SACCSG HL-2018. Barriers and enablers of a harmonized treatment protocol for childhood and adolescent Hodgkin lymphoma in South Africa

Jennifer Geel[a], Marc Hendricks[b], Yasmin Goga[c], Beverley Neethling[d], Vutshilo Netshituni[e], Rema Mathew[f], Johani Vermeulen[g], Anel van Zyl[h], Fareed Omar[i], Jan du Plessis[j], Liezl du Plessis[k], Elelwani Madzhia[l], Thandeka Ngcana[m], Thanushree Naidoo[n], Lizette Louw[o], Daynia E. Ballot[p] and Monika L. Metzger[q]

[a]Pediatric Haematology-Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [b]Pediatric Haematology-Oncology, University of Cape Town, Red Cross War Memorial Children's Hospital, Cape Town, South Africa; [c]Pediatric Haematology-Oncology, University of KwaZulu-Natal, Inkosi Albert Luthuli Hospital, Durban, South Africa; [d]Pediatric Haematology-Oncology, University of KwaZulu-Natal, Durban, Inkosi Albert Luthuli Hospital and Greys Hospital, Pietermaritzburg, South Africa; [e]Pediatric Haematology-Oncology, University of Limpopo, Polokwane-Mankweng Hospital Complex, Polokwane, South Africa; [f]Pediatric Haematology-Oncology, Walter Sisulu University, Frere Hospital, East London, South Africa; [g]Pediatric Haematology-Oncology, Walter Sisulu University, Dora Nginza Hospital, Qheberha, South Africa; [h]Pediatric Haematology-Oncology, University of Stellenbosch, Tygerberg Hospital, Cape Town, South Africa; [i]Pediatric Haematology-Oncology, University of Pretoria, Steve Biko Academic Hospital, Pretoria, South Africa; [j]Pediatric Haematology-Oncology, University of the Free State, Universitas Hospital, Bloemfontein, South Africa; [k]Pediatric Haematology-Oncology, University of the Free State, Kimberley Hospital, Kimberley, South Africa; [l]Pediatric Haematology-Oncology, Sefako Makgatho University, Dr George Mukhari Hospital, Garankuwa, South Africa; [m]Pediatric Haematology-Oncology, University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa; [n]Department of Radiation Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [o]Department of Nuclear Medicine, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [p]School of Clinical Medicine, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [q]Medecins sans Frontieres, Democratic Republic of the Congo

ABSTRACT

Introduction: Collaborative studies have contributed to improved survival of pediatric Hodgkin lymphoma in well-resourced settings, but few are documented in resource-constrained countries. The South Africa Children's Cancer Study Group initiated harmonization of management protocols in 2015. This article analyzes barriers and enablers of the process. **Methods:** Clinician-researchers at 11 state-funded pediatric oncology units completed preparatory questionnaires in June 2018. Parameters included infrastructure, access to therapeutic modalities and clinician numbers. A reassessment of 13 sites (two new pediatric oncology unit) in February 2021 ascertained changes in resources and identified challenges to full participation. Questions investigated the presence and quality of diagnostic radiology, availability of surgeons, cytology/pathology options and hematology laboratory facilities. **Results:** The response rate was 11/11 to survey 1 and

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CONTACT Jennifer Geel jennifer.geel@wits.ac.za Pediatric Haematology-Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South A

13/13 to survey 2. The anticipated pre-study barriers to participation of pediatric oncology units included time constraints and understaffing. PET-CT was unavailable to two centers. The majority of pediatric oncology units met the minimum criteria to participate. The interim survey confirmed chemotherapy and radiotherapy availability nearly 100% of the time. One site reported improved access to radiotherapy while another reported improved access to PET-CT. Barriers to participation included excessive times to obtain regulatory approvals, time constraints and lack of dedicated research staff. Enablers include the simple management algorithm and communication tools. **Conclusion:** This study demonstrates that multicenter collaboration and harmonization of management protocols are achievable in a middle-income setting. Minimal funding is required but full participation to run high-quality studies requires more financial investment. Focused funding and increased prioritization of research may address systemic barriers to full participation.

Introduction

Childhood cancer 5-year overall survival in high-income countries (HIC) has improved steadily from approximately 30% in the 1960s to 90% in the 21st century.[1] Much of this improvement is attributable to collaborative work, as childhood cancer is rare and recruitment of sufficient patients to achieve statistical significance requires multicenter collaboration. Since the 1970s, HL has been treated in cooperative group trials, leading to successively higher survival rates.[2] Groups such as the EuroNet Pediatric Hodgkin Network and the North America Children's Oncology Group have conducted multiple consecutive trials documenting improved survival rates exceeding 95%.[3]

The growing movement toward adapted treatment regimens in low-and-middle-income countries (LMIC) includes ATRs for HL, successfully used in Latin America.[4] While many ATRs are positioned as very simplistic guidelines suitable for highly resource-constrained settings, few have been explicitly positioned in the middle-income (MIC) or upper-middle-income (UMIC) setting, such as South Africa. The majority of children with cancer in HIC are enrolled on prospective clinical trials as matter of course,[5] while this is not the case in Africa or Asia.

"Harmonization" refers to a growing effort to employ the same standards and norms in diagnosing and treating various cancers. The term may also include the minimizing of redundant or conflicting standards that may have evolved independently. By introducing a harmonized national protocol, the intention is to achieve comparable survival outcomes to those realized in other countries (both HIC and MIC) and to standardize laboratory and imaging diagnostic tests.

Survival rates for children and adolescents with HL in South Africa range from 20% in under-resourced settings to 80% in established centers.[6] Harmonization of management protocols in a research setting has been identified as an approach to improve survival rates, decrease toxicity and streamline costs. There are no published African studies indicating that the use of a single risk-adapted, response-based protocol is feasible or whether national survival rates can be improved to approach those in HIC with such a strategy. This article outlines the implementation of a multicenter, national protocol and aims to

describe barriers and enablers of this growing harmonization movement with a particular focus on HL. The overall study model was conceptualized at the annual South African Children's Cancer Study Group (SASSCG) meeting in 2015 and consisted of a retrospective analysis[6] to create a baseline followed by a prospective study.

The South African HL prospective study protocol comprises a simple, risk-stratified, response-adapted approach to improve survival rates, paying particular attention to patients with HIV infection and advanced disease at presentation. This particular sub-study compared resources necessary to conduct a multicenter observational study at initiation and partway through the project process to assess whether harmonization is feasible in South Africa.

Materials and methods

Design of the prospective observational study SACCSG-HL2018

SACCSG-HL2018 was designed as a multicenter observational study to harmonize treatment approaches in South Africa, with an inbuilt feasibility assessment. The model proposed by Chung[7] was followed to plan the study. Three protocol meetings were held on 08/03/2016, 08/08/2016 and 15/09/2016 to interrogate results of the retrospective data and to plan the prospective protocol. Risk grouping was based on Pediatric Hodgkin Consortium risk assessment, with Standard Risk comprising Cotswold-modified Ann Arbor stage IA, IB and IIA; Medium Risk comprising Stage IX, IE, IIX, IIE and IIIA, and High Risk comprising Stage IIEX, Stage IIIB, IIIX, IIIE and Stage IV.[2] The simple treatment algorithm was designed to avoid errors (see Figure 1) favoring administration of chemotherapy in an out-patient setting.

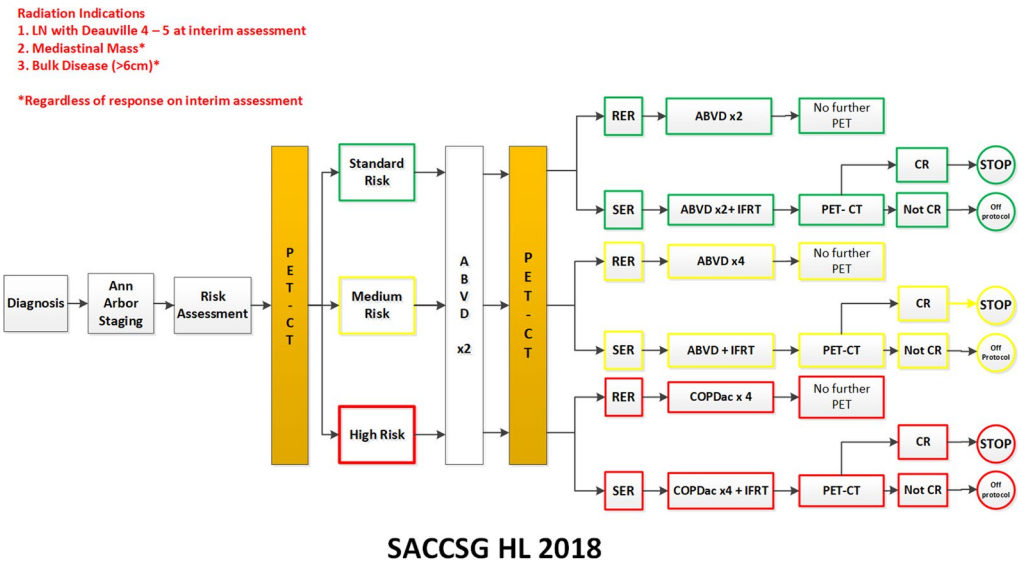

Figure 1. Protocol algorithm. ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine; PET-CT: Positron emission tomography-computerized tomography; RER: Rapid early response; SER: Slow early response; CR: complete response.

All children and adolescents with biopsy-proven, treatment-naive HL are included, including those with HIV infection. Exclusion criteria included those with preexisting cardiac dysfunction precluding treatment with anthracyclines and those with nodular lymphocyte predominant HL.

Patients with bulky disease, mediastinal masses and/or incomplete response based on interim PET-CT receive consolidation therapy with 25 Gy radiotherapy, preferably involved node or involved field, according to the capability of each unit.

The study was linked to a PhD project to enhance academic rigor, increase research capacity and attract grant funding. During the protocol development a supervisor (MM) with experience in LMIC collaborative studies, an economics expert (KE) and a statistician (TK) with experience in LMIC studies were included to contribute expertise in a study for resource-limited settings.

Prognostic markers with proven prognostic value in resource-constrained settings that were included were total white cell count, total lymphocyte count, hemoglobin, platelet count, absolute eosinophil count, erythrocyte sedimentation rate, copper, ferritin and lactate dehydrogenase. The ongoing observational prospective study aims to determine whether a harmonized protocol leads to better survival outcomes and whether alterations in these affordable, readily available blood tests correlate with PET-CT findings. If so, it is postulated that PET-CT could safely be omitted in settings that cannot perform this modality in patients classified as rapid early responders in a similar way that thymus and activation-regulated chemokine/CCL17 (TARC) levels have been used.[8]

A REDCap® database[9] was created to collect data which included treatment response and toxicities, survival outcome and adherence to the protocol. A pilot study was initiated in three pediatric oncology units on the University of the Witwatersrand circuit, and the REDCap® study database was iteratively adapted to ensure ease of use and accuracy of data. Specific features, new in this context, included body surface area calculators, International Classification of Disease codes and chemotherapy dose calculators. Central review of radiology and pathology was facilitated by uploading images and reports.

Participants in the feasibility sub-study

An invitation was sent to all state-funded pediatric oncology units to participate, each represented by a clinician-researcher and, without exception, all committed to the project. Study participants (clinician-researchers) including the principal investigator (PI), completed a brief survey to determine if their pediatric oncology unit met the criteria for participation (see Table 1, Supplementary material) in the prospective study.

Once the majority of pediatric oncology units had started enrolling patients, online meetings were held to incorporate ongoing quality assurance as problems or learning areas were detected. A WhatsApp® group was created to encourage rapid communication and updates, and participants were offered co-authorship on articles if they met the accepted publication criteria.[10] All participants signed an agreement to participate, communicate and collaborate.

Design of feasibility sub-study

The questions for the first survey were based on the pre-requisites in Table 1 (Supplementary material), to determine whether participating pediatric oncology unit

had sufficient staff, treatment modalities and infrastructure to follow the treatment protocol. Open-ended questions regarding challenges and solutions were posed. Survey 1 was created in REDCap to facilitate rapid responses and collation of data, and was conducted from 1 to 15 June 2018.

Once all sites opened for recruitment, a second telephonic assessment was conducted between1 and 28 February 2021 by the PI. The telephonic format was favored to elicit more nuanced responses, to enhance communication and try to devise solutions to problems in real time. This survey ascertained changes in infrastructure and resources identified challenges to full participation in the study. New questions were added to this questionnaire in response to protocol violations detected in the interim analysis. These violations included blood tests not being taken as specified in the protocol, PET-CT not being performed according to protocol and radiotherapy not being administered when indicated.[11] In addition, the capacity to consent and enroll study participants was assessed. These questions investigated the presence and quality of diagnostic radiology (X-ray, PET-CT), availability of surgeons, cytology/pathology options, hematology and chemistry laboratory facilities. Further data points included time to ethics committee approvals, physical infrastructure, treatment modalities and staffing levels. Open-ended questions were posed to elicit other challenges not covered in the preceding questions, as well as potential solutions.

Ethics and regulatory approvals

The study was approved by a scientific committee (postgraduate committee of the University of the Witwatersrand, "Wits") and the Wits human research ethics committee (M1711100) and registered on the National Health Research Database and the seven provincial Health Research Databases of each pediatric oncology unit. Approval was obtained by the national PI from the ethics committee of each participating pediatric oncology unit.

Results

Pre-study questionnaire 1

The response rate to the first questionnaire was 100% (11/11pediatric oncology units), and all fields were completed (see Table 1). Multiple respondents indicated severe understaffing, with a median of two full-time consultants and one medical officer per pediatric oncology unit, responsible for 26–150 new oncology patients annually and training a median of one fellow. Appropriate diagnostic radiological services (basic radiographs and PET-CT) were available in all 11 pediatric oncology units while staging PET-CT was readily available to 9/11 pediatric oncology units, with plans to transport patients to the nearest nuclear medicine facility in the remaining two pediatric oncology units. All participants reported access to the necessary chemotherapy agents, while radiotherapy was available 100% of the time in 9/11 pediatric oncology units and 75% of the time in 2/10 pediatric oncology units (see Tables 1 and 2). It was thus concluded that the majority of pediatric oncology units met the minimum requirements to participate.

Table 1. Preplanning survey 2018 prior to national rollout of study (2018).

Staffing	Median	Range
Number of full time consultants in unit	2	2–4
Number of registered pediatric oncologists/hematologists in unit	2	1–4
Number of senior registrars/fellows in the unit	1	1–2
Number of permanent medical officers in the unit	1	1–2
	Number	Percentage
Number of new oncology patients per year		
26–50	2	16.7
51–75	3	25.0
76–100	1	8.3
101–125	2	16.7
126–150	3	25.0
>150	1	8.3
Diagnostic modalities		
Access to appropriate radiological services, including review/ reports		
Chest X ray	11	100
CT scans	11	100
MRI	11	100
Access to PET CT		
Yes	9	82
No	2	18
Access to ABVD medications		
100% of the time	11	100
Access to COPDac medications		
100% of the time	11	100
Access to radiotherapy a reasonable distance from the pediatric oncology unit		
Up to 100% of the time	9	82
Up to 75% of the time	2	18
Type of radiotherapy available		
Involved node	2	18
Involved field	6	55
Involved region	3	27
Regular multidisciplinary team meetings held		
Yes	8	73
No	3	27
Access to pediatric intensive care facilities		
100% of the time	6	55
75% of the time	1	9
50% of the time	4	36

Mid-study questionnaire 2

The second questionnaire to participants from 13 sites, which included the original 11 sites and two new pediatric oncology units that had been established since the start of the project. The response rate was 13/13 (100%) and all questions were answered (see Table 3). Participants reported that all patients approached to enroll on the study agreed to participate.

The essential diagnostic modalities were available in the majority of sites. The required chemotherapy agents were available nearly 100% of the time, with all pediatric oncology units reporting a temporary shortage of doxorubicin from January to March 2020 due to a nationwide shortage. This shortage affected three patients for one cycle each and the patients remained on study. Access to radiotherapy was unchanged, with one site reporting improved access. One pediatric oncology unit that previously reported no access to PET-CT scans elected to transport patients to a referral center for this modality, while another still had no access, despite repeated requests and motivations to hospital management, thus

Table 2. Preplanning survey free text questions prior to national rollout of study (2018).

"Which barriers or challenges do you foresee?"	n = 11	%
Time constraints due to understaffing, high clinical and teaching load	4	36
Time constraints, unspecified	4	36
No barriers	3	27
Patient transport costs	3	27
No PET-CT facilities available	2	18
HREC approvals a long and complicated process	2	18
Adherence of patients to treatment a concern	1	9
No study nurses	1	9
Radiotherapy services are constrained	1	9
Serum copper not done at local laboratory	1	9

"Which potential solutions to the problems you have mentioned can you put forward?"
- Solutions that may be achievable through the study
- Research assistance.
- Provide a broad plan of where we are going to and how each part fits in.
- Streamline and simplify processes as much as possible.
- Discuss with chemical pathology laboratories how to get serum copper tests done.
- Systemic solutions that require government/other funding
- PET-CT scanning facilities within reasonable distance of the pediatric oncology unit.
- Improved staffing complement (pediatric oncologists, pediatric radiation oncologists, pediatric oncology trained nurses).
- Data capturer
- Administrative support

"If we were to access more funding for this project, are there are any specific things you would like funded to assist you to take part in this project?"
- Full time research coordinator
- Data capturer
- Administrative support
- Funding for traveling to group meetings, should it be required
- Assistance with counseling and ethics/ consent discussions
- Transport funding for patients to get to PET CT scans
- More nurses

"Do you have any particular comments or suggestions to make this project a success?"
- Everyone needs to contribute
- Prompt registration of patients, to be up to date and efficient with data collection, constant contact with and feedback from PI.
- Regular meetings

making 12/13 sites eligible for participation. Multiple responses indicated that, although the management algorithm had been formally introduced in all radiation departments, many individual radiation oncologists still did not agree to radiate certain patients as they did not agree with the indications for consolidation radiotherapy in these patients.

Enablers

Enablers of the project were the simple management algorithm, data-capture tool and communication methods. These methods included addressing protocol violations with individual researchers, WhatsApp® communications and team meetings for issues that pertained to many pediatric oncology units. Barriers to full participation included protracted time periods to receive regulatory approvals, severe time constraints, lack of research support staff and lack of PET-CT facility within a reasonable distance of one center. The added strain of the COVID-19 pandemic was reported by many participants as a potential factor for incomplete data capture, but it did not affect recruitment.

Table 3. Survey 2 2021 after national rollout of study.

Diagnostic modalities	n	%
Chest x-ray facilities available	13	100
Fine needle aspiration (FNA) biopsy results		
Good quality results within 72 hours	2	15
Good quality results within 7 days	1	8
Results often inconclusive	7	54
No longer perform FNA as results are inconclusive	3	23
Surgeons available to perform lymph node excisions		
Pediatric surgeons available in the hospital	10	77
General surgeons available in the hospital	2	15
Refer to another hospital for excision	1	8
Histopathology services		
Good quality results within 7 days	9	69
Good quality results within 14 days	3	23
Adequate quality results within 14 days	1	8
PET-CT facilities available		
Fused PET-CT in treating center	8	61
Refer to another center for PET-CT	4	31
PET-CT not available	1	8
Full blood count and differential available	13	100
Regulatory requirements		
Time to university ethics permission <6 months	11	85
Time to university ethics permission >18 months	2	15
Provincial ethics committees permission obtained <6 months (n = 8)	8	62
Good Clinical Practice or ethics course completed in the last 5 years	10	77
Good Clinical Practice or ethics course not completed in last 5 years	4	31
Enrollment		
1–27 patients (median 3.5)	11	85
0 patients	2	15
Infrastructure and staff		
Sufficient out-patient facilities to participate in the study	12	92
Insufficient out-patient facilities to participate in the study	1	8
Sufficient in-patient facilities to participate in the study	13	100
Sufficient nurses and doctors to participate in the study	11	85
Insufficient nurses and doctors to participate in the study	2	15
Pediatric oncology unit holds regular multidisciplinary team meetings	11	85
Pediatric oncology unit does not hold regular multidisciplinary team meetings	2	15
Oncology trained nurses per shift		
More than one	9	69
At least one	2	15
None	2	15
Research infrastructure		
Sufficient internet access to upload data on REDCap	12	92
Insufficient internet access to upload data on REDCap	1	8
Trained in the use of REDCap	13	100
Confident in the use of REDCap	8	62
Request REDCap refresher	4	31
Limited availability of research support staff	4	31
No availability of research support staff	10	77
Chemotherapy and radiotherapy		
Pharmacy available in my center able to mix chemotherapy timeously	12	92
Pediatric oncology doctors mix the chemotherapy themselves	1	8
ABVD available nearly 100% of the time	13	100
COPDac available nearly 100% of the time	13	100
Involved node radiation available	1	8
Involved field radiation available	12	92

The study objective of comparing interim PET-CT response with alterations in blood tests required a minimum of 42 patients with datasets including PET-CT at diagnosis and interim assessment, paired with blood results. At the time of writing, 114 participants had been enrolled and 70 appropriate data sets were available. No patients declined to

participate in the study, and all patients who were eligible for the study had been enrolled, although data capture was incomplete due to resource and time constraints.

Barriers

The funding sourced through formal channels required more time than anticipated to manage, due to a lack of familiarity with the process and restricted timelines set by some funders. (See Table 3) For example, one grant required the funding to be used within a four-month period, while another which was intended to supplement income for data capturers in each pediatric oncology unit could not be used for this purpose due to lack of time and capacity to manage the administrative requirements. For this reason, crowdfunding using sponsored sporting events was used to source funding that did not require stringent administrative oversights but still conformed to Wits University financial compliance criteria.

Discussion

Although a majority of childhood cancer research in Africa originates from a limited number of countries, including South Africa, there is minimal prospective research in this country, with most published manuscripts based on retrospective work.[12] Clinicians in South Africa thus rely on trials designed and implemented in high-income settings, which may not be appropriate for this patient population. This is the first South African study that has achieved involvement by all eligible pediatric oncology units, including enrollment, completion of treatment and publication of results.

This feasibility study determined whether a multicenter, harmonized management algorithm for pediatric and adolescent HL could successfully be implemented in all 14 South African state pediatric oncology units. Over the course of two years, the majority of participants reported access to the necessary diagnostic and therapeutic modalities required to participate.

The InPOG-HL-15-01 trial was the first collaborative multicenter prospective clinical trial for children with cancer in India.[13] This four-year trial accrued 410 patients onto a simple study protocol with an ABVD backbone, with interim assessment after two cycles. Our study protocol follows a similar design, incorporating more intensive chemotherapy (COPDac) for high-risk patients. Challenges in the Indian study included variation in the timing of the first interim assessment imaging, restricted access to PET-CT and radiotherapy, and disagreement about radiotherapy indications, fields and doses. Over the course of the trial, this became more homogenous. Some centers required multiple reminders to input data timeously as they were more accustomed to retrospective studies.[13] These factors are mirrored in our study, demonstrating similar challenges.

No patients declined to participate in this study which is an encouragement to clinician-researchers in this setting. Under-representation of children of African ancestry in clinical trials is a concern[14] and does not engender confidence in clinicians who do not see their patient populations represented in published reports and treatment guidelines emanating from high-income settings. Studies such as the SACCSG-HL-2018 are thus vital to generate setting-specific data for African patients.

Barriers to full participation

While absence of a comprehensive database and small sample sizes are barriers to running clinical trials in the pediatric oncology field in the North American setting,[15] this did not emerge as a barrier to this study, which is observational rather than experimental. Treatment represents standard of care, which may contribute to the high rate of patient participation.

Unwieldy regulatory requirements prohibited timely participation by many centers, with some centers taking more than 18 months to obtain approval. The stringent requirements of the multiple ethics and scientific committees assisted in the commitment to research governance, ie, improving belief in the project by ensuring that it was high quality, safe and ethical. However, the extremely long time frames of some of the ethics committees meant that patients were lost to recruitment. Although reciprocal approval across different HRECs was theoretically in place, this did not occur in reality. Having had the benefit of a few years running this study, it now appears that the more prudent course may have been to have each pediatric oncology unit submit their own HREC application which may have tested the commitment of the pediatric oncology units to participate. A systemic solution could include centralization of ethics committees to streamline the process.

Time constraints and understaffing are prominent concerns of many participants. As more South African multicenter, investigator-led studies are launched, it may become possible to co-fund additional staff to assist with administrative support, data capture and research coordination. While it is unlikely that research grants will be sufficient to pay for full salaries across the 14 sites, it may be possible to partially fund part-time staff members. South Africa's gross expenditure on research and development fell from a high of 0.95% of GDP in 2016[16] to 0.75% of GDP in 2019, according to the latest survey on research intensity.[17] Funding is thus becoming more difficult to source, due to factors such as the 2018 recession and the redirection of research funds to studies related to COVID-19. Currently, more funding is being sourced to support the study, and efforts to raise money through crowdfunding are ongoing.

Similar to the South African experience, barriers to conducting multicenter clinical trials in Africa include insufficient funding and staffing, lack of research environment, ethical and regulatory impediments.[18] The recommended number of pediatric oncologists to annual new patients is 1:15 or 1:25[19]: Holton and most participants in this study reported much higher patient numbers than recommended (Table 1). Lack of familiarity with grant writing and management in LMICs means that, even when funding is available, it may not always be utilized most effectively.[20] Training and support may increase the effective use of these limited resources.

The protocol violations found on interim assessment are valuable lessons in conducting investigator-led trials in this setting. Without the intensive funding and human resources available in multicenter pharma-sponsored trials, the same level of attention to detail as found in these studies is not possible in the LMIC setting. However, studies such as these are more reflective of real-life medical practice compared with sponsor-led trials with stricter inclusion and exclusion criteria. The study findings are more representative of the pediatric and adolescent HL population in UMICs, with the notable

inclusion of patients with HIV infection. The impact of substituting agents is unknown but will be evaluated as part of the study outcomes.

The COVID-19 pandemic was an increased stress on participants but did not appear to have affected site induction or recruitment significantly, although it may have affected the time to regulatory approval as ethics committees were inundated with requests to approve studies related to the pandemic.

Facilitators

Before this project was initiated, management regimens included intensive regimens with high toxicity requiring hospital admissions.[6] Adopting less toxic regimens may decrease treatment abandonment as there is increased convenience, lower morbidity and lower cost.[21] Such costs would include out-of-pocket expenses as the majority of pediatric oncology care is state-subsidized. These potential benefits may contribute to the commitment of the study participants to collaborate in this harmonization project and may help to improve the survival rate. Further enablers which could be exploited in future studies include regular communication, a simple management algorithm, free online data collection tool and research support from a national coordinator.

Facilitators include commitment to contributing to African research, improving patient outcomes, simple data collection process, team interaction, career advancement, improved training of researchers, financial and logistical support.[22] These factors are not isolated to childhood cancer research. A streamlined, centralized ethics review process to assist clinician-researchers with limited time and experience could also be beneficial.

Achieving the Sustainable Development Goals (SDG), a blueprint for global progress, requires concerted efforts to strengthen research capacity in LMIC. The SDG recognize research capacity as essential to the generation of novel, locally relevant knowledge to deliver appropriate services to prevent and control disease and suffering.[23] Projects such as SACCSG-HL-2018, which aims to create a locally relevant evidence base for the treatment of HL in South Africa, address this mandate closely, and are thus crucial to develop and support.

Growing concerns about local research agendas being set by researchers from HIC[24] indicate that South African institutions should strengthen research capacity and set locally relevant priorities to mitigate this.

Recommendations

A formal research training program may enable successful investigator-led clinical trials. Such training should include grant writing and management, recruitment and retention of study participants, research coordination and collaborative publishing. Protected time for research is essential. Funding is required to employ research and administrative support staff as clinicians who do not have sufficient time to participate fully. Research should be given greater priority to improve survival rates and ethics review processes should be streamlined.

Limitations

Before starting recruitment of sites, it might have been prudent to run a formal assessment of staff needs and workload such as the ASCO Clinical Trial Workload Assessment Tool[25] or the King's College NHS Feasibility checklist,[26] although these are tailored for high-income settings and there are no published similar tools in Africa.

Conclusion

Despite the obvious obstacles to conducting research in a resource-constrained setting, this study demonstrates that multicenter collaboration is achievable. The protocol described here represents an ATR suitable for a MIC setting, and harmonization of pediatric and adolescent HL treatment in this format is feasible in South Africa: the minimum requirements are available in the majority of centers, and clinicians are committed to the process. Minimal funding is required to initiate such a project, but full participation to run high-quality studies may require more financial investment. Focused funding and increased prioritization of research may address systemic barriers to full participation.

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ORCID

Jennifer Geel http://orcid.org/0000-0001-8792-3251
Marc Hendricks http://orcid.org/0000-0002-3636-0994
Yasmin Goga http://orcid.org/0000-0002-6740-2376
Beverley Neethling http://orcid.org/0000-0002-7580-8042
Vutshilo Netshituni http://orcid.org/0000-0003-2169-6038
Johani Vermeulen http://orcid.org/0000-0003-1180-6862
Anel van Zyl http://orcid.org/0000-0003-3370-0874
Fareed Omar http://orcid.org/0000-0002-2319-1087
Jan du Plessis http://orcid.org/0000-0002-1914-4202
Thandeka Ngcana http://orcid.org/0000-0003-4802-6317
Daynia E. Ballot http://orcid.org/0000-0003-4985-048X
Monika L. Metzger http://orcid.org/0000-0002-7102-4611

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