs) to deliver clinical services in a severely resource-constrained environment.[7] Historically, many services and research projects were established in collaboration with North American and European groups. In addition, regional African collaborations and training programs have led to studies that were

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Which pediatric oncology trials and research are being conducted in Africa?

Knowledge Generated

A number of multicountry collaborations are doing research in the African setting while collaborating with international partners.

Relevance

Multiple factors present challenges to establishing robust research opportunities in Africa, yet both African and international incentives are driving the process to establish sustainable trial and research capacities.

influenced by regional priorities, socioeconomic factors, and availability of resources.[6]

Numerous research projects are being conducted by various groups and institutions across the continent to increase understanding of local challenges and to improve management of patients, but a systematic African database does not yet exist. The aim of this review is to provide an overview of the current focus of pediatric oncology clinical research activity and clinical trials in Africa, identifying possibilities for collaborative research and current challenges in conducting trials while gaining access to international trials and offering recommendations with regard to potential improvements.

METHODS

The International Pediatric Oncology Society Global Mapping Survey

The International Pediatric Oncology Society (SIOP) conducted an electronic global mapping survey that initially focused on Africa.[8] The survey was initiated through the Pediatric Oncology International Network for Training and Education Website, SIOP Website, and various social media platforms in November 2018 and collected information with regard to multiple pediatric oncology services in Africa, including the research capabilities of the participating centers[8] (Data Supplement). Delegates who attended the 2019 SIOP-Africa congress in Egypt were invited to complete the survey. Preliminary results were presented at SIOP 2019 in France.[9,10] Subsequent updated raw data from newly completed surveys were made available to the authors. Where conflicting data were present, the highest capability was recorded for that country.

Screening of Clinical Trials Registers for African Trials

A preliminary search was performed in ClinicalTrials.gov on January 31, 2020, with the aim of identifying oncological studies starting from 2010 that contained the search terms "oncology," "neoplasm," "cancer," and "tumor," as well as names of individual African countries (Fig 1). Thereafter, records were screened, and duplicate entries, benign pathologies, and withdrawn trials were excluded. All records were divided into interventional and noninterventional trials (behavioral, observational, and preventive trials) according to the registry's classification. Only records that included children and adolescents < 19 years of age were identified to limit the search to pediatric trials. The preliminary search was performed by one investigator (M.Z.), and the eligibility of all identified trials was assessed by another investigator (J.v.H.). The excluded trials and the manually coded variables were not yet reviewed by a second investigator and are part of ongoing research. Therefore, only a descriptive, nondefinitive overview was formulated.

A meta-research analysis was recently conducted by de Rojas et al[11] to analyze the access to clinical trials investigating solid tumors for adolescents and young adults (AYAs) with cancer. Similar meta-research projects have been performed for palliative care[12] and AYAs with acute leukemia (manuscript in preparation). The databases of these meta-research projects were used to identify the number of trials accessible for African countries.

Overview of Journals Publishing Reports From Africa

A literature overview was conducted of publications indexed in PubMed, Medline, Global Health, Embase, African Index Medicus, and Google Scholar using the search terms "Africa," "children," "adolescents," "trials," "research," "study," "cancer," and "oncology," as well as related management modalities, including "nutrition," "radiotherapy," "surgery," and "chemotherapy." The search was performed from September to December 2019 for literature published after 2000. There were no limitations on the language of publications provided that summaries or abstracts in English were included. Abstracts from conference proceedings were also considered. An overview was given to evaluate research priorities, the promotion of research and education capabilities, cooperative groups conducting research, and factors that have an impact on trials in Africa.

Specific focus was placed on African oncology journals because these journals are a possible primary source of publication for African research teams. Data collected were journal impact factor, date of inception, and number of pediatric articles in relation to total articles published. In addition, three pediatric oncology journals with the highest

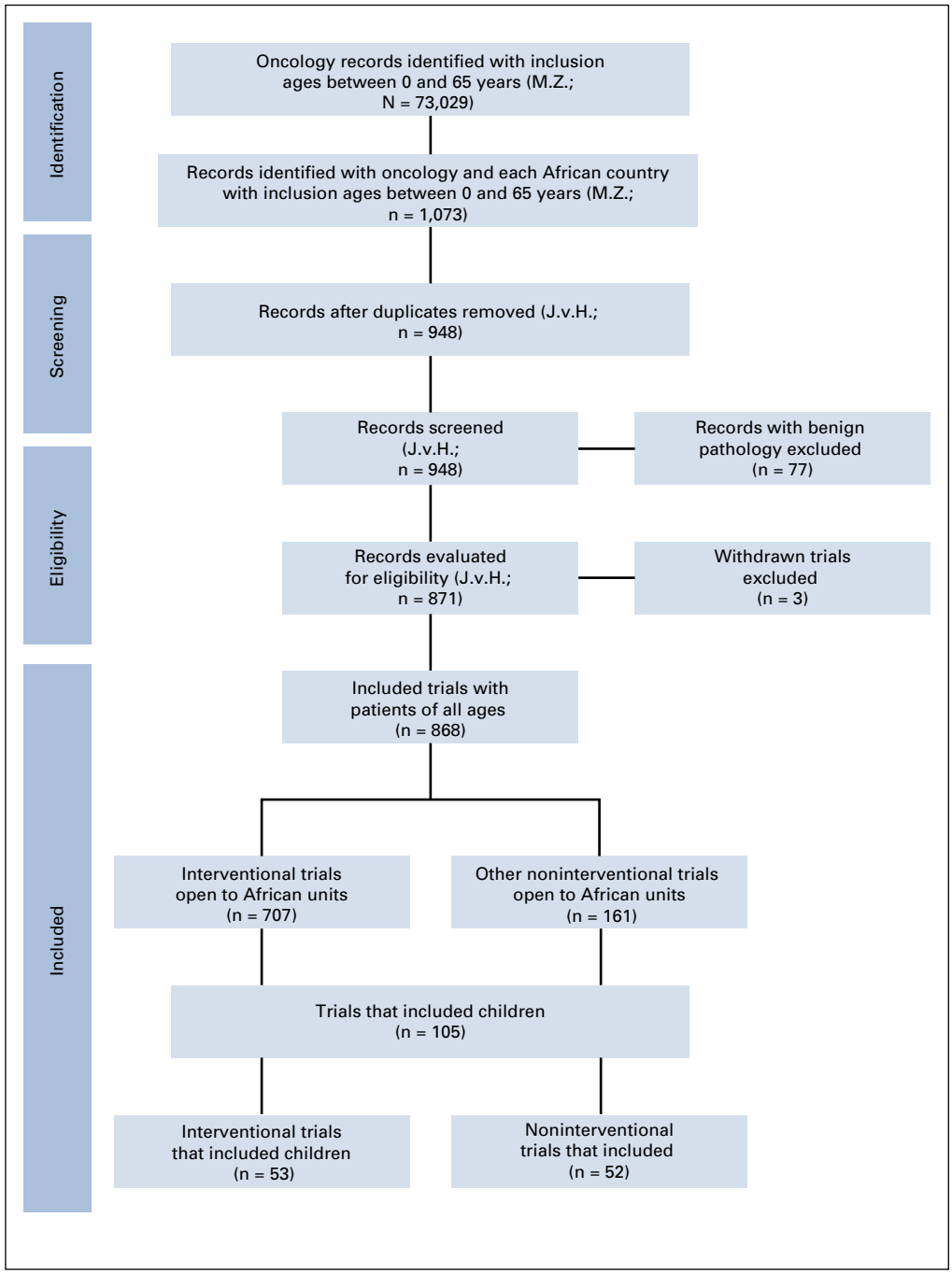

FIG 1. Preliminary search that identified the African oncology trials that included children and adolescents. For the pediatric treatment trial, the upper inclusion age limit was < 18 years. For the adult trial, the lower inclusion age limit was 18 years. Study type is according to ClinicalTrials.gov classifications.

impact factors were analyzed to determine how many reported on clinical trials conducted in Africa.

Survey of Expert Opinion and Literature Overview

The literature overview was supplemented with expert opinions on the current situation and challenges of clinical research in Africa. Experts identified through publications based in Africa, who had experience in conducting trials in Africa, or who were currently involved in research on the continent were randomly requested to answer the survey. Experts represented all regions of Africa with specialties in pediatric oncology, radio-oncology, and surgery. The survey was conducted through e-mail during December 2019 and contained open-ended questions related to collaborations, subject matter, research challenges, and trial-based experiences. Expertise in clinical, academic, and

research-related subjects was surveyed (Data Supplement), and results were summarized (Data Supplement). In addition, the response formed the basis for the narrative discussion of the literature overview and was illustrated with maps.

RESULTS

The SIOP Global Mapping Survey

The SIOP global mapping survey received responses from 47 (87%) of 54 African countries. Fourteen respondent countries (25.9%) reported not having full-time pediatric oncologists (Fig 2). Of the 47 responses, 23 (48.9%) countries had active clinical research programs. Five countries (10.6%) had active fellowship programs administered from within Africa, all of which had research teaching and outcomes as part of the program requirements[13-17] (Fig 3). Two countries (4.3%) had pathology research diagnostics, whole-genome sequencing, and molecular pathology for all diseases, while three (6.4%) had hematologic research diagnostic capabilities.

Screening of Clinical Trials Registers

Of 73,029 oncology trials registered with ClinicalTrials.gov, the preliminary search identified only 868 (1.2%) open in Africa (Fig 1). The majority were in South Africa and Egypt (413 and 381 trials, respectively; Data Supplement). Excluding South Africa, only 10.6% of trials (100 of 868) were registered by sub-Saharan countries collectively (Table 1).

Only 12.1% of African trials (105 of 868) included children < 19 years of age (Fig 1; Table 1), and five of them (4.8%) were open in multiple countries or part of collaborations. Most of the trials that included children and adolescents (n = 91) involved lower- and middle-income countries (LMICs), with 11 trials involving low-income countries (LICs). Eight (40.0%) of 20 LMICs were involved in these 91 trials. There were only three (12.0%) of the 25 LIC and two (25.0%) of the eight upper-middle-income countries registered trials that included children and adolescents.

Of the 105 trials, two (1.9%) were preventive studies, four (3.8%) were behavioral studies, 46 (43.8%) were observational trials, and the remaining 53 (50.5%) were interventional studies according to the ClinicalTrials.gov classification (Table 2; Data Supplement).

Meta-Research on AYA-Related Trials

The database of the meta-research investigating AYA-prevalent solid tumors[11] showed that 16 (0.7%) of 2,176 trials had participating centers in Africa. Only three (0.1%) trials were accessible to African adolescents (while the remaining were only accessible to adult patients). In a similar meta-research study that analyzed trials investigating acute leukemia, four (0.2%) of 1,766 had participating African centers. None included pediatric participants from Africa. A third study that involved palliative care meta-research showed that eight (1.6%) of 514 included trials that had participating African centers.[12] Only one (0.2%) included children and adolescents from Africa.[12] Among the four trials that included children and adolescents that were identified in the meta-research projects, two were exclusively conducted in Egypt. The remaining two were intercontinental trials with South Africa.

Review of Journals Publishing Reports From Africa

In Africa, there are five journals dedicated to publishing oncology research, all of which include both adult and

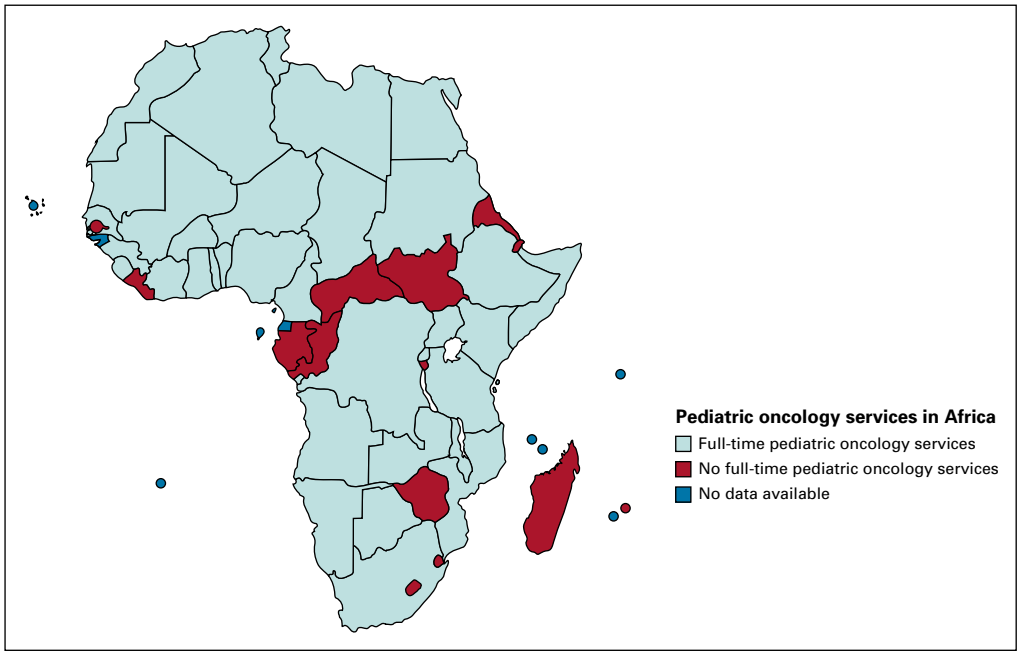

FIG 2. Countries with pediatric oncology services that include a pediatric oncologist.

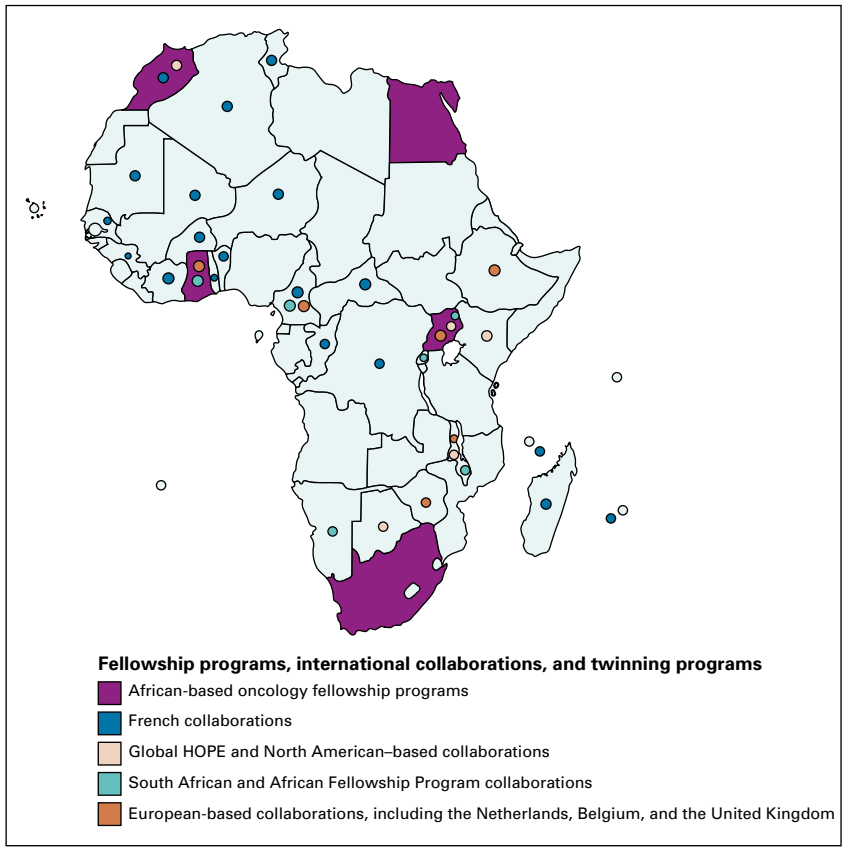

FIG 3. Fellowship programs, international collaborations, and twinning programs.

pediatric oncology research. The impact factors ranged from 0.85 to 2.47, and the number of articles reflecting clinical trials that included children and adolescents were < 1% of the total articles in the journals (Table 3).

Since its inception, *Pediatric Blood & Cancer* (PBC) has published 17 African trials. Of 2,362 articles published in PBC between 2014 and 2018, only 32 (1.4%) were from Africa (Table 4). The 5-year average acceptance rate for African submissions was 18% (range, 15%-24%) compared with 36% (range, 34.1%-40%) for non-African submissions (Table 4). Africa submitted 2.6% of all manuscripts for publication during the same period (P. Newburges, personal communication, October 2019). Some of the published African trials in PBC were conducted by Hesseling et al,[18,19] who used adapted treatment regimens (ATRs) for Burkitt lymphoma in Malawi, focusing on the administration of less costly multi-agent chemotherapy with minimal treatment intensity yet achieving acceptable event-free survival rates. The Franco-African Pediatric Oncology Group (GFAOP), with ATR GFALMB protocols graduating treatment intensity, published similar trials and improved treatment outcomes for Burkitt lymphoma.[20-22] Israëls et al[23,24] reported treatment outcomes of nephroblastoma in 8 sub-Saharan African POUs based on the ATR published by SIOP-PODC. In parallel, GFAOP published results of a study with an adaptation of the SIOP 2001 protocol used in seven sub-Saharan countries.[25]

Expert Opinions

Fourteen experts were surveyed. They represented North Africa (n = 3; 21.4%), East Africa (n = 1; 7.1%), West Africa (n = 1; 7.1%), Central Africa (n = 3; 21.4%), and Southern Africa (n = 4; 28.6%), and two were non-African based (14.4%). Of these experts, four (28.6%) of 14 have cross-regional experience. Expert responses are summarized in the Data Supplement. The most prominent themes discussed were related to the most common tumors (leukemias, nephroblastoma, and retinoblastoma), the improvement of supportive care, the lack of resources, the need for standardized treatments, and the need for greater collaborative studies in Africa. From the responses, it could be deduced that the most prominent prospective African trials were ATR to local needs, for example the Collaborative Wilms Tumor Africa Project,[26] Burkitt lymphoma treatment trials,[27] and Moroccan neuroblastoma adapted treatment study.[28]

The last survey question (Data Supplement) related to collaborations. Africa has several multicountry collaborative study groups: the GFAOP, Pediatric Oncology Group of East Africa, the South African Children's Cancer Study Group, and Pediatric Oncology East and Mediterranean group (Fig 4). SIOP-Africa is a body that aims to unify all groups and standardize and improve research efforts on the continent. The African Pediatric Neuro-oncology Society (APNOS) was founded in 2019 for the improvement of

TABLE 1. Overview of African Trials and Income Classification of Countries

Region	Trials That Included All Ages, No. (%)	Trials That Included Children and Adolescents < 19 years of Age, No. (%)
No. of countries involved	868	105
Single region	847 (97.6)	100 (95.2)
> 1 region	21 (2.4)	5 (4.8)
African region[a]		
Northern Africa	481 (55.4)	83 (79.0)
Western Africa	26 (3.0)	1 (0.9)
Eastern Africa	71 (8.2)	13 (12.5)
Central Africa	3 (0.3)	1 (0.9)
Southern Africa	410 (47.2)	7 (6.7)
Pediatric Trials per Income Group	**Countries With Trials That Included Children and Adolescents, No. (%)**	**Trials That Included Children and Adolescents, No. (%)[a]**
All (n = 54)	13 (24.1)	105 (0.78)
LIC (n = 25)	3 (12)	11 (0.5)
Lower MIC (n = 20)	8 (40)	91 (0.78)
Upper MIC (n = 8)	2 (20)	10 (0.7)
HIC (n = 1)	0	0 (0.0)

NOTE. From The World Bank.[67]

Abbreviations: HIC, high-income country; LIC, low-income country; MIC, middle-income country.

[a]The same clinical trials could be conducted in > 1 country; therefore, the numbers do not sum to the total number of trials, and consequently, percentages do not sum to 100.

outcomes in CNS tumors. The underlying topics and responses of the experts are addressed and analyzed in detail in the Discussion section.

DISCUSSION

With a largely youthful population and up to 20 per 100,000 children developing malignancies yearly,[29] Africa has great research and clinical trial potential, with various initial strategies already driving further development. This mirrors the development of research in the Asociación de Hemato-Oncología Pediátrica de Centro América group in LMICs of South America.[30] Yet, at present, Africa should identify ways to further develop this potential and support sustainability of research on the continent.

Childhood cancer is not a priority on a continent with high mortality rates in children age < 5 years and multiple competing demands, which has resulted in inadequate national policymaking and a lack of funding for research.[5] Increased survival in high-income countries (HICs) is associated with the integration of clinical trials into standard practice. In contrast, survival is much lower in under-resourced regions without collaborative networks.[7]

The current study shows that African children and adolescents have limited access to cancer trials and innovative therapies. This is true for even the most common cancer types,[29] children and adolescents who could be included in adult-related pathology trials, and high-demand supportive care disciplines. Many factors indirectly add complexities to conducting trials.

A first factor is clinical responsibilities and administrative limitations. Barriers to successful cancer treatment in LMICs include late presentation; comorbidities, such as infections and malnutrition; inadequate supportive care; and treatment abstinence and abandonment (P. Newburges, personal communication, October 2019). The ideal ratio of one pediatric oncologist to every 15-30 new patients per year is not yet achievable on a continent that reports severely constrained clinical and research services.[31] Therefore, clinical responsibilities are prioritized above research opportunities.[31] Contrary to HICs, where patient care is covered by national health insurance, families are responsible for the payment of their children's care in LMICs.[6]

A second factor is radiotherapy and surgical constraints. Twenty-nine sub-Saharan African countries, with an estimated population of 316 million, lack radiotherapy facilities.[32] This represents one MV radiotherapy machine per 3.56 million people. Likewise, Africa lacks multidisciplinary neurosurgical teams, and pediatric brain tumors are underdiagnosed.[33] In 2018, there were 488 neurosurgeons, or one per 3.3 million inhabitants.[34] In addition, few countries have cancer-trained pediatric surgeons. A report published in 2017 estimated that one general surgeon and 0.26 pediatric surgeons per million persons were available on the continent.[35]

A third factor is supportive and palliative care. The treatment intensity that can be delivered without an unacceptably high treatment-related morbidity and mortality is determined by the available level of supportive care.[36] This is especially relevant in sub-Saharan Africa, which has high rates of malnutrition; limited access to blood products; and the presence of various infections, including HIV. The METRO-MALI-01 studies[37,38] are an example of innovative research of metronomic therapy, which arose in the absence of curative options.

A fourth factor is economic considerations in research and management. Funding is a persistent problem where countries' health budgets are limited and cancer programs are underfunded because of a lack of or incorrect cancer data.[39] Oncology costs have escalated beyond governmental or private capacities to fund treatment, leading to dependency on foreign and pharmaceutical company trial support.[39] This lack of funds has a knockon effect in that research funding becomes reliant on nongovernmental organizations and private funding.[39] Sanofi Espoir Foundation's My Child Matters funds pediatric oncology

TABLE 2. Studies in Africa That Included Children and Adolescents According to Trial Type

Trial Type	No. (%)
No. of studies	105
Noninterventional[a]	52 (49.5)
Preventive	2 (1.9)
Behavioral	4 (3.8)
Observational	46 (43.8)
Interventional	53 (50.5)

[a]Study type according to information on ClinicalTrials.gov.

research and education-related activities, of which the ongoing SIOP global mapping project is one example.[40,41] The Bristol Myers Squibb Foundation supports research by training pediatric oncologists through the Global HOPE project.[42]

A fifth factor is quality of data and access to publication options. Data quality depends on robust information systems,[43] and many African registries are still in the process of development. The Hospital Based Registry of Childhood Cancer in POUs in Francophone Africa, administered by GFAOP, collates data from five clinical studies for the management of Burkitt lymphoma, nephroblastoma, retinoblastoma, Hodgkin lymphoma, and acute lymphoblastic leukemia (ClinicalTrials.gov identifier: NCT03803735). The African Cancer Registry Network has recorded a relatively low incidence of CNS malignancies and leukemia compared with global figures but has shown the impact of infection-related malignancies such as Kaposi sarcoma, Burkitt lymphoma, Hodgkin lymphoma, and viral hepatitis-related liver malignancies. Both retinoblastoma and nephroblastoma have a higher incidence than in HICs, which thus identifies priorities for clinical services and trials.[30] The few African journals that exist have low impact factors and limited reach. Many African researchers do not have access to research funds for publication fees in open access journals, limiting the number of publications that are open access.

A sixth factor is regulatory and ethical challenges in conducting trials. Africa covers a large surface area, with 1.3 billion people.[43,44] Access to quality medical care is limited for many by geographical distances, intermittent conflict, political turbulence, and severe resource constraints related to past colonization. The heterogeneity of cultures, customs, and resource allocations leads to differing ethical concerns around the continent. There are many opportunities for researchers to engage with a largely unstudied African population, but both the pediatric patient population and the health care workers serving them are vulnerable to often unwitting exploitation by researchers from better-resourced settings.[45,46] Collaborations with researchers from outside the local setting may experience difficulties in ensuring respect for the recruited participants and study communities, fair selection of the study population, and achievement of fully informed consent in the quest to produce scientifically valid research.[47] Inconsistent and weak ethical regulations are experienced as barriers to progress, and there has been little incentive to include African researchers in trial design and publication.[7] The pediatric population is largely excluded from treatment trials because Africa has no regulatory requirements, such as legislated by the European Pediatric Medicines Regulation for treatments to be studied in children and adolescents for market approval.[48]

Finally, there are other reasons that indirectly add complexities to conducting trials. All experts surveyed in this study agreed with Ford et al,[49] who identified the most commonly reported barriers to participation in trials as socioeconomic status, ethnic minority status, cultural background, literacy level, lack of education about clinical trials, comorbidities, costs of trial participation, and inadequate or absent infrastructure.[50] The reluctance of governments and populations in Africa to participate in trials could be the result of historical transgressions and ethical ambiguities of colonial research and treatment campaigns while marginalizing African therapeutics and traditional healing.[51] These many challenges may seem insurmountable to the creation of a complex and locally responsive research agenda, but there are many encouraging developments.

Increasing the number of and access to clinical trials in Africa is a process that requires strengthening of research activities across the continent, first by improving clinical care and then by increasing research capacity. This can be achieved by increasing experience, efficiency, and the capacity to conduct trials. Improvement of supportive care and finding innovative, locally relevant solutions to prevent treatment-related toxicities could decrease clinicians' work burden, allowing them to engage in research. For these to be sustainable, government policies should support both clinical and educational opportunities to develop research in conjunction with nongovernmental support initiatives.

Research capacities are improved by linking higher education degrees to research development, including capacitating nursing staff as active members of research teams.[52] Six countries offer formal training in pediatric oncology (Fig 3). Egypt, Morocco, and South Africa have accredited clinical and research-based programs, while Senegal, Ghana, and Uganda have programs that are currently gaining full accreditation.[13,14,53] The African Pediatric Fellowship Program provides opportunities for pediatricians from outside South Africa to train in subspecialties, including oncology, in South African training centers.[54] The collaborative fellowship training between the Dana-Farber Cancer Institute and The Children's Cancer Hospital in Egypt offers postgraduate training in pediatric oncology, radiation oncology, and infectious diseases to various African countries.[55] Other specialists are trained outside Africa or on the continent by non-

TABLE 3. Representation of Pediatric Oncology Clinical Trials in Local and International Journals

Journal	Year of Inception	Impact Factor	Articles Published Since Inception, No.	Articles Reporting on African Clinical Trials in Children Since Inception, No. (%)	Open Access Options and APCs
African					
African Journal of Cancer (English/French)	2009	1.180	384	1 (< 1)	Open access options
Journal of the Egyptian National Cancer Institute	2005	0.850	251	1 (< 1)	Open access, no APC
Southern African Journal of Gynecologic Oncology	2009	None	147	0 (0)	Open access
South African Journal of Oncology	2017	None	30	0 (0)	Open access with APC
Infectious Agents and Cancer (focus on infection-associated malignancies)	2006	2.470	854	0 (0)	Open access with APC
International pediatric oncology					
Pediatric Blood & Cancer (including medical and pediatric oncology)	2002 (1975)	2.468	NA[a]	17 (NA)	Open access options
Journal of Pediatric Hematology/Oncology	1979	0.947	NA[a]	1 (NA)	Open access options
Pediatric Hematology and Oncology	1984	1.137	NA[a]	2 (NA)	Open access options

Abbreviations: APC, article publication charge; NA, not available.

[a]The exact total number of journal manuscripts since inception predating electronic publishing NA.

African–administered training programs, such as the Global HOPE initiative in Botswana, Malawi, and Kenya.[56]

Strong research initiatives have been developed by collaborations among Africa, North America, and Europe (Fig 2). The creation of more research collaborations both within and between countries, focusing on ATRs, will improve access to clinical trials for more African patients.[27,57,58] An example of the success of multinational research collaborations is the Collaborative Wilms Tumour Africa Project,[26] which has demonstrated direct clinical benefit and raised the survival rate of children with nephroblastoma from 52% to 68%.[23] Similarly, in its first prospective trial, the GFAOP improved the outcomes of Burkitt lymphoma by one third from 50% to 60%.[20,21] This was achieved by applying ATRs formulated by the SIOP-PODC-ATR group in a stepwise manner, with increased research capacity and survival outputs as priorities of the trials.[24,36,59] Similarly, clinician-researchers in South Africa have developed multicenter national clinical trials to improve outcomes of patients with Hodgkin lymphoma,[60] neuroblastoma,[61] and germ cell tumors.[62] The development of a limited number of treatment protocols using the ATR framework to create regimens suitable for particular settings will both improve data quality and allow increased reproducibility and validation of study data. Failure to involve local staff in the planning stages may hinder trial suitability and sustainability.[45] Therefore, increasing the African Collaborative Research Network is paramount.

Research on the impact of pediatric cancer treatment informs policymakers and funders about the cost and affordability of cancer treatment programs.[62] A Malawian study reported on both financial and survival benefits by using a locally adapted, less intensive regimen compared with a more intensive regimen sourced from an HIC setting.[18] Survival benefits were attained partially by decreasing treatment-related mortality. The learning curve of health care workers with increased work experience and a focus on supportive care improved survival during a GFAOP-related lymphoma study from 54% during the first year to 73% during the third year, while treatment-related death rates decreased from 27% to 10% during the same period without changing treatment protocols.[22]

Studies to lower the burden on children, their families, and the treatment facilities without jeopardizing the treatment efficiency and survival rates were successful in diffuse intrinsic pontine glioma.[63] Similar cost savings and survival improvements were shown in a Ugandan trial of a locally adapted protocol for Burkitt lymphoma.[18]

The Society for Neuro-oncology of Sub-Saharan Africa and APNOS are African collaborations aimed at improving diagnosis and management of pediatric CNS tumors. Both organizations collaborate with the Pediatric Radiation Oncology Society to educate and train clinicians to improve outcomes in CNS tumors.[64,65] To date, no clinical trials have yet been planned.

We acknowledge the following limitations to this study: Data in the SIOP global mapping survey depended on the input from a wide variety of sources and reflect experiences from individual respondents. A single trial registry site, ClinicalTrials.gov, was used for retrieving trial data. Although this is the largest publicly available trial registry, it may exclude unregistered trials or trials that are conducted in Africa but registered in a non-African country, such as the Hospital Based Registry of Childhood Cancer in POUs in Francophone Africa (ClinicalTrials.gov identifier: NCT03803735).

TABLE 4. *Pediatric Blood & Cancer* Acceptance Per Submission Rate by Region

	Year, No. of Total (%)					
Region	**2014**	**2015**	**2016**	**2017**	**2018**	**5-Year Average**
Africa	6/25 (24)	6/32 (19)	6/38 (16)	6/39 (15)	8/42 (19)	32/176 (18)
Asia and Pacific	10/196 (5)	48/281 (17)	71/288 (25)	50/323 (22)	78/361 (22)	257/1,449 (18)
Europe	116/296 (39)	104/292 (36)	121/308 (39)	131/345 (38)	110/308 (36)	582/1,549 (38)
Middle East	17/112 (15)	15/112 (5)	19/117 (16)	10/71 (14)	16/94 (17)	77/506 (15)
North America	260/518 (50)	258/541 (48)	306/569 (54)	277/564 (49)	271/572 (47)	1,372/2,764 (50)
South and Central America	10/31 (32)	8/45 (18)	11/41 (27)	8/46 (17)	5/43 (12)	42/206 (20)

The preliminary search was done by one author (M.Z.), and further screening was done by only one author (J.v.H.). Consequently, the data could only be used for descriptive purposes, and the findings have to be validated. There is an acknowledged selection bias when reporting expert opinion, even when substantiated by published literature.

This study generated the following recommendations: To be of use in African settings, it is essential that clinical trial protocols be designed by taking into account local circumstances.[4] The establishment and improvement of African cancer registries will assist in identifying local priorities. More sophisticated clinical trials are possible in certain settings and should be stimulated by the genomic variety in African populations, potential accrual of large study numbers, and widespread desire to improve access to quality care.

Increased efficiency should not entail lowering clinical and research standards or ethical soundness. Rather, emphasis should be placed on minimizing factors that currently delay implementation of trials, such as suboptimal infrastructure and the complexity of multiple ethical reviews. As with international review boards, an African central ethics review board may expedite approvals while boards gain expertise in pediatric oncology.[66]

Therapy intensity has to be tolerable for the patient and provider yet simple enough to be delivered in resource-constrained settings. Africa innately lends itself to the development of unique expertise in nutrition, palliative care, translational oncology, and socioeconomic barriers to care.[6,50] Patients often present in advanced stages with low overall survival. Therefore, palliative care research should be a priority.

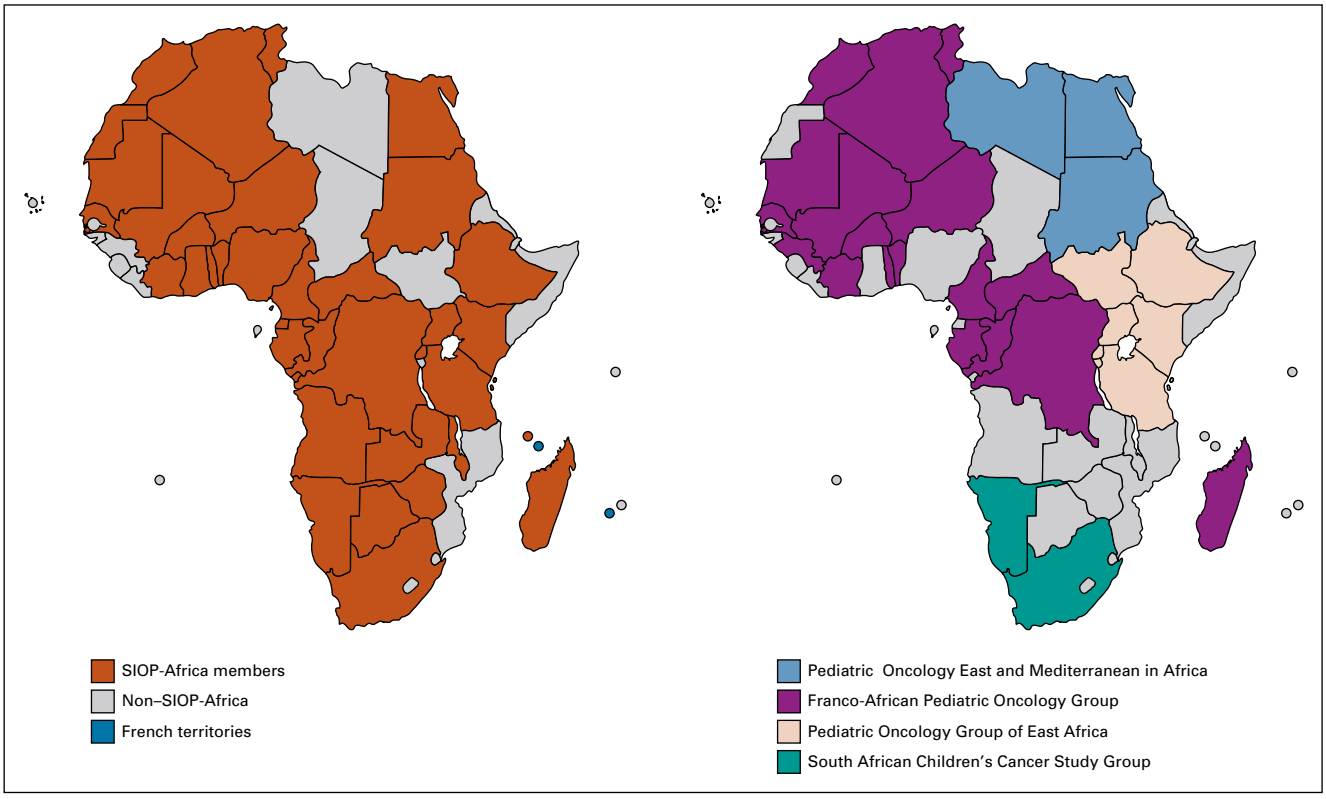

FIG 4. African-based collaborative groups. SIOP, International Pediatric Oncology Society.

Once curative, supportive, and palliative services have been strengthened, the capacity to conduct prospective clinical trials will grow. The unique biologic characteristics of a relatively unexamined population and the application of novel therapeutic options are exciting research avenues. Study populations must then have access to these agents to prevent a further widening of the medical gap between HICs and LMICs, with clinical trials of novel agents or approaches initiated or sponsored by the pharmaceutical industry conforming to local agendas.

In conclusion, there is robust, quality research being done in Africa with further potential for clinical trials in pediatric oncology. Several initiatives from national, continental, and international collaborative groups are increasing research capacity. While significant challenges remain, growing awareness of the importance of evidence-driven, locally adapted cancer care is encouraging for the expansion of clinical research on the continent. Improvement of access to clinical trials in Africa will improve survival rates.

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REFERENCES

1. Population Reference Bureau: International data https://www.prb.org/international/geography/africa
2. Ward ZJ, Yeh JM, Bhakta N, et al: Estimating the total incidence of global childhood cancer: A simulation-based analysis. Lancet Oncol 20:483-493, 2019
3. Force LM, Abdollahpour I, Advani SM, et al: The global burden of childhood and adolescent cancer in 2017: An analysis of the Global Burden of Disease Study 2017. Lancet Oncol 20:1211-1225, 2019
4. Gupta S, Howard SC, Hunger SP, et al: Treating childhood cancers in low- and middle-income countries, in Gelband H, Jha P, Sankaranarayanan R, et al (eds): Disease Control Priorities (ed 3): Volume 3, Cancer. Washington, DC, The World Bank, 2015, pp 121-146
5. Ezeani A, Odedina F, Rivers D, et al: SWOT analysis of oncology clinical trials in Africa: A town hall report from the Global Congress on Oncology Clinical Trials in Blacks. JCO Glob Oncol 6:966-972, 2019

6. Israëls T, Ribeiro RC, Molyneux EM: Strategies to improve care for children with cancer in sub-Saharan Africa. Eur J Cancer 46:1960-1966, 2010
7. Israëls T, Molyneux EM: Paediatric oncology: Collaborating in Africa-small steps to sustainable success. Nat Rev Clin Oncol 11:691-692, 2014
8. International Society of Pediatric Oncology: Global map of paediatric oncology services. https://siop-online.org/globalmapping
9. Geel J: V111 SIOP19-0244 SIOP maps paediatric oncology services in Africa to address inequalities in childhood cancer services. Presented at the 51st Congress of the International Society of Paediatric Oncology (SIOP), Lyon, France, October 23-26, 2019
10. Geel J: V112 SIOP19-1022 SIOP mapping of African paediatric oncology services: Implications for training and education. Presented at the 51st Congress of the International Society of Paediatric Oncology (SIOP), Lyon, France, Oct 23-26, 2019
11. de Rojas T, Neven A, Terada M, et al: Access to clinical trials for adolescents and young adults with cancer: A meta-research analysis. JNCI Cancer Spectr 3: pkz057, 2019
12. Vinches M, Neven A, Fenwarth L, et al: Clinical research in cancer palliative care: A metaresearch analysis. BMJ Support Palliat Care 10:249-258, 2020
13. Hessissen L, Patte C, Martelli H, et al: African School of Pediatric Oncology initiative: Implementation of a pediatric oncology diploma program to address critical workforce shortages in French-speaking Africa. JCO J Glob Oncol 10.1200/JGO.19.00161
14. Pediatric Oncology East & Mediterranean: Homepage. www.poemgroup.org
15. The Colleges of Medicine in South Africa: Sub-specialty Certificate in Medical Oncology of the College of Paediatricians of South Africa: Cert Medical Oncology(SA) Paed. https://www.cmsa.co.za/view_exam.aspx?QualificationID=91
16. Uganda Cancer Institute: The Pediatric Hematology-Oncology (PHO) Fellowship Programme. https://www.uci.or.ug/the-pediatric-hematology-oncology-pho-fellowship-programme
17. Ghana College of Physicians & Surgeons: Fellowship - Curriculum for Paediatric Oncology: Faculty of Child Health, 2017. https://gcps.edu.gh/jaymens_up/2018/01/CURRICULUM-FOR-FELLOWSHIP-FOR-PAEDIATRIC-ONCOLOGY-June-2017.pdf
18. Hesseling PB, Broadhead R, Molyneux E, et al: Malawi pilot study of Burkitt lymphoma treatment. Med Pediatr Oncol 41:532-540, 2003
19. Hesseling P, Broadhead R, Mansvelt E, et al: The 2000 Burkitt lymphoma trial in Malawi. Pediatr Blood Cancer 44:245-250, 2005
20. Traoré F, Coze C, Atteby JJ, et al: Cyclophosphamide monotherapy in children with Burkitt lymphoma: A study from the French-African Pediatric Oncology Group (GFAOP). Pediatr Blood Cancer 56:70-76, 2011
21. Bouda GC, Traoré F, Couitchere L, et al: Advanced Burkitt Lymphoma in sub-Saharan Africa pediatric units: Results of the Third Prospective Multicenter Study of the Groupe Franco-Africain d'Oncologie Pédiatrique. JCO J Glob Oncol 10.1200/JGO.19.00172
22. Harif M, Barsaoui S, Benchekroun S, et al: Treatment of B-cell lymphoma with LMB modified protocols in Africa—report of the French-African Pediatric Oncology Group (GFAOP). Pediatr Blood Cancer 50:1138-1142, 2008
23. Israëls T, Paintsil V, Nyirenda D, et al: Improved outcome at end of treatment in the collaborative Wilms tumour Africa project. Pediatr Blood Cancer 65:e26945, 2018
24. Israëls T, Moreira C, Scanlan T, et al: SIOP PODC: Clinical guidelines for the management of children with Wilms tumour in a low income setting. Pediatr Blood Cancer 60:5-11, 2013
25. Yao AJ, Moreira C, Traoré F, et al: Treatment of Wilms tumor in sub-Saharan Africa: Results of the Second French African Pediatric Oncology Group Study. JCO J Glob Oncol 10.1200/JGO.18.00204
26. International Society of Pediatric Oncology: Collaborative Wilms Tumour Africa Project. https://siop-online.org/collaborative-wilms-tumour-africa-project
27. Hesseling PB, Molyneux E, Tchintseme F, et al: Treating Burkitt's lymphoma in Malawi, Cameroon, and Ghana. Lancet Oncol 9:512-513, 2008
28. Salman Z, Kababri M, Hessissen L, et al: An intensive induction protocol for high risk neuroblastoma in Morocco. J Glob Oncol 2:80s-81s, 2016
29. Stefan C, Bray F, Ferlay J, et al: Cancer of childhood in sub-Saharan Africa. Ecancermedicalscience 11:755, 2017
30. Barr RD, Antillón Klussmann F, Baez F, et al: Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA): A model for sustainable development in pediatric oncology. Pediatr Blood Cancer 61:345-354, 2014
31. Ribeiro RC, Antillon F, Pedrosa F, et al: Global pediatric oncology: Lessons from partnerships between high-income countries and low- to mid-income countries. J Clin Oncol 34:53-61, 2016
32. Howard SC, Davidson A, Luna-Fineman S, et al: 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). Pediatr Blood Cancer 64: e26879, 2017
33. Bishr MK, Zaghloul MS: Radiation therapy availability in Africa and Latin America: Two models of low and middle income countries. Int J Radiat Oncol Biol Phys 102:490-498, 2018
34. Dewan MC, Rattani A, Fieggen G, et al: Global neurosurgery: The current capacity and deficit in the provision of essential neurosurgical care. Executive summary of the Global Neurosurgery Initiative at the Program in Global Surgery and Social Change. J Neurosurg 10.3171/2017.11.JNS171500 [epub ahead of print on April 1, 2018]
35. Toobaie A, Emil S, Ozgediz D, et al: Pediatric surgical capacity in Africa: Current status and future needs. J Pediatr Surg 52:843-848, 2017
36. Chantada G, Luna-Fineman S, Sitorus RS, et al: SIOP-PODC recommendations for graduated-intensity treatment of retinoblastoma in developing countries. Pediatr Blood Cancer 60:719-727, 2013
37. Fousseyni T, Diawara M, Pasquier E, et al: Children treated with metronomic chemotherapy in a low-income country: METRO-MALI-01. J Pediatr Hematol Oncol 33:31-34, 2011
38. André N, Banavali S, Snihur Y, et al: Has the time come for metronomics in low-income and middle-income countries? Lancet Oncol 14:e239-e248, 2013
39. Sambo LG, Dangou JM, Adebamowo C, et al: Cancer in Africa: A preventable public health crisis. J Afr Cancer 4:127-136, 2012
40. Ribeiro RC, Steliarova-Foucher E, Magrath I, et al: Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: A descriptive study. Lancet Oncol 9:721-729, 2008
41. Howard SC, Zaidi A, Cao X, et al: The My Child Matters programme: Effect of public-private partnerships on paediatric cancer care in low-income and middle-income countries. Lancet Oncol 19:e252-e266, 2018
42. Bristol-Myers Squibb Foundation: Global HOPE, 2020. https://www.texaschildrens.org/departments/global-hematology-oncology-pediatric-excellence-hope-0
43. United Nations Department of Economic and Social Affairs: World population prospects 2019. http://population.un.org
44. One World Nations Online: Official and spoken languages of African countries. https://www.nationsonline.org/oneworld/african_languages.htm
45. Foxalla K: The current state of African oncology research publication: How to increase Africa's research impact. Ecancermedicalscience 13:ed93, 2019
46. Wasswa P: Pediatric oncology clinical trials in sub-Saharan Africa. Appl Clin Trials 27:32-33, 2018

47. Emanuel EJ, Wendler D, Killen J, et al: What makes clinical research in developing countries ethical? The benchmarks of ethical research. J Infect Dis 189:930-937, 2004
48. Vassal G, Geoerger B, Morland B: Is the European pediatric medicine regulation working for children and adolescents with cancer? Clin Cancer Res 19:1315-1325, 2013
49. Ford JG, Howerton MW, Lai GY, et al: Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. Cancer 112:228-242, 2008
50. Zeigler-Johnson CM, Gueye SM, Rebbeck TR: Building infrastructure for cancer research in Africa. J Afr Cancer 3:52-58, 2011
51. Tilley H: Medicine, empires, and ethics in colonial Africa. AMA J Ethics 18:743-753, 2016
52. Day S, Challinor J, Hollis R, et al: Paediatric oncology nursing care in low- and middle-income countries: A need for baseline standards, in Magrath I (ed): Cancer Control 2015. Cancer Care in Emerging Health Care Systems. Woodbridge, United Kingdom, pp 111-116, 2015
53. Bey P, Moreira C, Couitchere L, et al: Implementation of multidisciplinarity in French-African Group of Pediatric Oncology (GFAOP) sub-Saharan teams: A process build by the teams. Pediatr Blood Cancer 66:e27989, 2019
54. Wilmshurst JM, Morrow B, du Preez A, et al: The African Pediatric Fellowship Program: Training in Africa for Africans. Pediatrics 137:e20152741, 2016
55. Zaghloul MS, Bishr MK: Radiation oncology in Egypt: A model for Africa. Int J Radiat Oncol Biol Phys 100:539-544, 2018
56. Slone JS, Slone AK, Wally O, et al: Establishing a pediatric hematology-oncology program in Botswana. JCO J Glob Oncol 10.1200/JGO.17.00095
57. Moreira C, Nachef MN, Ziamati S, et al: Treatment of nephroblastoma in Africa: Results of the first French African pediatric oncology group (GFAOP) study. Pediatr Blood Cancer 58:37-42, 2012
58. Traoré F, Eshun F, Togo B, et al: Neuroblastoma in Africa: A survey by the Franco-African pediatric oncology group. J Glob Oncol 2:169-173, 2016
59. Israëls T, Renner L, Hendricks M, et al: SIOP PODC: Recommendations for supportive care of children with cancer in a low-income setting. Pediatr Blood Cancer 60:899-904, 2013
60. Geel JA, Chirwa TC, Rowe B, et al: Treatment outcomes of children with Hodgkin lymphoma between 2000 and 2010: First report by the South African Children's Cancer Study Group. Pediatr Blood Cancer 64:e26536, 2017 [Erratum: Pediatr Blood Cancer 66:e27985, 2019]
61. Van Heerden J, Hendricks M, Geel J, et al: Overall survival for neuroblastoma in South Africa between 2000 and 2014. Pediatr Blood Cancer 66:e27944, 2019
62. Denburg AE, Laher N, Mutyaba I, et al: The cost effectiveness of treating Burkitt lymphoma in Uganda. Cancer 125:1918-1928, 2019
63. Zaghloul MS, Eldebawy E, Ahmed S, et al: Hypofractionated conformal radiotherapy for pediatric diffuse intrinsic pontine glioma (DIPG): A randomized controlled trial. Radiother Oncol 111:35-40, 2014
64. Paediatric Radiation Oncology Society: Homepage. https://intpros.org
65. Society for Neuro-Oncology Sub-Saharan Africa: Report of the first Sub-Saharan Africa Neuro-Oncology Collaborative (S-SANOC) planning meeting. http://www.snossa.org/report-of-the-first-sub-saharan-africa-neuro-oncology-collaborative-s-sanoc-planning-meeting
66. Page SA, Nyeboer J: Improving the process of research ethics review. Res Integr Peer Rev 2:14, 2017
67. The World Bank: World Bank Country and Lending Groups https://datahelpdesk.worldbank.org/knowledgebase/articles/906519